Cyclam-strapped porphyrins and their iron(III)–copper(II) complexes as models for the resting state of cytochrome *c* oxidase

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The ESR study of two cyclam-strapped porphyrins in which, on one side, the cyclam is attached with a variable length linker to the porphyrin and, on the other side, a non-coordinating strap protects the iron from any intermolecular interaction, is reported. Variation of the linker length is made possible by the use of either a Michael reaction or a nucleophilic substitution, leading respectively to three or two carbon atom links. It is shown that in the case of the shortest link, the oxidized iron–copper complex exhibits a spin interaction. The distance between the two metal centers is evaluated to be around 4.5 Å, a value consistent with the one found in the natural enzyme.

In the last two decades, great efforts have been devoted towards the synthesis of more and more sophisticated models of hemoproteins[1] such as myoglobin (Mb), cytochrome P-450 (P-450) or cytochrome *c* oxidase (C*c*O). In the case of the latter, the "self-assembly" approach[2] appeared to be the most fruitful route to characterize possible catalytic intermediates playing a part in the reduction of dioxygen into water *via* a $4H^+/4e^-$ process.[3] Two recent crystallographic studies of this enzyme[4] confirmed the structure of the active site as Fe_{a_3}–Cu_B, as already suspected from ESR measurements, UV-vis or Raman resonance spectroscopies.[5]

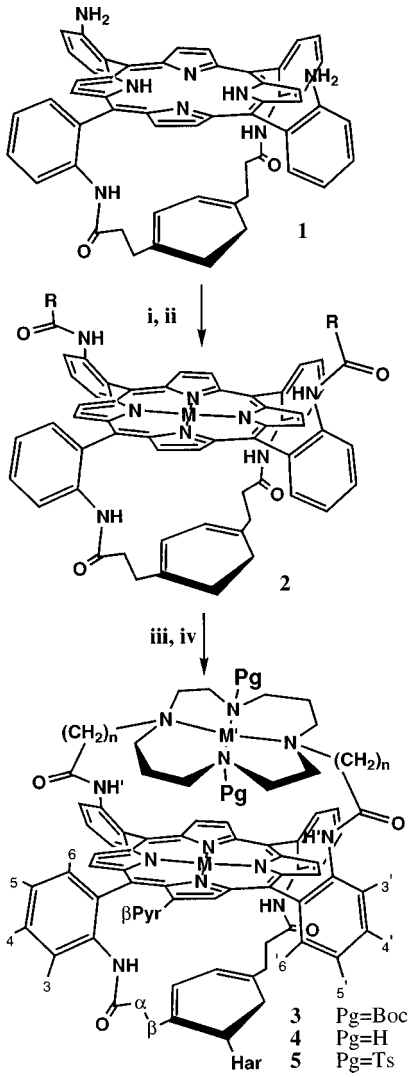
So far, most of the reported structures are relevant to the oxo type, displaying a magnetically coupled heme–copper complex. For example, Karlin *et al.* reported the X-ray structure of a μ-oxo complex[6] obtained by air oxidation of an iron(II) porphyrin and a tetraaza copper(I) complex at −80 °C. Separately, Holm *et al.* published a structure in which iron and copper are bridged by a cyanide.[7] It is worth noting that this type of reaction is expected to lead to the thermodynamically most stable complex (*e.g.*, oxo *vs.* peroxo complex) because the distance between the two metal centers can change if necessary. This is certainly why more recently, a new generation of models appeared in which the two chelating structures are maintained in a defined geometry by covalent attachments.[8]

Considering that the covalent linkage of the chelating structures is crucial, we wish to report our work concerning the synthesis and characterization of spectroscopic model compounds containing a copper(II) atom held at about 3–4 Å from an iron(III) atom. Almost ten years ago, a model containing an iron(III) porphyrin and a copper(II) cyclam covalently attached by a single linker was reported by Weiss *et al.* An ESR study of the bimetallic complex did not reveal any metal–metal interaction.[8b] A possible explanation for this result is that the single linkage does not guarantee the cofacial geometry required for the bimetallic interaction. As a bis-covalently attached system could satisfy the topological requirements, we intended to prepare new porphyrin-cyclam systems where the chelating structures are maintained in a defined geometry by two linkers. Two different lengths for the linkers have been considered in order to favor the bimetallic interaction.

Our initial attempt to synthesize such models involved the use of the 1,8-ditosyl cyclam[9] and a correctly functionalized porphyrin *via* a Michael reaction. Using a similar approach, we also developed the preparation of a model containing a 1,8-diBoc cyclam[10] bridged over a porphyrin by either a 3 ($-CH_2CH_2CO-$) or 2 ($-CH_2CO-$) carbon atom linker (Scheme 1). This new type of compound is expected to avoid the flexibility of the previously reported systems and to insure the desired "face-to-face" conformation of the two metal centers. Additionally, this synthetic route has been applied to a single strapped porphyrin[11] to avoid any uncontrolled reactions on the "open" face.

Results and discussion

The synthetic pathway implies the functionalization of a single strapped porphyrin **1** by either acryloyl or chloroacetyl chloride to obtain new porphyrins able to react with nucleophilic reagents such as diprotected cyclams. To obtain the desired cofacial conformation, 1,8-diprotected cyclams have been employed. Indeed, the use of 1,4- or 1,5-diprotected cyclams would lead to "twisted" systems, which are not favorable for an interaction between the two metal centers. Moreover, one can conceive that a system including porphyrins $\mathbf{2aH_2}$ or $\mathbf{2bH_2}$ and a "*cis*"-diprotected cyclam (in 1,4 or 1,5 positions) induces a looser and longer linkage than the one with 1,8-diprotected cyclam. Actually, even a 1,8-diprotected cyclam strapped over the porphyrin allows a certain degree of flexibility as proved by ^{1}H NMR studies. Indeed, NMR spectra of both ligands $\mathbf{3aH_2}$ and $\mathbf{3bH_2}$, which differ only by the length of their chain, $\mathbf{3aH_2}$ having a shorter one, show very broad signals at room temperature for both the aliphatic and aromatic regions. This observation can be accounted for by the slow swinging movement of the straps around their two points of attachment on the *meso*-phenyl groups, which is not totally inhibited at this temperature. When the same spectrum is recorded at higher temperature (up to 400 K, Fig. 1), one can see that the signals become sharper and sharper. This result is expected as an increase of temperature allows an easier and faster interconversion between conformers. It has to be pointed out that there is no significant difference in rigidity between the two different strap lengths ($n = 1$ or 2), as illustrated by the sharpness of most of their NMR signals at the same temperature (*i.e.*, 400 K) (Fig. 2).



