Electrocatalytic reduction of dioxygen to water by tren-capped porphyrins, functional models of cytochrome *c* oxidase†

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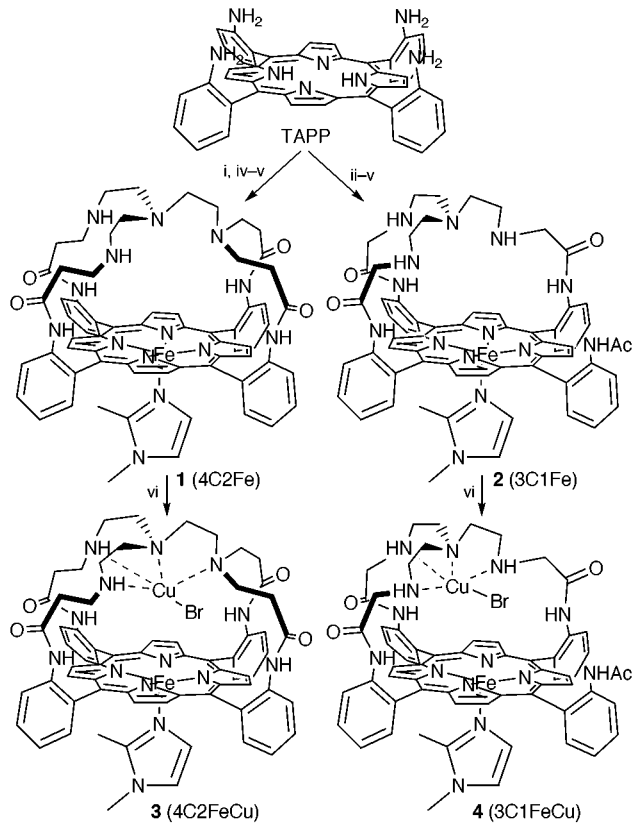
Two different tren-capped porphyrins—in which the two metals, iron and copper, are more or less off-centered—are shown to be efficient catalysts for the reduction of O_2 to H_2O; surprisingly, their iron-only complexes are shown to be even more effective 4e$^-$ catalysts when adsorbed on a graphite electrode.

The biological reduction of dioxygen to water is an essential reaction that produces energy in the mitochondria. The protein that drives this reaction, the cytochrome *c* oxidase (C*c*O), is the terminal enzyme of the respiratory chain. Additionally, this reaction is coupled with proton translocation across the inner membrane, for the synthesis of ATP.[1] The design and synthesis of new functional analogs is absolutely critical for the understanding of the structural features required for this reaction. This area has been reviewed several times[2] and in particular through the application of 'cofacial metallodiporphyrin' models.[3] The first biomimetic model of C*c*O with a copper complex covalently bound above the porphyrin in a well-defined geometry was reported five years ago.[4] In 1995, the X-ray analysis of bovine heart oxidase[5] revealed that the Cu_B was 4.5 Å from the Fe_{a3} and 1 Å away from the normal axis of the heme iron position. These observations led us to design the 'Arbor' porphyrins,[6] a new series of biomimetic models based on tren [tris(2-aminoethyl)amine] capped porphyrins and for which we have already pointed out that the secondary amino groups could be crucial for the interaction with dioxygen.[7] Since the description of the 'Arbor' porphyrins, several compounds closely related to them have recently appeared in the literature but in both cases with a tri-alkylated cap.[8,9] Until a few months ago,[10] the only biomimetic models having catalytic activity were a cobalt(II) porphyrin associated with a copper(I) triazacyclononane[11] and a copper(I) imidazole-picket iron(II) porphyrin.[12] We report herein our observations about the reduction reaction of dioxygen catalyzed by two different, but still related, model compounds (Scheme 1), for which the relative position of the two metal centers is precisely tuned. The coordination site of the copper ion is highly dependent on the number of 'linker arms' which attach the tripodal cap to the porphyrin core. Compound **4** was obtained by grafting the tren molecule on a chloroacetamido picket porphyrin, leading to a ligand in which the cap is more off-centered and closer to the porphyrin than in model **3** (where a Michael acceptor was used). To the best of our knowledge, this is the first series of two Fe/Cu model complexes differing only in the relative position of copper *vs*. iron, achieved in this work not only by the use of two different linkers but also by a specific strategy that consists in using a non-protected tren molecule.

