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ARTICLE

Modelling haemoproteins: Porphyrins and cyclodextrins as sources of inspiration

Maxime Vonesch,^a Jennifer A. Wytko,^a Hiroaki Kitagishi,^{b*} Koji Kano^{b*} and Jean Weiss^{a*}Received 00th January 20xx,
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Abstract: The association of hydrophobic cavities with porphyrin derivatives has been used to mimic haemoprotein structures. The most employed cavity in this field is β -cyclodextrin (β -CD) and scaffolds combining β -CDs and porphyrins are expected to inspire the combination of porphyrins and cucurbiturils in a near future. Aside from providing water solubility to various porphyrinic structures, the β -CD framework can also modulate and control the reactivity of the metal core of the porphyrin. After a general introduction of the challenges faced in the field of haemoprotein models and the binding behavior of β -CDs, the article will discuss covalent and non-covalent association of porphyrins with β -CDs. In each approach, the role of the CD differs according to the relative position of the concave CD host, either directly controlling the binding and transformation of a substrate on the metalloporphyrin or playing a dual role of controlling the water solubility and selecting the axial ligand of the metal core. The discussion will be of interest to the cucurbituril community as well as to the cavitand community as the information provided should be useful for the design of haemoprotein mimics using cucurbiturils (CBs).

Introduction

Understanding molecular functions in natural systems is the origin of the bio-inspired chemistry research field. Due to their implication in a wide range of biological processes, haemoproteins, in which the properties of an iron porphyrin (heme) derivative are controlled by the hydrophobic pocket of a globular polypeptide (globin), have been extensively studied.¹ From the initial challenge addressing the difference between the distal face vs proximal face (Figure 1)² in the binding of exogenic ligands³ to Fe^{II}, to the design of elaborate capped architectures, this field has become strongly dependent on the synthetic chemist's abilities to produce finely tuned structures that mimic protein active sites.⁴ Thus, under the pressure of rapid publishing and fast, intellectually rewarding projects, the field of haemoprotein models slowly seems to reach a conceptual dead-end due to the extreme sophistication of protein models and the endless synthetic efforts associated with stepwise functionalization of an active catalytic heme.⁵ Whereas the combination of concave subunits with transition metal-based catalysts has emerged as a promising method to control the topography of substrate-metal interactions during a transformation,⁶ the combination of concave hosts with heme platforms has somehow been

underexploited and so far restricted to the use of cyclodextrins. Among the concave platforms commonly used in supramolecular chemistry, cyclodextrins (CDs) share with cucurbiturils (CBs) an intrinsic water solubility that is very interesting for the development of bio-inspired models operating in physiological medium.

For the sake of clarity, Figure 2 summarizes the noteworthy positions located on a tetraphenylporphyrin and provides a general drawing of a cyclodextrin. In porphyrins, "meso" refers to the position at the methylene bridge between two pyrrolic units. The labels "o", "m" and "p" indicate positions on an aromatic ring at the meso position. Although most of the work discussed hereafter deals with β -CDs, the general formula of a CD is represented in Figure 2, where $n = 0$ corresponds to an α -CD, $n = 1$ to a β -CD and $n = 2$ to a γ -CD.

Figure 1. Representation of oxygenated myoglobin (PDB#1MBO) showing the influence of the distant histidine 64 (top) and the direct binding of the proximal histidine 93 (bottom).

^a Institut de Chimie de Strasbourg, UMR 7177 CNRS-Université de Strasbourg, 4 rue Blaise Pascal 67000 Strasbourg, France, jweiss@unistra.fr

^b Department of Molecular Chemistry and Biochemistry, Doshisha University, Kyotanabe, Kyoto 610-0321, Japan, hkitagis@mail.doshisha.ac.jp, kojikano1223@gmail.com

* Footnotes relating to the title and/or authors should appear here.

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Figure 2. a) Schematic structure of a tetra-aryl porphyrin and labeling of noteworthy positions; b) Generic structure of cyclodextrins and differentiation of the primary and secondary faces.