Scheme 1 Preparation of copper cyclam-strapped iron porphyrins. *Reagents and conditions:* i, $CH_2=CHCOCl$ or $ClCH_2COCl/Et_3N$/dry THF; ii, $FeCl_2$/2,6-lutidine/THF/55 °C; iii, 1,8-diprotected cyclam in THF or MeOH/50 °C; iv, 5 equiv. $M'(OAc)_2$/EtOH/reflux/12 h. (**a** refers to the shorter link, with R = $-CH_2Cl$ or $n = 1$; **b** refers to the longer one, with R = $-CH{=}CH_2$ or $n = 2$). **2aH$_2$** : R = $-CH_2Cl$, M = 2H; **2aFe**: R = $-CH_2Cl$, M = FeCl; **2bH$_2$** : R = $-CH{=}CH_2$, M = 2H; **2bFe**: R = $-CH{=}CH_2$, M = FeCl; **3aH$_2$** : $n = 1$, Pg = Boc, M = 2H, no M′; **3aZn**: $n = 1$, Pg = Boc, M = Zn, no M′; **3aFe**: $n = 1$, Pg = Boc, M = FeCl, no M′; **3bH$_2$** : $n = 2$, Pg = Boc, M = 2H, no M′; **3bZn**: $n = 2$, Pg = Boc, M = Zn, no M′; **3bFe**: $n = 2$, Pg = Boc, M = FeCl, no M′; **3bFeCu**: $n = 2$, Pg = Boc, M = FeCl, M′ = $Cu(AcO)_2$; **4aFe**: $n = 1$, Pg = H, M = FeCl, no M′; **4aFeCu**: $n = 1$, Pg = H, M = FeCl, M′ = $Cu(AcO)_2$; **4bH$_2$** : $n = 2$, Pg = H, M = 2H, no M′; **5bH$_2$** : $n = 2$, Pg = Ts, M = 2H, no M′; **5bCuCu**: $n = 2$, Pg = Ts, M = Cu, M′ = $Cu(AcO)_2$; **5bCoCo**: $n = 2$, Pg = Ts, M = Co, M′ = $Co(AcO)_2$. **6**: 1,8-diBoc cyclam; **7**: 1,8-diTs cyclam.

A typical experimental procedure for the preparation of cyclam strapped-porphyrins (**3** or **5**) requires refluxing the single strapped-porphyrins (**2**) with an excess of 1,8-diprotected cyclam (**6** or **7**, 1.5 equiv.) in methanol or THF for 48 h. As we previously reported,[9] no reaction occurs at room temperature with either the ditosyl or diBoc cyclam. The major difference between these two protective groups is certainly the fact that the tosyl group must be considered permanent under our reaction conditions, whereas the Boc group is very easy to remove. Moreover, the increased yield induced by the use of the Boc group (60%) must be emphasized in comparison with the 12% yield obtained with the tosyl group. After extraction, chromatography and precipitation in a mixture of CH_2Cl_2/pentane, compounds **3aH$_2$** and **3bH$_2$** have been characterized by IR/UV-vis/^{1}H/^{13}C spectroscopies as well as FAB mass spectrometry.

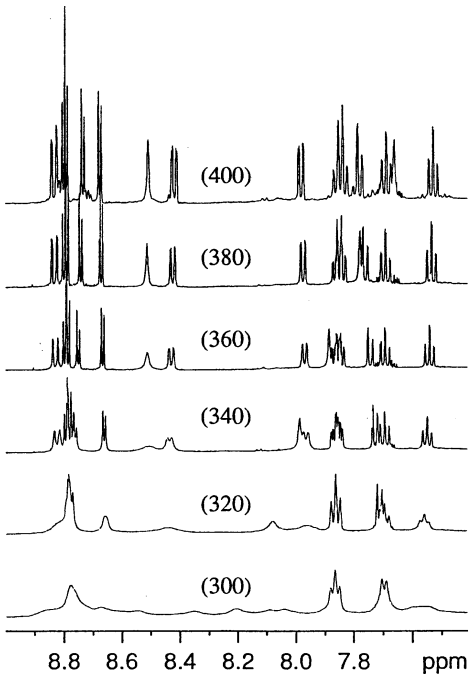


Fig. 1 ^{1}H NMR (500 MHz) spectra of **3bH$_2$** in DMSO-d_6 at temperatures ranging from 300 to 400 K.

The observation of the ^{1}H NMR spectra, in terms of negative chemical shifts, of porphyrins **3aZn** (upper trace) and **3bZn** (lower trace) at 400 K (Fig. 2) reflects the effect of the length of the linkers between the two macrocycles. Indeed, most of the signals of the strapped cyclam are upfield-shifted by an average value, 1 ppm larger in the case of **3aZn** with the shorter link than in the case of **3bZn** with the longer one. In the absence of an X-ray structure of the strapped-porphyrins, we used the negative chemical shifts of several cyclamic protons to estimate the intermacrocyclic distance using Abraham's diagram.[12] If the average distance from the cyclam protons to the vertical at the center of the porphyrin is taken as 2.53 Å, and with the largest measured downfield shift being −1.82 ppm (**3aZn**, shorter link, trace a), we can deduce that the cyclam lies between 4 and 5 Å from the porphyrin. One can compare this value with the ones obtained from X-ray structures of related compounds. For instance, when the cyclam is attached to the porphyrin by four acryloyl linkers, the cyclam lies at an average distance of 4.05 Å from the porphyrin plane.[13] In the case of a dioxocyclam tethered to a porphyrin by two chloroacetyl linkers, this same distance is 3.99 Å.[14] On the other hand, the difference of chemical shift for the most upfield-shifted signal in both **3aZn** (shorter link, trace a) and **3bZn** (longer chain, trace b) is 0.83 ppm. This relatively small difference, when placed on Abraham's diagram (*vide supra*), implies a difference of 1.5 Å in terms of distance to the porphyrin. In other words, for **3bZn**, the cyclam is expected to lie *ca.* 6.5 Å away from the metal center of the porphyrin. So, the approximated distance between the two coordination sites in **3aZn** is an encouraging result as in the resting state of the enzyme the intermetallic distance is of the same order, but is shorter than in models **3b**, with the longer chain, for which no particular properties in terms of intermetallic interactions were expected.

The access to heterobimetallic species follows the same synthetic pathway as the one described above starting from the iron(III) porphyrin (**2aFe** or **2bFe**). Interestingly, contrary to what Weiss *et al.* reported,[8b] no activation of the addition reaction was noticed when the iron complex is employed. This result might be explained by the role played by the fifth ligand of the iron: if the ligand stays on the open face of the porphy-