The synthetic routes to the two different final complexes are shown in Scheme 1. The atropisomer $\alpha\alpha\alpha\alpha$ of the *meso*-(tetra-*o*-aminophenyl)porphyrin (TAPP)—or its singly acetylated derivative—was acylated by either chloroacetyl chloride or acryloyl chloride. These acylations lead to either the three chloroacetyl or the four acryloyl picket porphyrins, which are eventually used in the iron insertion reaction. The capping reaction is carried out on the iron complexes, before copper insertion, to avoid any possible cross-metallation. Then, an excess of nitrogenous base (1,2-dimethylimidazole) is added to stabilize the iron(II) as a five coordinate complex. By combining two crucial structural features: a) the distance between the two coordination sites and b) the off-centering of the two metals, it might be possible to know if one of these two compounds is more efficient than the other one for O_2 electroreduction.

Among the four possible ligands that could be synthesized (3 or 4 linkers and one or two methylene groups), the two studied complexes **3** and **4**‡ (which are the most different compounds in terms of Fe–Cu distance and relative positions of the two metal centers) were found to be active catalysts for the four electron reduction of dioxygen in aqueous solution. This has been assessed by rotating ring-disk voltammetry. Experiments have been performed at pH = 6.86 ($HPO_4^{2-}/H_2PO_4^-$ buffer), an acidity level close to the physiological pH at which cytochrome



Scheme 1 *Reagents and conditions*: (i) CH_2=CHCOCl, NEt_3, THF; (ii) CH_3COCl, NEt_3, THF, 0 °C; (iii) $ClCH_2COCl$, NEt_3, THF; (iv) $FeBr_2$, 2,6-lutidine, THF, 55 °C; (v) tren, MeOH, 50 °C; (vi) CuBr, CH_3CN, 60 °C.

† Further experimental and spectroscopic data are available from the RSC web site, see http://www.rsc.org/suppdata/cc/1999/1523/

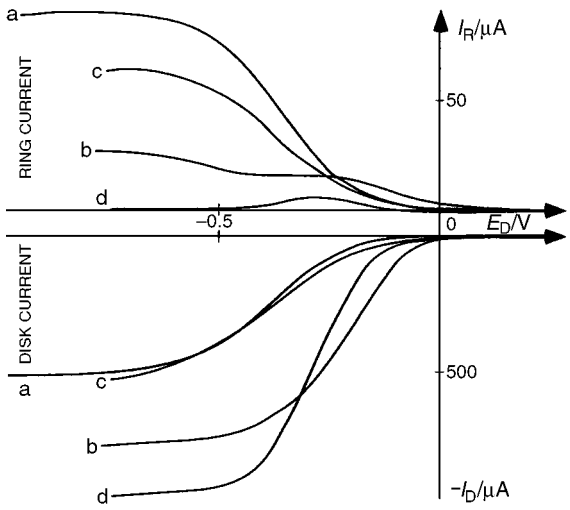


Fig. 1 Rotating ring-disk voltammetry for O_2 reduction; graphite disk impregnated with **1** or **3**. pH = 6.86; N_r = 250 rpm; reference: SCE; $P(O_2)$ = 1 atm; potential of the platinum ring-electrode: 0.8 V. a: bare graphite electrode. b,c: first and third consecutive voltammogram after coating with **3** (4C2FeCu). d: after coating with **1** (4C2Fe).

c oxidase operates; however, as dicobaltbisporphyrins require acidic media for the 4e$^-$ reduction, the catalytic efficiencies of **3** and **4** have also been tested at low pH (0.1 M $HClO_4$).