The next pages will focus on porphyrin-cyclodextrin architectures that could be inspirational for the development of new haemoprotein models, artificial enzymes and water-soluble catalysts. Architectures leading to electronic interactions between a photoactive porphyrin and either a CD⁷ or a guest in the CD^{8,9} are out of scope of this article due to the intrinsic inertness of hemes; however, information can be found in relevant leading references cited above. In some cases, porphyrin-cyclodextrin conjugates have been used for biomedical applications in which the CD subunit is used as a drug carrier until its release is triggered by applying a stimulus to the porphyrin.¹⁰ Again, due to weak relevance in terms of haemoprotein models, these scaffolds will not be discussed but information can be found in the reference section of selected publications.¹⁰⁻¹¹

As always, two approaches, one covalent and the other non-covalent, have been developed to combine cyclodextrins and porphyrins. The cartoons in Figure 3 depict various positions of the CD moieties observed in cyclodextrin(s)/heme conjugates (A-F). All but two (E and F) feature covalent bonding between the CD(s) and the porphyrin. The properties of the scaffolds will be discussed in sections arranged as a function of the covalent or non-covalent link between the porphyrin and the cyclodextrin(s).

Covalent porphyrin-CD(s) conjugates

In general, covalent linkages between the porphyrin and the cyclodextrin are connected to the primary face of the CDs, due to synthetic issues. This consideration is rather important in regard to the difficult functionalisation of cucurbiturils. As pointed out by several experts in the field, the modification of CBs is mostly restricted to the introduction of a single function.¹² Thus, the design of covalent conjugates of type A, B or C is already feasible by replacing the CDs by CBs.^{12b}

The first type A conjugate was reported in 1982 by Kobayashi and consisted in a scaffold comprising a β -CD linked to a *meso*-tritolyl-*o*-hydroxyphenyl-porphyrin derivative by an ester bridge (Figure 4).¹³ The drawback of classical

haemoprotein models,³ namely their poor solubility in water, was pointed out in the introduction of the paper and magnetically induced circular dichroism (MCD) studies of the corresponding Fe-porphyrin showed that conformational changes in water (vs DMSO) correlated with interactions between the porphyrin and the CD. However, no evidence for functional mimicry of haemoprotein was observed.

Figure 3. Cartoons depicting reported porphyrin-CD scaffolds assembled by covalent links with mono-functionalized CDs (A-C), di-functionalized CDs (D), or non-covalent bonding (E,F).

Although unrelated to haemoprotein models, it is worth mentioning that a similar structure, with a β -cyclodextrin and a *meso*-tritolyl-*p*-benzoato-porphyrin, was described soon after by Weedon.¹⁴ The *p*-position of the linker forbid the folding that brings the porphyrin in contact with the cyclodextrin and thus separates an electron donating Zn-porphyrin and an electron accepting guest in the CD, enhancing the lifetime of a charge separated state after excitation of the Zn-porphyrin.

Figure 4. The first covalent porphyrin-CD scaffold reported in the literature.

These two examples of type A scaffolds, and especially the electron transfer properties described in the last example initiated a field of study concerning biomedical applications using photoactive porphyrin derivatives (non "heme") and guests in the CDs that are out of the scope of this article, but can nevertheless be applied to mono-functionalised cucurbiturils. As far as catalytic activity is concerned, the concept has been extended to Mn-porphyrins for the investigation of superoxide dismutase (SOD) activity using a β -CD derivative connected by an ether link to the *p* position of a MnTPP.¹⁵ The SOD activity was 15 times higher in the conjugate than in the reference compounds. In addition, the enhancement in activity is greater than that observed in a simultaneously reported Mn-salophen/ β -CD conjugate. This non-hemic approach and the reactivity of Mn-porphyrins was also exploited using α -CDs conjugated with MnTPP, which acts as a clamp-like catalyst. The presence of the CD host enhances the proximity between a polybutadiene substrate and the Mn catalytic site. The presence of the CD (α or β) favours the formation of trans-epoxides, whereas replacement of the CD by its permethylated analogue inverts the selectivity to favour the cis-epoxides, a typical behaviour of MnTPP alone.¹⁶

Thus, in the case of a single covalent link in *o*, *m* or *p* positions between a porphyrin and a CD, the influence and effect of the CD can be hard to assess or hard to interpret due to a less preorganized scaffolding. To achieve a higher level of organisation in the porphyrin-CD conjugates, the number of either links or recognition points needs to be increased. Increasing the number of hosts in type B or C architectures will allow the positioning of a substrate recognised at its extremities by the CD units on top of a Fe-porphyrin, inducing a regioselective character in the interactions between the iron centre and the substrate. The use of multiple connections allows the CDs to control the access to the metallic core of the Fe-porphyrin in type D scaffolds. In this case, substrate selection and folding may induce regioselectivity in the interactions with the iron porphyrin core. Both strategies are discussed chronologically in the next paragraphs.