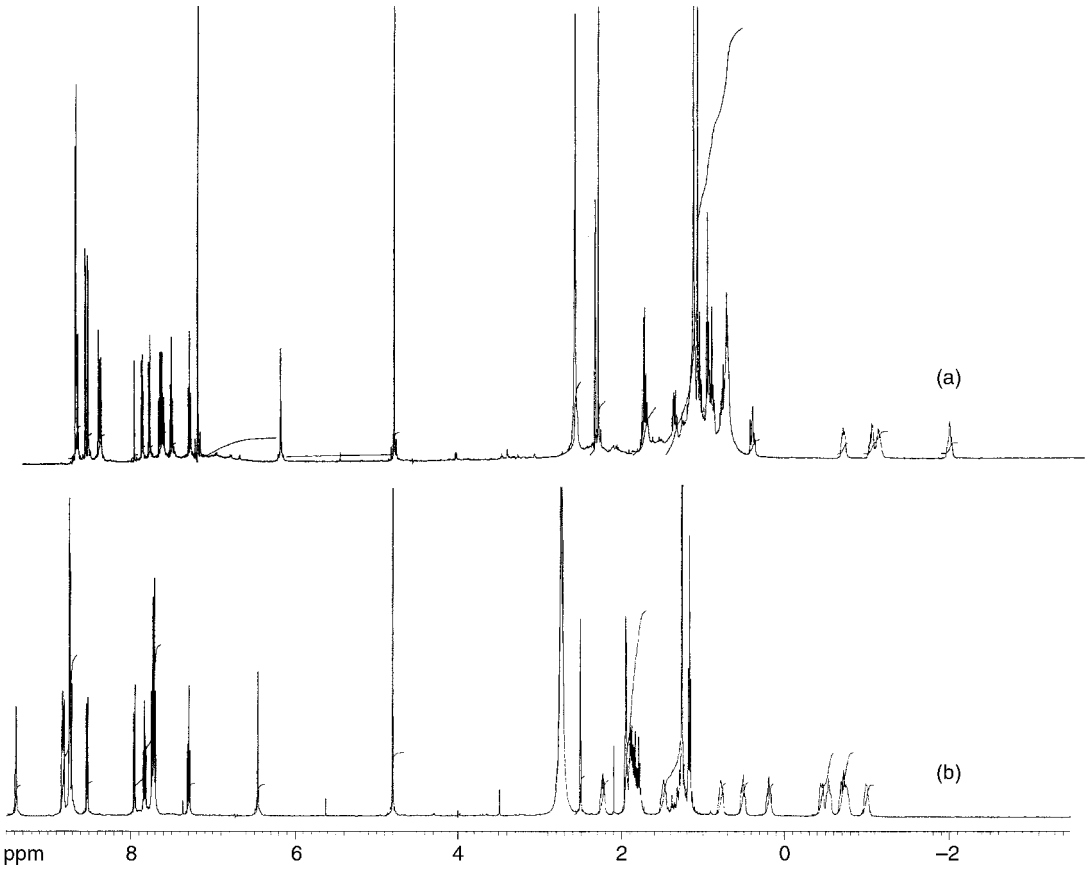


Fig. 2 ^{1}H NMR (500 MHz) spectra of (*a*) **3aZn** and (*b*) **3bZn** in DMSO-d_6 at 400 K.

rin, it might slow down the coupling reaction for steric hindrance reasons. Preparation of the cyclam-strapped iron porphyrins (**3aFe** and **3bFe**) was achieved using the procedure described above. The complexes were characterized by IR/UV-vis spectroscopies as well as mass spectrometry. The cyclam structure was then metallated by cupric acetate in refluxing methanol. Mass spectrometry confirmed the expected structure and the ^{1}H NMR spectrum displays a broad resonance at 80 ppm typical of the β-pyrrolic hydrogens in this type of iron(III) porphyrin. At this point, it is worth noting that according to Karlin *et al.*,[15] if a bridging ligand is present between iron and copper, an upfield shift of this resonance to around 65 ppm (or 70 ppm if protonated)[16] would be observed. The absence of this shift in the observed resonances seems to indicate that either the fifth ligand of the iron is on the distal face of the porphyrin or there is no bridging ligand with the copper atom.

ESR studies of dicopper, iron–copper and dicobalt complexes have been carried out to validate our approach. Indeed, in order to estimate the intermetallic distance, ESR measurements of the dicopper complexes in frozen solution have proven their usefulness[17–19] and support the ^{1}H NMR estimations.

This method, first described by Eaton and Eaton, relies on a purely dipolar interaction between the two spins, but can also be applied if the exchange interaction between the spins is large enough to simply allow the observation of the transitions between triplet levels.[20] At 100 K, for **5bCuCu** only the signal related to the porphyrinic copper was observed (Fig. 3, trace a). We rationalized this unexpected observation by considering the relative intensities of the signals for the copper ions in the porphyrin and in the cyclam at the same concentration: indeed, the signal due to the cyclam–copper complex is very weak compared to its porphyrin analog and appears at the same field. Thus, the signal corresponding to the cyclam–copper complex is hidden by the intense copper–porphyrin signal. When the temperature is decreased to 5 K, ESR measurements of **5bCuCu** revealed the presence of $\Delta M_s = 1$ and $\Delta M_s = 2$ transitions resulting from a triplet state involving an essentially magnetic dipolar interaction between the two copper(II) atoms (Fig. 3, trace b). This interesting result led us to two conclusions: the presence of the forbidden transition ($\Delta M_s = 2$) not only confirms the presence of copper in the cyclam but also proves that the two copper ions are close enough to interact. Moreover, from this spectrum observed for the longest linkers, it is possible to calculate the relative ratio between the half-field forbidden transition I_1 ($\Delta M_s = 2$) and the intensity of the allowed transition I_2 at $g = 2$. This

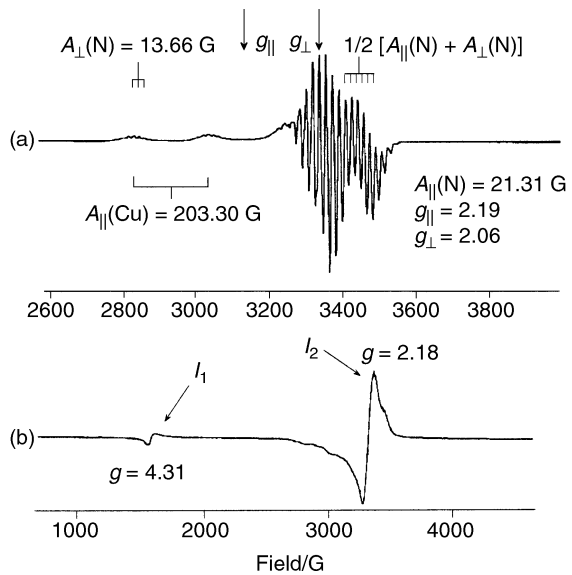
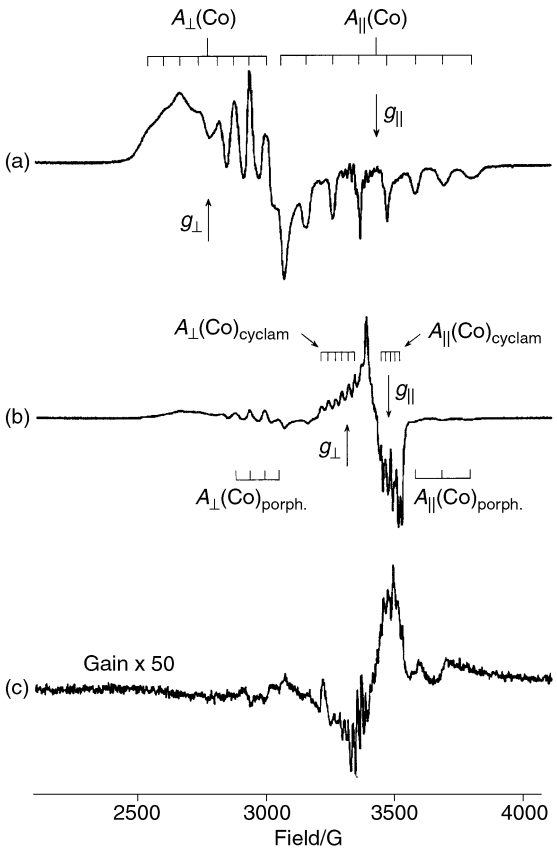


Fig. 3 ESR spectra of dicopper complex **5bCuCu** in frozen dichloromethane solutions: (*a*) at 100 K, (*b*) at 5 K.

ratio is related to the interspin distance r between the two metal centers by:[20] $I_1/I_2 = 20/r^6$. The r value obtained by this method is 4.5 Å (±0.9 Å) for **5bCuCu**, which is in good agreement with both results obtained using Abraham's diagram and the 4.5 Å measured for the iron–copper resting state of cytochrome *c* oxidase.[4]

In parallel with the ESR studies on the dicopper complexes, we also studied the ESR spectra of the dicobalt systems. Indeed, since the report of Basolo *et al.* about synthetic oxygen carriers, much information concerning cytochrome *c* oxidase has been obtained through the study of cobalt dinuclear complexes and their oxygen adducts.[21] It is noteworthy that, up to date, the only efficient *homo*bimetallic models for the 4-electron reduction of dioxygen to water are cobalt complexes such as the Co_2FTF4 diporphyrin.[22]

