A water-soluble supramolecular complex that mimics the heme/copper hetero-binuclear site of cytochrome c oxidase†‡

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In mitochondria, cytochrome c oxidase (CcO) catalyses the reduction of oxygen (O₂) to water by using a heme/copper hetero-binuclear active site. Here we report a highly efficient supramolecular approach for the construction of a water-soluble biomimetic model for the active site of CcO. A tridentate copper(II) complex was fixed onto 5,10,15,20-tetrakis(4-sulfonatophenyl)porphinatoiron(III) (FeIII TPPS) through supramolecular complexation between FeIII TPPS and a per-O-methylated β-cyclodextrin dimer linked by a (2,2'-6',2'-terpyridyl)copper(II) complex (CuITerpyCD₂). The reduced FeIII TPPS/CuITerpyCD₂ complex reacted with O₂ in an aqueous solution at pH 7 and 25 °C to form a superoxo-type FeIII–O₂⁻/Cu¹ complex in a manner similar to CcO. The pH-dependent autoxidation of the O₂ complex suggests that water molecules gathered at the distal Cu site are possibly involved in the FeIII–O₂⁻/Cu¹ superoxo complex in an aqueous solution. Electrochemical analysis using a rotating disk electrode demonstrated the role of the FeTPPS/CuTerpyCD₂ hetero-binuclear structure in the catalytic O₂ reduction reaction.

Introduction

Cytochrome c oxidase (CcO) is the terminal enzyme in the mitochondrial respiratory chain. CcO consumes most of the molecular oxygen (O₂) processed by living organisms by reducing it to water (H₂O). The four-electron/four-proton reduction process (O₂ + 4e⁻ + 4H⁺ → 2H₂O) takes place at the heme a₃/Cu₉ hetero-binuclear active centre of CcO (Fig. 1a). For the catalytic O₂ reduction reaction, the reaction mechanism schematically depicted in Fig. 1b has been proposed. In the catalytic cycle, the fully reduced heme a₃/Cu₉ site (FeIII/Cu¹, compound R) reacts with O₂ to form an oxymyoglobin-like superoxo complex of heme a₃ (FeIII–O₂⁻/Cu¹, compound A). Compound A is rapidly (~0.5 ms) converted to an oxoferryl intermediate (FeIV=O/CuH⁴–OH, compound P) via O–O bond cleavage assisted by H atom injection from a vicinal tyrosine residue. Mechanistic investigations have suggested that one or more water molecules near the bound O₂ can facilitate the conversion of compound A to compound P.

To understand the reaction mechanism, synthetic heme/copper models have been constructed using tetraarylporphinatoiron(II) (PFeII) combined with Cu¹ complexes (Cu¹Lₙ, where L is a nitrogen donor ligand; n (coordination number) = 3 or 4). However, upon oxygenation of the PFeII/Cu¹Lₙ model systems in anhydrous organic solvents, μ-peroxo-type bridged structures, i.e., PFeIII–O₂–CuIIₙ, complexes, tend to form instead of compound A-like superoxo species. In native CcO, the μ-peroxo-type bridged structure has not been

Fig. 1 (a) Heme a₃/Cu₉ hetero-binuclear active site of CcO (PDB ID: 1OCO) and (b) the simplified mechanism for the O₂ reduction reaction catalysed by CcO.
experimentally identified, although it has been proposed as a transitional precursor of compound P. The structural differences between the native and model systems (superoxo vs. μ-peroxo) might be attributed to the influence of water. A model study by Naruta and co-workers demonstrated that the μ-peroxo complex (PFeIII−O2−CuIILO3) formed at −70 °C was converted to the superoxo complex (PFeIII−O2−CuIILO3) at −30 °C by the action of water molecules. In native CcO, highly ordered water molecules have been detected in the vicinity of heme α/CuB. A quantum chemical calculation suggested that a water molecule in the vicinity of CuB decreases the energy barrier of the transformation of compound A to compound P. In this context, a water-soluble PFeII/CuIL3 model compound would be useful to investigate the role of water on the reactivity of the Fe/Cu hetero-binuclear complex with O2. However, very few heme/copper mimics functioning under aqueous conditions have been prepared so far, except for the system constructed in the engineered heme pocket of myoglobin.