Surprisingly, the first approach that was developed combined difunctionalized CDs and tetrafunctionalized porphyrins, leading to a type D scaffold. In 1991, the lipoxygenase-like activity of a porphyrin sandwiched between two β -CDs (Scheme 1) was reported by Kuroda.¹⁷ The CD is linked to the free base of TPP by thioether bridges in *o* positions of the aromatic *meso* substituents of the porphyrin. The nearly fourfold symmetry of the scaffold renders the synthesis less difficult than for type B scaffolds and positions the CD cavity on top of the porphyrin centre. The porphyrin is used as a sensitizer to generate singlet oxygen able to oxidize the unsaturated bonds of an unsymmetrical diene.

Due to the structure of the CDs, the scaffold exists as a mixture of isomers that are used together as hosts during the oxidation of the substrates depicted in Scheme 1. In comparison to results obtained with free base tetrakis(*p*-sulphonatophenyl)porphyrin (H_2TPPS) or a mixture of non-linked H_2TPPS and β -CD that generates mostly the conjugated dienes a and d with the same specificities, the porphyrin-CD

assembly shows a clear regio-selectivity for the oxidation at the 12-13 bond. In this pioneering work, the use of a stoichiometric amount of the porphyrin-CD assembly seems required to maximise the regioselectivity (82% specificity for a mixture of a and b compared to 18% specificity for a mixture of c and d), suggesting that the affinity of the product vs reagent for the β -CD cavity is similar, thus poisoning the catalyst.

Scheme 1. Schematic structure of the free base porphyrin-bis-cyclodextrin assembly and distribution of products resulting from regio/stereo selective singlet oxygen oxidation in aqueous media.

In naturally occurring haemoproteins, the stability and reactivity of the ferrous and ferric iron core is controlled by the globular peptidic environment, and by the nature of the proximal ligand. To avoid the problem of the proximal ligand and its influence, as well as to enhance the reactivity of the metal centre, in many models the iron has been replaced by manganese. Taking advantage of a rather straightforward synthetic approach, the group of Breslow reported at the end of the 90s a four-fold, symmetrical, type C structure using a β -CD and a MnTPP connected by thioether links at the *p* position of the *meso* aryl substituents.¹⁸ The scaffold mimicked the reactivity of cytochrome P450 and catalytically hydroxylated unactivated carbon atoms (ethene carbons of a diphenylethane derivative (top substrate, Figure 5)) in 50% conversion with notable regio- and stereoselectivities and turnovers numbers (> 600) that compare quite well with typical P450 enzymes. For cholesterol derivatives bearing protecting groups that display a high affinity for the β -CD, only one position was hydroxylated in the case of a rather rigid substrate (middle substrate, Figure 5), whereas a more flexible derivative (bottom substrate, Figure 5) showed multiple hydroxylation sites. In the case of type C structures, it is difficult to conclude about the binding geometry of a substrate when several orientations of a pseudo-linear organic structure can result from the binding in vicinal CDs or diametrically opposite CDs, depending on the substrate's length and

Figure 5. A manganese porphyrin-tetra β -CD conjugate that mimics the activity of cytochrome P450 and three substrates that were each tested separately. In the case of selective hydroxylation, arrows indicate the reactive sites.

flexibility. In this regard, type B structures can provide a great deal of information but, due to the lower symmetry of the porphyrin moiety, such scaffolds generally require a greater synthetic effort.