ESR studies of a frozen dichloromethane solution of **5bCoCo** in an inert atmosphere give rise to a classical $S = 1/2$ cobalt(II) porphyrin signal at $g \approx 2$ (Fig. 4, trace a). As for the copper complex, the signal of the cyclam–cobalt(II) is hidden by the more intense signal of the cobalt(II) of the porphyrin at the same g value. This accounts for a system where no interaction occurs between the two metal centers at 100 K. But, after dioxygen was bubbled through the re-heated solution, dramatic changes in the spectrum were noted (Fig. 4, trace b). Two kinds of signals are present: one can be attributed to the initial cobalt-porphyrin complex while the other seems to correspond to a superoxo binding mode involving the cobalt chelated by the cyclam with typical low binding constants.[8c]



Compound	$A_\perp$/G	$A_\parallel$/G	$g_\perp$	$g_\parallel$
5bCoCo (a)	61.5	103.9	2.49	2.03
5bCoCo (b) porph.	61.5	105.5	2.10	2.00
5bCoCo (b) cyclam	26.4	13.2		

Fig. 4 ESR spectra of dicobalt complex **5bCoCo** in frozen dichloromethane solutions at 100 K: (*a*) alone, (*b*) with O_2, (*c*) with 1,5-diphenylimidazole and O_2.

Apparently, dioxygen seems to bind preferentially to the more accessible metallated cyclam to form a superoxo complex, whether inside or outside the cavity of the bimacrocycle.

In order to force dioxygen to interact inside the cavity, the distal side of the cyclam was protected with an excess of a bulky base (1,5-diphenylimidazole). In the presence of the base, the recorded ESR spectrum is almost silent at 100 K (Fig. 4, trace c). This observation is consistent with a μ-peroxo diamagnetic Co–O–O–Co complex, which is expected to be ESR silent. The minor remaining signal can be attributed to a side reaction of superoxo formation occurring during the oxidation. This result shows that the topology of our ligand is suitable as we succeed in enforcing the binding of the dioxygen molecule inside the cavity, as expected for spectroscopic cytochrome *c* oxidase models.

Iron and copper are the two metal centers involved in cytochrome *c* oxidase activity and ESR spectroscopy is efficient to study their interaction in the oxidized state as both iron(III) and copper(II) are paramagnetic and have characteristic ESR features. As expected, ESR spectra measured for **4aFeCu** and **3bFeCu** show different fingerprints. When the three-carbon atom linker is employed, the spectrum of a frozen dichloromethane solution of **3bFeCu** (Fig. 5, trace c) can be considered as the sum of a classical high spin iron(III) porphyrin signal centered at $g = 5.96$ (Fig. 5, trace a) and the typical signal for a $S = 1/2$ Cu(II) ion in a tetragonal field at $g = 2.08$ with a poorly resolved parallel component g, as in Cu(II)(1,8-diBoc cyclam) (Fig. 5, trace b). This spectrum is typical for an iron(III)–copper(II) complex showing no interaction between the two metals, probably due to a too long intermetallic distance.[21]

With the shorter linker, the same experimental procedure does not allow any copper insertion in the protected cyclam, hence the removal of the Boc group, leading to the series of products labeled **4**. Thus, after deprotection, the complexation was carried out under the same conditions as described above, leading to **4aFeCu**. At 100 K, ESR measurements did not reveal any signal for **4aFeCu**. An antiferromagnetic coupling between the two metal centers is evoked to explain this observation. On the other hand, by lowering the temperature down to 4 K, two distinct signals were observed: one corresponds to an iron(III) porphyrin while the other is consistent with a $S = 1/2$ Cu(II) ion in a tetragonal field (Fig. 6). This phenomenon, first reported by Gunter *et al.*,[3b] is the consequence of a weak interaction between iron and copper. Indeed, a rapid electronic relaxation effect induced by the proximity of the

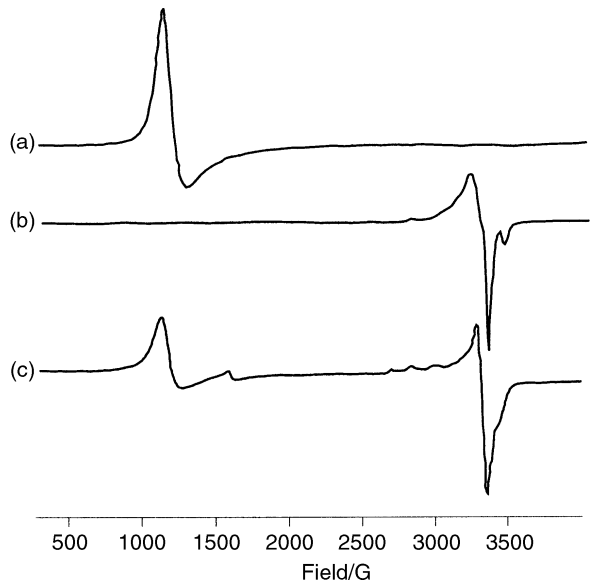


Fig. 5 ESR spectra in frozen dichloromethane solutions at 100 K of: (*a*) TPPFe(III)Cl, (*b*) (1,8-diBoc cyclam)Cu(II) **6Cu**, (*c*) **3bFeCu**.

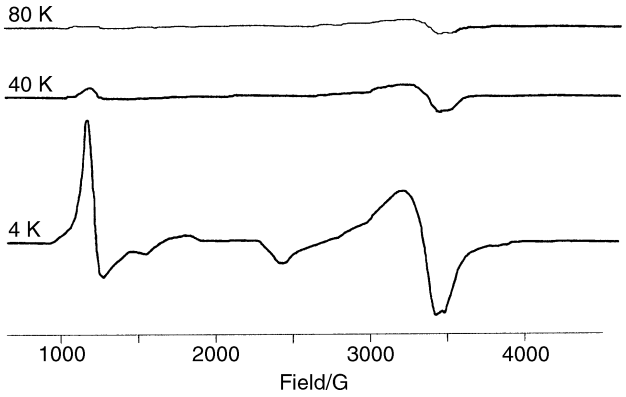


Fig. 6 ESR spectra of **4aFeCu** in frozen dichloromethane solution at three different temperatures.

two metals is responsible for the silent ESR signal at 100 K.[8g] When the temperature is decreased, the relaxation slows down, giving rise to the observed pattern.

The signal at $g = 2.8$ was also observed by Gunter and coworkers and was attributed to ferriporphyrin aggregates formed in concentrated solutions by Smith and Martel[17] and by Gunter *et al.*[3b] In our case, the distal handle prohibits this aggregation. Thus, our results are more in line with the explanation proposed by Scheidt, Reed and colleagues,[8a] which deals with the existence of a spin mixture of $S = 3/2$ and $S = 5/2$ ferriporphyrin. Indeed, in the **4aFeCu** complex, the short distance between the two metal centers may require the iron atom to be closer to the center of the porphyrin plane and induce the partial spin change.

In conclusion, in this paper are reported the synthesis, coordination and characterization of new metallated cyclam-strapped porphyrins as models for the oxidized state of cytochrome *c* oxidase. Abraham's ^{1}H NMR method was used to estimate the intermetallic distance, which was confirmed by Eaton's ESR relation. In the case of the three-carbon atom linker, this distance is shown to be in good agreement with the enzyme. Homo- and heterobimetallic complexes were essentially characterized using ESR spectroscopy. Studies of the dicopper and dicobalt systems show a bimetallic interaction as well as the possibility to coordinate a molecule of dioxygen between the two cobalt atoms. Iron–copper systems were also prepared. As in the resting state of the enzyme, the study of the complexes revealed a bimetallic interaction. These results show the advantages of the adopted approach in which the two coordination centers are maintained at a defined but variable distance with some flexibility. They also point out the need to design new synthetic approaches in which most of the critical structural features, such as the protection of the metals, the distance between the two coordination centers and the rigidity of the superstructure, are controlled.