In this study, we describe an aqueous synthetic PFe/CuL3 hetero-binuclear model system built on a porphyrin/cycloextrin supramolecular complex (Scheme 1). This system takes advantage of the very stable formation of a self-assembling 1 : 2 complex of 5,10,15,20-tetrakis(4-sulfonatophenyl)porphinatoiron (FeTPPS) with per-O-methylated β-cycloexdrins (CDs). We have previously studied the porphyrin/cycloexdrin complexes as simple biomimetic models of heme proteins that function under aqueous conditions, where the molecular cage of per-O-methylated β-CDs provided a microscopic hydrophobic environment for FeTPPS similar to the heme pocket of heme proteins. Here, we have synthesised a per-O-methylated β-CD dimer linked by a CuII−terpyridine complex (CuIIterpyCD2, Scheme 1) to replicate the distal tridentate CuB site of CcO. The structural characterisation of the supramolecular FeTPPS/CuIIterpyCD2 complex and its reactivity towards O2 are described.

Results and discussion

Synthesis of a water-soluble FeIII−CuII hetero-binuclear complex

The synthetic route of a supramolecular FeIII−TPPS/CuIIterpyCD2 complex is shown in Scheme 1 and experimental details are described in (ESI†). Briefly, the terpyridyl ligand was inserted as a linker of the CD dimer (TerpyCD2) by the reaction of 5,5’-bis(mercaptomethyl)-2,2’:6,2”-terpyridine with 2,3-monoepoxy-per-O-methylated β-CD (Epo-OMe-β-CD). The addition of CuSO4·5H2O to TerpyCD2 in an aqueous solution generated two absorption bands at 336 and 350 nm (Fig. 2a), which corresponded to the ligand to metal charge transfer bands of the terpyridyl-CuII 1 : 1 complex. In the UV-vis titration, a biphasic spectral change was observed (Fig. 2a inset), indicating that the 1 : 2 complex of CuII with TerpyCD2 (λmax = 333 nm) was first formed and then it was converted to the thermodynamically stable 1 : 1 complex upon further addition of CuII.

Fig. 2 Complexation of TerpyCD2 with CuII in aqueous solution. (a) UV-vis spectral change of TerpyCD2 (33 μM) upon stepwise addition of CuSO4 in water at 25 °C. The inset shows changes in absorbances as a function of [CuSO4]/[TerpyCD2]. The biphasic titration curve indicates transient formation of the 1 : 2 complex before forming the thermodynamically stable 1 : 1 complex (CuIIterpyCD2) during the titration. (b) Electrospray mass spectrum (positive mode) of the 1 : 1 mixture of TerpyCD2 and CuSO4 in H2O. The inset shows the simulated isotope distribution patterns for the [CuIIterpyCD2]2+ complex.

Scheme 1 Preparation of the supramolecular FeIII−TPPS/CuIIterpyCD2 complex.
changes were completed at one equivalent of Cu$^{2+}$. The complexation between TerpyCD$_2$ and Cu$^{2+}$ was also monitored by electrospray mass spectroscopy. In the 1 : 1 mixture of CuSO$_4$ and TerpyCD$_2$ in H$_2$O, the 1 : 1 complex (Cu$^{II}$TerpyCD$_2$) was observed at $m/z$ 1577 and 1059 (Fig. 2b), which corresponds to [Cu$^{II}$TerpyCD$_2$]$^{2+}$ and [(H$_2$O)Cu$^{II}$TerpyCD$_2$ + H]$^{+}$, respectively.

The 1 : 2 complex was also detected as a small ion peak when the 1 : 2 mixture of CuSO$_4$ and TerpyCD$_2$ in H$_2$O was analysed by electrospray mass spectroscopy (data not shown).