As illustrated for **3** (Fig. 1), models **4** and **3** have identical effects on the reduction of O_2 at pH 6.86, when adsorbed on the graphite disk. The reduction waves for the first scan (curve b) begin at −0.1 V and have almost the same limiting current. From comparison with the dioxygen reduction on a bare edge-plane graphite electrode (curve a), it can be concluded that the number of electron exchanged per O_2 molecule is 2.8. The production of H_2O_2 is detected at the platinum ring (ring current, curve b) almost immediately at the beginning of O_2 reduction, which means that the two and four electron reduction processes occur simultaneously. A second and third scan with the same electrode (curve c) show that the catalyst is degraded, as proved by the lower reduction current. When the electrode is in contact with an aqueous acidic solution (0.1 M $HClO_4$), O_2 reduction starts at a higher potential (0.1 V); the 4e$^-$ process occurs also under these conditions but the catalytic efficiency is lost more rapidly than in the neutral medium. The number of electrons for the electrocatalytic reduction of O_2, measured as described above, is only apparent as the catalyst is degraded during the reduction. Surprisingly, changes in the structure of the molecule do not seem to significantly affect the activity of these models of cytochrome *c* oxidase. The first hypothesis which explains the loss of activity could be the leaching of copper from its rather labile complex. The second could be the decoordination of the fifth ligand of the iron. These two structural features have been presented as essential to the catalytic activity in related biomimetic models.[11] However, catalysts **1** and **2**, the respective analogs of **3** and **4** without copper, cleanly catalyze the 4e$^-$ reduction, as shown for **1** in Fig. 1 (curve d). This simple test has never been reported even for close structural models bearing imidazole pickets.[8,12]

These experimental observations led us to several conclusions. Firstly, the loss of activity that occurs during the O_2 reduction is not due to the decoordination of the copper ion in contact with aqueous media as the iron-only compounds are even more efficient catalysts. The second conclusion derived from this study is that the fifth ligand does not need to be covalently bound to the porphyrin.

The fact that the iron catalysts are efficient for the reduction of dioxygen to water excludes the formation of a μ-peroxo intermediate between iron and copper atoms as a prerequisite for O_2 activation, as it has been postulated.[1a,d] However, it is compatible with a peroxo derivative, probably protonated.[2b] In the case of the enzyme, Yoshikawa *et al*. have suggested that this hydroperoxo complex is formed by addition of a proton delivered by Tyr 244.[13] In the case of the present model compounds, whether the proton transfer from the solution to the peroxo entity is mediated by the tren cap, or these secondary amino groups stabilize the hydroperoxo complex, are questions that could not receive proper answers in this preliminary work.

In conclusion, this new series of catalysts are efficient and selective for the electroreduction of dioxygen to water, without copper in the tripodal cap. This is in favor of the formation of a hydroperoxo complex rather than a μ-peroxo complex. Surprisingly, these results seem to be in contradiction with what has already been reported for related model compounds.[9] This difference of reactivity could be explained by structural differences; more explicitly, the existence of secondary amino groups in our compounds. These are certainly protonated when the compounds are in an aqueous environment at pH 6.86. Indeed, it would be of great interest to know if iron-only models such as the imidazole picket porphyrin of Holm[8] or its analog with an intramolecular nitrogen base described by Collman[12] are also efficient 4e$^-$ catalysts or not. It should however be stressed that these conclusions have been reached by the observation of molecules adsorbed on a graphite electrode in contact with water, a situation different from the environment of the active site of the enzyme. This study is presently in progress with other new molecules, to investigate if these tren-capped porphyrins represent a particular case or if this unexpected reactivity is general for iron–copper cytochrome *c* oxidase models.

Notes and references

‡ *Selected data* for complex **1** obtained after step (iv) in Scheme 1: 64%. HRMS (LSIMS): *m/z* 1091.4132 calc. for $C_{62}H_{59}N_{12}O_4Fe$ [M − H]$^+$, found 1091.4160. For **1** before the capping reaction: 90%; δ_H(500 MHz, pyridine-d_5, 323 K) 8.82 (d, *J* 7.0, 4H, arom.), 8.74 (s, 8H, β-pyr.), 8.23 (large s, 4H, -NHCO), 7.98 (d, *J* 7.0, 4H, arom.), 7.77 (t, *J* 7.5, 4H, arom.), 7.47 (t, *J* 7.5, 4H, arom.), 5.90 (d, *J* 17.0, 4H, –CH=), 5.17 (m, 4H, =CH_2), 5.06 (m, 4H, =CH_2). For **3**: HRMS (LSIMS): *m/z* 1169.3299 calc. for $C_{62}H_{58}N_{12}O_5FeCu$ [M$^{+\bullet}$], found 1169.3324. For **4**: Before copper insertion, HRMS (LSIMS): *m/z* 1036.3586 calc. for $C_{58}H_{52}N_{12}O_4Fe$ [M$^{+\bullet}$], found 1036.3527. For more extensive experimental details, see Note †.

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