Experimental

Physical measurements

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer and referenced to the residual proton solvents. Mass spectra were performed at the University of Rennes I (CRMPO). UV-visible and IR spectra were respectively recorded on Varian Cary 1E and Bruker IFS 66 spectrometers. ESR spectra were recorded on a Bruker ESP 300 with *N*,*N*′-diphenylpicrylhydrazine as reference ($g = 2.0036$).

Preparations

All solvents (ACS for analysis) were purchased from Carlo Erba. THF was distilled from potassium metal whereas methanol was distilled from magnesium turns. CH_2Cl_2 was used as received. Triethylamine was distilled on CaH_2. The starting materials were generally used as received (Acros, Aldrich) without any further purification. All reactions were performed under an argon atmosphere and monitored by TLC (silica, CH_2Cl_2–MeOH). Column flash chromatography was performed on silica gel (Merck TLC-Kieselgel 60H, 15 μm). Elemental analyses were obtained on an EA 1108 (Fisons Instruments).

1. In a 250 mL round bottom flask equipped with a stir bar and a nitrogen inlet were introduced 150 mL of freshly distilled THF and 0.28 mL of dry NEt_3. In another flask, TAPP [isomer $\alpha\beta\alpha\beta$[23] of *meso*-(tetra-*o*-aminophenyl)porphyrin, 1 mmol, 674 mg] was dissolved in 20 mL of dry THF and loaded in two 10 mL gas syringes. A third syringe was loaded with the diacyl chloride of *para*-phenylene dipropionic acid (1 mmol, 259 mg). The simultaneous addition of the two reagents was driven by a syringe pump during 24 h at room temperature. At the end of the addition, stirring was maintained for an additional hour. The solvent was then removed under vacuum and the remaining material redissolved in CH_2Cl_2. The organic phase was then washed twice with aqueous 5% NaOH, concentrated under vacuum and directly loaded on a 15 μm silica gel column (4 × 20 cm). The first eluted product (with CH_2Cl_2) was the unreacted starting porphyrin (150 mg, 0.22 mmol), whereas the major product **1** (35%) was eluted with 0.5% MeOH–CH_2Cl_2, the undesired bis-strapped porphyrin being eluted with 1% MeOH–CH_2Cl_2. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K): $\delta = 8.98$ (d, 4H, $J = 5.0$ Hz, $H_{\beta pyr}$); 8.85 (d, 4H, $J = 4.5$ Hz, $H_{\beta' pyr}$); 8.48 (d, 2H, $J = 7.0$ Hz, H'_6); 8.21 (d, 2H, $J = 8.0$ Hz, H'_3); 7.89 (t, 2H, $J = 7.5$ Hz, H'_4); 7.88 (d, 2H, $J = 7.5$ Hz, H_6); 7.71 (t, 2H, $J = 7.5$ Hz, H'_5); 7.61 (t, 2H, $J = 7.0$ Hz, H_4); 7.18 (t, 2H, $J = 7.5$ Hz, H_5); 7.09 (d, 2H, $J = 8.0$ Hz, H_3); 5.83 (s, 2H, NHCO); 4.32 (s, 4H, H_{ar}); 3.43 (s, 4H, NH_2); 1.45 (br m, 4H, $CH_2\alpha$); 1.28 (br m, 4H, $CH_2\beta$); −2.49 (s, 2H, $NH_{pyrrole}$); IR (KBr): ν/cm^{-1} = 3450 (NH_2); 3410 (NH); 1687 (C=O); MS (FAB$^+$): $m/z = 861$ [$(M + H)^+$, 100%]; UV-vis (CH_2Cl_2): λ/nm ($10^{-3} \cdot \varepsilon$/dm^3 mol^{-1} cm^{-1}) 420 (277.5); 513 (16.8); 545 (4.2); 586 (5.0); 651 (3.1).

2aH$_2$. A 250 mL three-neck round bottom flask equipped with a stir bar was charged with **1** (0.2 mmol, 200 mg), dry THF (100 mL), and Et_3N (0.8 mmol, 120 μL). After cooling in an ice bath, chloroacetyl chloride (0.8 mmol, 63 μL) dissolved in 10 mL of dry THF was injected dropwise. The reaction mixture was allowed to stir for 3 h at 0 °C. THF was finally removed under vacuum. The resulting powder was dissolved in CH_2Cl_2 and directly loaded on silica gel for chromatography. The expected compound **2aH$_2$**, eluted with 1% MeOH–CH_2Cl_2, was obtained in 88% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K): $\delta = 8.80$ (d, 4H, $J = 4.5$ Hz, $H_{\beta pyr}$); 8.78 (d, 4H, $J = 4.5$ Hz, $H_{\beta' pyr}$); 8.55 (d, 2H, $J = 7.5$ Hz, H_3); 8.40 (d, 2H, $J = 7.0$ Hz, H'_3); 8.02 (d, 2H, $J = 8.0$ Hz, H'_6); 7.96 (d, 2H, $J = 7.5$ Hz, H_6); 7.88 (t, 2H, $J = 8.0$ Hz, H'_5); 7.83 (t, 2H, $J = 8.0$ Hz, H_4); 7.78 (s, 2H, NH′CO); 7.72 (t, 2H, $J = 7.0$ Hz, H'_4); 7.53 (t, 2H, $J = 7.0$ Hz, H_5); 5.81 (s, 2H, NHCO); 4.18 (s, 4H, H_{ar}); 3.33 (s, 4H, CH_2Cl); 1.36 (m, 4H, $CH_2\alpha$); 1.26 (m, 4H, $CH_2\beta$); −2.51 (s, 2H, $NH_{pyrrole}$); IR (KBr): ν/cm^{-1} = 3368 (NH); 3315 (NH); 1681 (C=O); MS (FAB$^+$): $m/z = 1013$ [$(M + H)^+$, 100%]; UV-vis (CH_2Cl_2): λ/nm ($10^{-3} \cdot \varepsilon$/dm^3 mol^{-1} cm^{-1}) 420 (230.2); 515 (26.8); 540 (4.2); 585 (6.9); 640 (2.0). Anal. Calcd. for $C_{60}H_{46}Cl_2N_8O_4$: C, 71.07; H, 4.57; N, 11.05; found: C, 71.12; H, 4.67; N, 11.02.

2aFe. HR-MS (LSI-MS) m/z calcd: 1066.2212 $[M]^+$ for $C_{60}H_{44}Cl_2FeN_8O_4$; found: 1066.2190 for the complex without any axial ligand.