The Cu$^{II}$TerpyCD$_2$ complex was then titrated with Fe$^{III}$TPPS (Fig. 3a). The Soret band of Fe$^{III}$TPPS shifted from 408 nm to 418 nm, indicating that a µ-oxo-dimer of Fe$^{III}$TPPS dissociated to the monomeric monohydroxo complex (Fe$^{III}$(OH)$^{-}$TPPS)$^{19}$ through interaction with Cu$^{II}$TerpyCD$_2$. The spectral changes were completed upon addition of one equivalent of Cu$^{II}$TerpyCD$_2$ to Fe$^{III}$TPPS, indicating a quantitative 1 : 1 complexation. The obtained complex was then analysed by electrospray mass spectroscopy. The two main ion peaks were detected at $m/z$ 1385 and 2078 as tri- and di-anionic species, respectively (Fig. 3b). Considering total charges of the complexes, the peaks at $m/z$ 1385 and 2078 were assigned to the µ-oxo and µ-hydroxo Fe$^{III}$TPPS/Cu$^{III}$TerpyCD$_2$ complexes, i.e., [PFe$^{III}$-O-Cu$^{III}$CD$_2$]$^{3-}$ and [PFe$^{III}$-(OH)-Cu$^{III}$CD$_2$]$^{2-}$, respectively. The assignments were confirmed by the isotope pattern simulations (Fig. 3b inset). Evidence of the µ-oxo (Fe$^{III}$-O-Cu$^{III}$) structure was also provided by its characteristic absorption bands at 453 and 567 nm, which appeared when the pH of the solution was increased (Fig. S3$^\ddagger$). The red-shifted Soret band at alkaline conditions indicates formation of the PFe$^{III}$-O-Cu$^{III}$ µ-oxo complex. The pH titration revealed the acid–base equilibrium of [PFe$^{III}$-O-Cu$^{III}$CD$_2$]$^{3-}$ and [PFe$^{III}$-(OH)-Cu$^{III}$CD$_2$]$^{2-}$ with $pK_a = 8.8$. This $pK_a$ value is consistent with that previously predicted by Karlin and Blackburn ($pK_a = 8 \pm 2.5$).$^{28}$ The electron paramagnetic resonance (EPR) spectra showed significantly weak signals at $g = 6.09$ and 2.08 in the Fe$^{III}$TPPS/Cu$^{III}$TerpyCD$_2$ complex (Fig. S4$^\ddagger$) because of the antiferromagnetic coupling between the two metal ions as a result of their close proximity. The optimized molecular structure (Fig. 4) also illustrates the proximity of Fe and Cu ions in the Fe$^{III}$TPPS/Cu$^{III}$TerpyCD$_2$ complex; the Fe/Cu distances for the non-bridged and oxo-bridged forms are 5.23 and 3.52 Å, respectively. The distances are similar to those in native CcO, in which the oxidised heme $a_d$/Cu$_{b}$ distance were found in the range of 4.4–4.9 Å.$^4$

**Characterisation of an O$_2$ adduct of the Fe$^{II}$/Cu$^1$ complex**

The Fe$^{III}$TPPS/Cu$^{III}$TerpyCD$_2$ complex was reduced with excess sodium dithionite (Na$_2$S$_2$O$_4$) to obtain the fully reduced PFe$^{II}$/Cu$^{II}$CD$_2$ complex in the deoxy state in an O$_2$-free solution ($\lambda_{max}$ at 430, 554, and 601 nm, Fig. 5, black line). The dissolved O$_2$ in the solution was completely consumed by excess dithionite, and the redox potential of dithionite is negative

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**Fig. 3** Characterisation of the supramolecular Fe$^{III}$TPPS/Cu$^{III}$TerpyCD$_2$ complex. (a) UV-vis spectral changes of Fe$^{III}$TPPS (3 μM) upon stepwise addition of Cu$^{II}$TerpyCD$_2$ in 0.05 M phosphate buffer at pH 7.0 and 25 °C. The inset shows the changes in absorbance at 418 nm as a function of the molar ratio ([Cu$^{II}$TerpyCD$_2$]/[Fe$^{III}$TPPS]). (b) Electrospray mass spectrum (negative mode) of the 1 : 1 mixture of Fe$^{III}$TPPS and Cu$^{II}$TerpyCD$_2$ in H$_2$O. The inset shows the simulated isotope distribution patterns for the µ-oxo- and µ-hydroxo-bridged Fe$^{III}$TPPS/Cu$^{III}$TerpyCD$_2$ complexes.

**Fig. 4** Optimized molecular structures of the FeTPPS/CuTerpyCD$_2$ inclusion complexes in the Fe/Cu non-bridged and Fe/Cu oxo-bridged forms. The models are shown from both side and top views. Hydrogen atoms are omitted for clarity. Molecular mechanics calculations were carried out using CONFLEx/MM3 (extensive search) parameters in Scigress version 2.2.1 software program (Fujitsu).
enough to reduce both FeIII and CuII to FeII and CuI.29,30 After the reduction, the solution was passed through a short gel-filtration column (Sephadex G-25) under aerobic conditions to remove excess SO42− and its oxidised products. The UV-vis spectrum of the resulting solution showed absorption maxima at 419 nm and 542 nm (Fig. 5, blue line); the Q-band was very different from that of the oxidised state (FeIIITPPS/CuII TerpyCD2, λmax (Q-band) = 570 nm, green line) and similar to that of the O2 complex of the previously reported FeIIITPPS/CD dimer system.28 Introduction of CO gas into the solution caused further spectral changes with absorption maxima at 418 nm and 535 nm (Fig. 5, red line). The sharp Soret band is characteristic of the CO–FeIIITPPS complex,26 indicating that a ligand exchange from O2 to CO occurs in this system.

The O2 complex was further characterized by EPR and resonance Raman (rR) spectroscopic analyses. The EPR spectrum of the O2 adduct of FeIIITPPS/CuII TerpyCD2 measured at 77 K was completely silent (Fig. S4†), which was consistent with the spectra of other O2 complexes of the PFeIIIC0 CuILn heterobinuclear systems.31-33 The rR analysis at 77 K (frozen solution of the O2 adduct) using 405 nm excitation revealed a characteristic band at 578 cm−1, which shifted to 551 cm−1 under an 18O2 atmosphere (Fig. 5 inset). The isotope shift (Δν = 27 cm−1) corresponds to the expected value for the νO−O stretching mode.15 The wavenumber is quite similar to those of the PFeIIIC0 O2−/CuILn superoxo complexes in the previously reported native34 and synthetic model systems as listed in Table 1.14,15,35

Furthermore, the O−O bond stretching mode (νO−O) was not enhanced in this system. This is a relevant observation as the νO−O band is often observed in the range of 750–900 cm−1 in the PFeIIIC0 O2−/CuILn μ-peroxo complexes, but not in the case of the FeIIIC0 O2−/CuILn superoxo complexes (Table 1).14,15,35-37 Based on the rR data, the configuration of the present O2-adduct of FeIIITPPS/CuII TerpyCD2 is assigned as the superoxo-type PFeIIIC0 O2−/CuILn complex (Fig. 6), which is the same coordination mode as in compound A of native CrO1,3,14,38

The superoxo PFeIIIC0 O2−/CuII CD2 complex was gradually converted to another state when the solution was allowed to stand at pH 7 and 25 °C under aerobic conditions (Fig. 7). The absorption spectra showed several isosbestic points and the final spectrum (shown as a green line in Fig. 7) was coincident to that of the oxidised FeIIITPPS/CD dimer complex (Fig. S4†). The first-order rate constants (kobs) for the conversion were determined from the absorbance change at various pH conditions. Interestingly, the superoxo complex was more rapidly converted at lower pH (Fig. 7 inset). The linear pH/log kobs dependency at pH 7−10 (slope = −0.11) suggests that the conversion is partially accelerated by a proton-coupled process.39 Collman et al. have reported that the rate of the O2 reduction catalysed by their PFe/CuILn model complex is pH-dependent and increases at lower pH.40 We have previously reported that the autoxidation rate of the O2 complex in the PFeIIIC0 CD dimer system without any distal functions is independent of pH in the neutral pH region (7−10), whereas it is accelerated at

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**Table 1** The Fe−O and O−O stretching frequencies (νFe−O/cm−1, νO−O/cm−1) in the O2 complexes of native CrO and synthetic PFe/CuILn compounds

| Medium                  | νFe−O (18O2) cm−1 | νO−O (18O2) cm−1 |
|-------------------------|------------------|------------------|
| H2O, pH 7.4             | 572 (548)        | —                |
| H2O, pH 7.2             | 571 (545)        | —                |
| CH3Cl                   | 570 (544)        | —                |
| DMF                     | 575 (549)        | —                |
| CH3CN/THF               | 574 (548)        | —                |
| CH3CN                   | 578 (551)        | H2O, pH 7.0      |

**μ-Peroxo group**

| Medium                  | νFe−O (18O2) cm−1 | νO−O (18O2) cm−1 |
|-------------------------|------------------|------------------|
| MeTHF                   | 876, 863 (820)   | —                |
| CH3CN/THF               | 799 (752)        | —                |
| CH3CN                   | 787, 803 (751)   | —                |

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**Fig. 6** Oxygenation of the FeIIITPPS/CuII TerpyCD2 complex to form a superoxo PFeIIIC0 O2−/CuII CD2 complex.
pH below 6 and above 10. Therefore, the pH-rate dependency at the neutral pH region suggests that the water molecules gathered at the distal Cu site promote the conversion of the PFeIII–O2/Cu’CD2 complex to the oxidised PFeIII–(OH)–CuII’CD2 complex.