$2bH_2$. $2bH_2$ was prepared according to the above-mentioned procedure using acryloyl chloride instead of chloroacetyl chloride (yield 52%). ^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ 8.89 (d, 4H, $J = 5.0$ Hz, $H_{\beta pyr}$); 8.87 (d, 4H, $J = 5.0$ Hz, $H_{\beta' pyr}$); 8.83 (br s, 2H, H_3); 8.50 (d, 2H, $J = 7.5$ Hz, H'_6); 8.16 (d, 2H, $J = 8.0$ Hz, H'_3); 7.98 (d, 2H, $J = 7.5$ Hz, H_6); 7.93 (t, 2H, $J = 8.0$ Hz, H'_4); 7.89 (t, 2H, $J = 8.2$ Hz, H_4); 7.76 (t, 2H, $J = 7.5$ Hz, H'_5); 7.53 (t, 2H, $J = 7.5$ Hz, H_5); 6.72 (s, 2H, NH′CO); 5.83 (d, 2H, $J = 15$ Hz, CH=CH_2); 5.82 (s, 2H, NHCO); 5.05 (unres d, 2H, CH=CH_2); 4.96 (unres d, 2H, CH=CH_2); 4.2 (s, 4H, H_{ar}); 1.32 (m, 4H, CH_2 α); 1.25 (m, 4H, CH_2 β); −2.52 (s, 2H, $NH_{pyrrole}$); IR (KBr): $\nu/cm^{-1} = 3410$ (NH); 1670 (C=O); MS (FAB$^+$): $m/z = 969$ [$(M + H)^+$, 100%]; UV-vis (CH_2Cl_2): λ/nm ($10^{-3} \cdot \varepsilon/dm^3\ mol^{-1}\ cm^{-1}$) 419 (215.7); 512 (24.6); 542 (5.7); 583 (7.6); 639 (2.8).

2bFe. HR-MS (LSI-MS) m/z calcd: 1022.2991 $[M]^+$ for $C_{62}H_{46}FeN_8O_4$; found: 1022.3040 for the complex without any axial ligand.

$3aH_2$. In a 100 mL round bottom flask equipped with a stir bar, a reflux condenser and a nitrogen inlet, $2aH_2$ (0.03 mmol, 30 mg) and THF (40 mL) were heated at 50 °C. Then, 1,8-diazabicyclo[5.4.0]undecene-7 (DBU, 1 mmol, 160 μL), 1,8-diBoc cyclam **6** (0.036 mmol, 16 mg) and a catalytic amount of NaI were added. Heating was maintained for 48 h before the solvents were removed under vacuum. The residual powder was dissolved in CH_2Cl_2 and purified by silica gel column chromatography. The major compound, the expected porphyrin $3aH_2$, was eluted with 4% MeOH–CH_2Cl_2. After evaporation, the dried powder (20 mg) was collected in 50% yield. ^{1}H NMR (500 MHz, $CDCl_3$, 323 K): δ 9.81 (s, 2H, NHCO); 8.93 (d, 2H, $J = 4.7$ Hz, $H_{\beta pyr}$); 8.92 (d, 2H, $J = 4.4$ Hz, $H_{\beta' pyr}$); 8.89 (d, 2H, $J = 5.6$ Hz, H_6); 8.88 (d, 2H, $J = 5.1$ Hz, $H_{\beta'' pyr}$); 8.84 (d, 2H, $J = 4.6$ Hz, $H_{\beta''' pyr}$); 8.50 (m, 2H, H_3); 8.39 (br, 2H, NH′CO); 8.15 (d, $J = 8.2$ Hz, 2H, H'_3); 8.07 (d, 2H, $J = 6.8$ Hz, H'_6); 7.88 (t, 2H, $J = 7.6$ Hz, H'_5); 7.86 (t, 2H, $J = 8.8$ Hz, H_5); 7.71 (t, 2H, $J = 8.1$ Hz, H'_4); 7.53 (t, 2H, $J = 7.6$ Hz, H_4); 5.79 (s, 2H, NHCO); 4.27 (s, 4H, H_{ar}); 2.61 (d, 2H, $J = 16$ Hz, CH_2 α); 2.43 (d, 2H, $J = 16$ Hz, CH_2 α′); 1.29–0.98 (br m, 36H, $H_{But\ carbamate}$, CH_2 α, CH_2 β, H_{cyclam}); 0.57 (br t, 2H, $J = 10.5$, H_{cyclam}); −0.74 (br m, 4H, H_{cyclam}); −1.90 (br m, 2H, H_{cyclam}); −2.39 (s, 2H, $NH_{pyrrole}$); IR (KBr): $\nu/cm^{-1} = 3417$ (NH); 3313 (NH); 1694 (C=O); MS (FAB$^+$): $m/z = 1342.2$ [$(M + H)^+$, 100%]; UV-vis (CH_2Cl_2): λ/nm (10^{-3} ε/dm^3 mol^{-1} cm^{-1}) 421 (218.7); 513 (13.4); 547 (4.4); 587 (5.0); 642 (2.5). Anal. Calcd. for $C_{80}H_{84}N_{12}O_8 \cdot CHCl_3$: C, 66.59; H, 5.86; N, 11.50; found: C, 67.08; H, 6.30; N, 10.53.

3aZn. ^{1}H NMR (500 MHz, DMSO-d_6, 400 K): δ 8.85 (d, 4H, $J = 4.5$ Hz, $H_{\beta pyr}$); 8.83 (d, 2H, $J = 8.5$ Hz, H_{ar}); 8.73 (d, 2H, $J = 4.5$ Hz, $H_{\beta' pyr}$); 8.70 (d, 2H, $J = 4.5$ Hz, $H_{\beta'' pyr}$); 8.58 (s, 2H, NH′CO); 8.54 (d, 2H, $J = 7.5$ Hz, H_{ar}); 8.04 (d, 2H, $J = 7.5$ Hz, H_{ar}); 7.95 (t, 2H, $J = 8$ Hz, H_{ar}); 7.83 (t, 2H, $J_o = 8.8$ Hz, $J_m = 1.5$ Hz, H_{ar}); 7.79 (t, 2H, $J_o = 8.1$ Hz, $J_m = 1.5$ Hz, H_{ar}); 7.69 (t, 2H, $J = 8.0$ Hz, H_{ar}); 7.47 (t, 2H, $J = 8.0$ Hz, H_{ar}); 6.36 (s, 2H, NHCO); 4.97 (s, 4H, H_{ar}); 2.76 (d, 4H, CH_2); 1.6–0.7 (br m, 36H, $H_{But\ carbamate}$, CH_2 α, CH_2 β, H_{cyclam}); 0.58 (br m, 2H, H_{cyclam}); −0.53 (br m, 2H, H_{cyclam}); −0.87 (br m, 2H, H_{cyclam}); −0.95 (br m, 2H, H_{cyclam}); −1.82 (br m, 2H, H_{cyclam}).

3aFe. HR-MS (LSI-MS) m/z calcd: 1394.5728 $[M]^+$ for $C_{80}H_{82}FeN_{12}O_8$; found: 1394.5763 for the complex without any axial ligand. UV-vis (CH_2Cl_2): λ/nm ($10^{-3} \cdot \varepsilon/dm^3\ mol^{-1}\ cm^{-1}$) 418 (112); 504 (11.8); 578 (6.2).

$3bH_2$. The Michael acceptor porphyrin $2bH_2$ (0.09 mmol, 90 mg) was dissolved in a mixture of $CHCl_3$–MeOH 2 : 20 (25 mL) in a 50 mL round bottom flask equipped with a stir bar. 1,8-diBoc cyclam **6** (0.46 mmol, 240 mg) and a catalytic amount of 1,8-bis(dimethylamino)naphthalene were added. The solution was then heated at 55 °C for 96 h. After cooling and removal of the solvent under vacuum, the resulting solid was dissolved in a minimum amount of CH_2Cl_2 and directly loaded onto a silica gel for column chromatography. The product was eluted with 5% MeOH–CH_2Cl_2. Evaporation of the solvent yielded the expected compound (60%). ^{1}H NMR (500 MHz, $CDCl_3$, 323 K): δ 9.81 (s, 2H, NH′CO); 8.96 (d, 2H, $J = 7.9$ Hz, H'_3); 8.91 (d, 2H, $J = 4.8$ Hz, $H_{\beta pyr}$); 8.89 (d, 2H, $J = 4.8$ Hz, $H_{\beta' pyr}$); 8.87 (d, 2H, $J = 4.8$ Hz, $H_{\beta'' pyr}$); 8.86 (d, 2H, $J = 4.8$ Hz, $H_{\beta''' pyr}$); 8.40 (d, 2H, $J = 6.9$ Hz, H_6); 8.15 (d, 2H, $J = 7.9$ Hz, H_3); 7.91 (t, 2H, $J = 8.2$ Hz, H_4); 7.79 (t, 2H, $J = 7.9$ Hz, H'_4); 7.73 (t, 2H, $J = 7.7$ Hz, H_5); 7.50 (d, 2H, $J = 6.9$ Hz, H'_6); 7.30 (t, 2H, $J = 7.4$ Hz, H'_5); 5.83 (s, 2H, NHCO); 4.23 (s, 4H, H_{ar}); 2.14 (br m, 2H, H_{cyclam}); 2.03 (br m, 2H, H_{cyclam}); 1.89 (br m, 2H, H_{cyclam}); 1.52 (br m, 4H, CH_2 α′); 1.34 (br m, 32H, $H_{But carbamate}$, CH_2 α, CH_2 β, CH_2 β′); 0.76 (br m, 2H, H_{cyclam}); 0.36 (br m, 2H, H_{cyclam}); −0.12 (br m, 2H, H_{cyclam}); −0.57 (br m, 2H, H_{cyclam}); −0.85 (br m, 2H, H_{cyclam}); −1.04 (br m, 2H, H_{cyclam}); −1.17 (br m, 2H, H_{cyclam}); −2.51 (s, 2H, $NH_{pyrrole}$); ^{13}C NMR (125.767 MHz, $CDCl_3$, 323 K): 171.6; 171.1; 155.2; 139.2; 137.8; 136.9; 133.9; 133.0; 132.8; 132.5; 131.2; 130.5; 130.1; 126.0; 124.9; 122.7; 122.3; 118.1; 116.7; 80.2; 49.9; 48.2; 47.8; 43.8; 41.9; 34.2; 29.9; 28.7; 20.2; IR (KBr): $\nu/cm^{-1} = 3350$ (NH); 3330 (NH); 1691 (C=O); MS (FAB$^+$): $m/z = 1369.8$ [$(M + H)^+$, 100%]; UV-vis (CH_2Cl_2): λ/nm (10^{-3} ε/dm^3 mol^{-1} cm^{-1}) 421 (270.4); 514 (23.1); 547 (3.8); 587 (4.8); 642 (1.7). Anal. Calcd. for $C_{82}H_{88}N_{12}O_8 \cdot CHCl_3 \cdot CH_2Cl_2$: C, 64.10; H, 5.83; N, 10.68; found: C, 64.76; H, 5.82; N, 10.85.

3bZn. ^{1}H NMR (500 MHz, DMSO-d_6, 400 K): δ 9.39 (s, 2H, NH′CO); 8.83 (d, 2H, $J = 5.0$ Hz, $H_{\beta pyr}$); 8.81 (d, 2H, $J = 4.5$ Hz, $H_{\beta' pyr}$); 8.74 (d, 4H, $J = 4.5$ Hz, $H_{\beta'' pyr}$); 8.53 (d, 2H, $J_o = 7.5$ Hz, $J_m = 1.5$ Hz, H_{ar}); 7.96 (d, 2H, $J = 7.5$ Hz, H_{ar}); 7.83 (t, 2H, $J_o = 8.0$ Hz, $J_m = 1.5$ Hz, H_{ar}); 7.73 (t, 2H, $J_o = 8.0$ Hz, $J_m = 1.5$ Hz, H_{ar}); 7.72 (t, 2H, $J = 7.8$ Hz, H_{ar}); 7.71 (t, 2H, $J_o = 7.0$ Hz, $J_m = 1.5$ Hz, H_{ar}); 7.30 (t, 2H, $J_o = 7.5$ Hz, $J_m = 1.5$ Hz, H_{ar}); 6.46 (s, 2H, NHCO); 4.80 (s, 4H, H_{ar}); 2.52 (br d, 4H, CH_2 α); 1.93 (br d, 4H, CH_2 β); 1.48 (br m, 2H, H_{cyclam}); 1.26 (br s, 30H, $H_{But carbamate}$); 0.78 (br m, 2H, H_{cyclam}); 0.51 (br m, 2H, H_{cyclam}); 0.19 (br m, 2H, H_{cyclam}); −0.44 (br m, 2H, H_{cyclam}); −0.54 (br m, 2H, H_{cyclam}); −0.72 (br m, 2H, H_{cyclam}); −0.99 (br m, 2H, H_{cyclam}).

3bFe. MS (FAB$^+$): $m/z = 1423.2$ [$(M + H)^+$, 100%]; UV-vis (CH_2Cl_2): λ/nm (10^{-3} ε/dm^3 mol^{-1} cm^{-1}) 418 (118.4); 507 (19.5); 576 (10.5).

$4bH_2$. This procedure is general for the deprotection of the diBoc cyclam-porphyrins $3aH_2$ and $3bH_2$. Under argon, 20 mg (0.015 mmol) of 1,8-diBoc cyclam porphyrin was dissolved in 10 mL of dry CH_2Cl_2. Stirring at room temperature was maintained while a 1 : 1 v/v mixture of CH_2Cl_2–TFA was added using a syringe. The solution immediately turned green. The reaction mixture was then allowed to stir for an additional 5 h. Finally, solvents were partially removed (80%) under vacuum before 30 mL of water were added as well as 50 mL of CH_2Cl_2. The biphasic mixture was then carefully neutralized using gaseous ammonia. Finally, the two phases were separated using a separating funnel. The organic layer was washed three times with 50 mL of water and once with brine before being concentrated to 5 mL. The solution was then directly poured on silica gel (SiO_2 15 μm, 20 × 2 cm) prepared with pure CH_2Cl_2 for chromatography. The desired deprotected compound was quantitatively collected (90%) using a *ca.* 10% mixture MeOH–CH_2Cl_2. ^{1}H NMR (500 MHz, pyridine-d_5, 373 K): δ 9.85 (s, 2H, NH′CO); 9.02 (d, $J = 4.7$