The quantum chemical study on native CcO6 proposes that a water molecule coordinating to the distal copper ion facilitates the conversion of compound A to compound P through the formation of the hydroperoxo FeIII–O–OH intermediate that has not been experimentally detected. Thus, the involvement of a water molecule in the present PFeIII–O2/Cu’CD2 complex is likely to occur. In addition, molecular modelling suggests that a water molecule bound to the distal copper ion can induce protonation of the superoxo complex (Fig. 8a), where the methoxy groups of the CD dimer are suitable to provide two hydrogen bonding sites to the water. The pH-dependent decomposition of the superoxo complex, as shown in Fig. 7, might be explained by the acid–base equilibrium of the water molecule (Fig. 8b), where the proton donation to the superoxo complex is likely to induce the O–O bond cleavage as proposed in CcO6 and/or the proton-assisted autoxidation reaction similar to myoglobin.41,42

The O2 binding in the present complex was practically irreversible; the O2 complex of FeIII-TPPS/CuIII-TerpyCD2 was never converted to its FeII/CuI deoxy complex, even when the O2 complex once formed was dissolved in a deoxygenated buffer (Fig. S5†). In contrast, the deoxy complex was observed in the FeIII-TPPS/TerpyCD2 complex without copper under the same experimental conditions.43 This result indicates that the O2 bound to PFeIII is tightly held by the distal CuI’L3 complex, as previously demonstrated by the Fe/Cu superoxo complex.14 The tight O2 binding was also confirmed by observing ligand exchange with CO. The ligand exchange occurred slowly over ~30 min when the Fe/Cu superoxo complex was dissolved in a CO saturated buffer (Fig. S5†), whereas it occurred instantaneously in the absence of distal Cu complex or in the absence of O2 (Fig. S5†). The ligand exchange of O2 with CO also rapidly occurs in the previous FeII-TPPS/CD dimer systems.26,24

Electrochemical analysis for the O2 reduction
To evaluate the O2-like function of this system, we monitored the electrocatalytic O2 reduction reaction.45–47 The cyclic voltammogram (CV) of the FeIII-TPPS/CuIII-TerpyCD2 complex immobilized on a glassy carbon electrode showed a reversible redox couple at E1/2 = –0.21 V (vs. Ag/AgCl) in a deoxygenated buffer solution (under Ar, Fig. 9a, black line). The result is similar to those of the previously reported PFe/CuL hetero-binuclear systems; the FeIII/FeII and CuII/CuI redox waves appear at the same potentials.31,46 In an air-saturated buffer, the CV of the FeIII-TPPS/CuIII-TerpyCD2 complex showed a large catalytic current below –0.25 V because of O2 reduction (Fig. 9a, blue line). A comparison of the CVs of the FeIII-TPPS/CuIII-TerpyCD2 complex with those of the reference samples, i.e., FeIII-TPPS and FeIII-TPPS/TerpyCD2 (Fig. 9b), clearly indicates the effect of the Fe/Cu hetero-binuclear structure in the O2 reduction; the FeIII-TPPS/CuIII-TerpyCD2 complex showed a very large catalytic current starting from a lower onset potential (ΔEonset = –40 mV). The O2 reduction process was then studied by linear sweep voltammetry (LSV) using a rotating disk electrode (RDE, Fig. 9c). The LSVs of the FeIII-TPPS/CuIII-TerpyCD2 and FeIII-TPPS/TerpyCD2 complexes showed diffusion limited catalytic O2 reduction currents below –1.0 V vs. Ag/AgCl. In the case of FeTPPS without the CD dimer, the current was never saturated in LSV due to a slow reaction rate of the iron porphyrin with O2.
Conclusions

In conclusion, we have synthesized a water-soluble biomimetic model complex for the heme $a_3$/Cu$_b$ hetero-binuclear active centre of CcO by utilizing a supramolecular complexation, and characterised its reactivity with O$_2$. To the best of our knowledge, this is the first example of a totally synthetic CcO model that works in a completely aqueous solution. In common with compound A of native CcO, we have identified the PFe$^{III}$/O$_2$/Cu$^I$CD$_2$ superoxo complex as the O$_2$ adduct in our model system in aqueous solution, whereas the PFe$^{III}$/O$_2$/Cu$^I$L$_m$ peroxo complexes tend to form in the other synthetic model systems in anhydrous organic solvents. The pH-dependent conversion of the PFe$^{III}$/O$_2$/Cu$^I$CD$_2$ superoxo complex to its oxidised μ-hydroxo PFe$^{III}$-(OH)/Cu$^{II}$CD$_2$ complex suggested the involvement of water molecules in the formation of the superoxo complex in aqueous solution. We believe that our aqueous model system will help to clarify the long-standing arguments with regard to the native and synthetic model systems in CcO chemistry.

Conflicts of interest

The authors declare no conflict of interest.

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