Hz, 4H, $H_{\beta pyr}$); 8.94 (d, $J = 5.0$ Hz, 2H, $H_{\beta pyr}$); 8.67 (m, 4H, H_{ar}, $H_{\beta pyr}$); 8.63 (d, $J = 7.0$ Hz, 2H, H_{ar}); 8.30 (d, $J = 8.0$ Hz, 2H, H_{ar}); 7.98 (m, 2H, H_{ar}); 7.92 (t, $J = 8.0$ Hz, 2H, H_{ar}); 7.88 (s, 2H, NHCO); 7.84 (t, $J = 7.5$ Hz, 2H, H_{ar}); 7.79 (t, $J = 7.7$ Hz, 2H, H_{ar}); 7.49 (t, $J = 7.6$ Hz, 2H, H_{ar}); 4.45 (s, 4H, H_{ar}); 2.52 (m, 4H, CH_2 α, CH_2 β); 2.34 (m, 4H, CH_2 α, CH_2 β); 2.09 (m, 2H, H_{cyclam}); 1.87 (m, 2H, H_{cyclam}); 1.65–1.48 (m, 12H, H_{ansa}, H_{cyclam}); 1.29 (m, 4H, H_{cyclam}); 0.95 (m, 2H, H_{cyclam}); 0.65 (m, 2H, H_{cyclam}); 0.30 (m, 2H, H_{cyclam}); 0.02 (m, 2H, H_{cyclam}); −2.0 (m, 2H, H_{cyclam}); −2.52 (s, 2H, $NH_{pyrrole}$); IR (KBr): ν/cm^{-1} = 3450–3420 (NH); 3320 (NH); HR-MS (LSI-MS) m/z calcd: 1169.5878 $[M - H]^+$ for $C_{72}H_{73}N_{12}O_4$; found: 1169.5885; UV-vis (CH_2Cl_2): λ/nm ($10^{-3} \cdot \varepsilon/dm^3$ mol^{-1} cm^{-1}) 420 (216.9); 514 (13.0); 546 (4.4); 587 (5.0); 643 (3.1). Anal. Calcd. for $C_{72}H_{72}N_{12}O_4 \cdot CH_2Cl_2$: C, 69.90; H, 5.95; N, 13.40; found: C, 69.86; H, 6.11; N, 13.26.

4aFe. HR-MS (LSI-MS) m/z calcd: 1195.4758 $[M - H]^+$ for $C_{70}H_{67}FeN_{12}O_4$; found: 1195.4796 for the complex without any axial ligand.

$5bH_2$. $5bH_2$ was synthesized by the procedure described for **$3bH_2$** but using the 1,8-diTs cyclam **7** (yield 12%). ^1H NMR (500 MHz, $CDCl_3$, 323 K): δ 9.61 (s, 2H, NH′CO); 8.90 (d, $J = 8.4$ Hz, 2H, H_{ar}); 8.83 (m, 4H, $H_{\beta pyr}$); 8.65 (d, $J = 4.4$ Hz, 2H, $H_{\beta' pyr}$); 8.46 (m, 2H, $H_{\beta'' pyr}$); 8.18 (d, $J = 7.3$ Hz, 2H, H_{ar}); 8.09 (d, $J = 8.0$ Hz, 2H, H_{ar}); 7.88 (t, $J = 7.6$ Hz, 2H, H_{ar}); 7.79 (t, $J = 7.3$ Hz, 2H, H_{ar}); 7.67 (t, $J = 7.4$ Hz, 2H, H_{ar}); 7.60 (d, $J = 8.4$ Hz, 4H, Ts); 7.48 (d, $J = 7.2$ Hz, 2H, H_{ar}); 7.30 (t, $J = 7.8$ Hz, 2H, H_{ar}); 7.37 (d, $J = 8.4$ Hz, 4H, Ts); 5.68 (s, 2H, NHCO); 4.07 (s, 4H, H_{ar}); 2.45 (s, 6H, CH_3); 2.16–2.00 (m, 8H, CH_2); 1.48 (m, 4H); 1.30 (t, $J = 6.4$ Hz, 4H, CH_2); 0.87 (t, $J = 6.8$ Hz, 4H, CH_2); 0.40 (m, 4H, H_{cyclam}); 0.01 (m, 2H, H_{cyclam}); −0.55 (m, 2H, H_{cyclam}); −0.79 (m, 4H, H_{cyclam}); −1.69 (m, 4H, H_{cyclam}); −2.69 (s, 2H, $NH_{pyrrole}$); IR (KBr): ν/cm^{-1} = 3360 (NH); 3330 (NH); 1670 (C=O), 1338 and 1157 (SO_2N); MS (FAB^+): $m/z = 1077$ $[(M + H)^+$, 100%]; UV-vis (CH_2Cl_2): λ/nm (10^{-3} ε/dm^3 mol^{-1} cm^{-1}) 421 (229.6); 513 (23.1); 546 (13.6); 585 (13.5); 642 (10.2).

6. **6** was synthesized as previously reported.[10] ^1H NMR (500 MHz, $CDCl_3$, 300 K): δ 3.33 (t, $J = 6.5$ Hz, 8H); 2.83 (s, 2H); 2.79 (t, $J = 5.5$ Hz, 4H); 2.67 (t, $J = 6.5$ Hz, 4H); 1.76 (q, $J = 6.5$ Hz, 4H); 1.43 (s, 18H). ^{13}C NMR (125.767 MHz, $CDCl_3$, 300 K): 156.6; 79.9; 64.0; 49.5; 47.4; 46.6; 29.8; 28.9. IR (KBr): ν/cm^{-1} = 1691 (C=O); MS (FAB^+): m/z = 401 $[(M + H)^+$, 100.0%]; 301 $[(M - Boc)^+$, 19.9%]; 201 $[(M - 2Boc)^+$, 58.4%]. Anal. Calcd. for $C_{20}H_{40}N_4O_4 \cdot MeOH$: C, 58.30; H, 10.25; N, 12.95; found: C, 59.10; H, 10.13; N, 13.48.

7. **7** was synthesized as described in the literature.[24] ^1H NMR (500 MHz, $CDCl_3$, 300 K): δ 7.64 [d, $J = 8.5$ Hz, 4H, H_{ar}(Ts)]; 7.33 [d, $J = 8.5$ Hz, 4H, H_{ar}(Ts)]; 3.30 (m, 4H, α-CH_2); 3.10–3.14 (m, 12H, α-CH_2); 2.43 (s, 6H, CH_3); 2.20 (q, 4H, β-CH_2). ^{13}C NMR (125.767 MHz, $CDCl_3$, 300 K): 145.0; 133.5; 130.6; 128.2; 50.8; 50.5; 49.4; 45.9; 26.6; 22.1; IR (KBr): ν/cm^{-1} = 1339, 1159 (SO_2N); MS (FAB^+): $m/z = 509$ $[(M + H)^+$, 100%].

Metal insertion. Homobimetallic complexes. In a typical reaction, under argon, a 100 mL round bottom flask equipped with a stir bar and a condenser was charged with the free base (120 mg), THF (50 mL) and 2,6-lutidine (40 drops). The reaction was refluxed and a five-fold excess of an ethanolic solution of the metal was added. After 16 h, the solvent was removed under vacuum. The residue was then dissolved in dry and degassed CH_2Cl_2 (crucial in the case of the dicobalt complex) and filtered twice through a coarse frit under argon. Evaporation to dryness yields the homobimetallic complex. **5bCoCo**: MS (FAB^+): $m/z = 1653$ $[(M + 2H - AcO^-)^+$, 8%], 1534 $[(M + H - Co - AcO^-)^+$, 35%]; 1477 [(free base + H)$^+$, 100%].

Heterobimetallic complexes. This preparation proceeds in three steps. First, iron was inserted in the single-strapped porphyrin with Michael acceptor or chloroacetyl pickets (**$2aH_2$** or **$2bH_2$**) by heating a solution of the porphyrin in THF at 55 °C, with iron bromide and 2,6-lutidine in a dry box maintained below 1 ppm of dioxygen. The reaction was monitored by UV-vis. When the reaction was completed, the solvent was then evaporated to dryness and the residue dissolved in CH_2Cl_2. The suspension was then filtered through a path of celite. Finally, dry HCl was briefly bubbled through the filtrate to allow oxidation as well as ligand exchange. The complex was purified by silica gel column chromatography using 5% MeOH–CH_2Cl_2 as eluent. The diprotected cyclam (**6** or **7**) was then condensed using the same procedure as described above for the free base. Copper insertion and purification of the final complexes were accomplished according to the experimental procedure employed for the preparation of the dicopper complexes.

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