These considerations probably triggered some very informative work by Woggon, who reported a type B Ru^{II} TPP-bis- β -CD conjugate.¹⁹ Dioxo-ruthenium porphyrins are very efficient oxidative catalysts and, in the enzyme model designed, the CD hosts are diametrically opposed at the periphery of the RuTPP. In this configuration, oxidative cleavage of β,β -carotene compares well with the activity of β,β -carotene 15,15' dioxygenase, which produces retinal in approximately 25% yield. Replacement of one end group by an aromatic mesityl, which has a higher affinity for the CD hosts, renders the 15,15' cleavage highly selective. Using scaffolds in which one face of the porphyrin is blocked by an inert alkyl strap, very convincing studies showed that the two CD hosts position the 15,15' bond in the vicinity of the Ru^{II} active site.²⁰

Among the strategies and results described so far, all approaches involving CDs bearing only one functional group linked to the porphyrin are applicable to CB-porphyrin scaffolds using mono-functionalized CB derivatives. The versatility of cucurbiturils as hosts should open new avenues for porphyrin-CB conjugates and their use as enzyme models or mimics.

Whereas an obvious synthetic drawback, mostly concerning the porphyrin moiety, is inherent to the covalent engineering of porphyrin-CD conjugates, the advantage of the covalent approach is that the solubility of the porphyrin in aqueous medium is not a prerequisite. The hydrosolubility of the final conjugate is provided by the CD(s). On the contrary, the formation of self-assembled scaffolds based on self-assembly processes and, quite generally, hydrophobic interactions, requires an initial and at least partial water

solubility of all partners. The next paragraphs will show that the non-covalent strategies also lead to new properties and control the binding on iron porphyrins that have been used in the literature for the fixation and transport of small exogenic ligands and, only recently, to catalysis.

Non-covalent porphyrin(s)-CD(s) scaffolds

The first trace of non-covalent interactions involving CDs and porphyrins dates back to the early 80s and the work of Tsuchida.²¹ In this seminal work, a series of *N*-substituted 2-methylimidazoles, which are both good axial ligands for metalloporphyrins and good guests for α -CDs, were used to form ternary complexes of imidazole, CD and protoporphyrin IX (heme), as shown in Figure 6. The association constants for the binding of the encapsulated imidazole to the iron porphyrin are 15 to 30 times higher than for the same imidazoles in the absence of the CD. This work also mentions that the ternary ferrous complexes formed stable oxygen adducts in aqueous DMF at -30°C . Two decades later, similar results were obtained with a water soluble tetrapyrrolium porphyrin.²²

Figure 6. Ternary complex heme-imidazole- α -CD.

Another report focused on the disruption of aggregates observed with protoporphyrin IX and related hemes in aqueous solutions in the presence of α - or γ -CDs. This effect was assigned to hydrophobic interactions.²³ Whereas the investigation of disaggregation effects of CDs on porphyrin arrays has been pursued over the years,²⁴ the association of porphyrins and CDs has been investigated in-depth over the last decades and found to arise from a set of weak interactions such as hydrophobic^{25,26} and/or electrostatic interactions.^{27,28} This association has been largely exploited for the formation of large supramolecular objects such as pseudo-rotaxanes,²⁹ cages³⁰ and porphyrin arrays,³¹ and general reviews can be found in the literature.³²

The first relevance of self-organized, type E porphyrin-CDs assemblies to haemoprotein models was noted by Lawrence in the early 90s.³⁴ Although the reported work concerned only a free base porphyrin bearing four protonated aminopropylether substituents in *o* positions combined with a methylated β -CD, several important conceptual considerations were provided.³³ As shown in Figure 7, tetraphenylborate anions were chosen to provide steric bulk to stabilise the pseudorotaxane structure. The K_{11} and K_{12} values for methylated β -CD with tetraarylporphyrin were 7.7×10^4 and $5.9 \times 10^4 \text{ M}^{-1}$, respectively, in succinic acid buffer at pH 5.0 and 60 °C. Lower binding constants were observed with iron(III) porphyrins, with $K_{11} = 3.5 \times 10^4$ and $K_{12} = 9.0 \times 10^2 \text{ M}^{-1}$ in citric buffer at pH 3.0 and 25 °C. In addition to the utilization of a methylated CD, the B(Ph)_4^- anions also preclude the solubility in aqueous medium. Despite these drawbacks, emphasis was placed on the versatility of the synthetic methodology, which was foreseen as applicable to a wide range of haemoprotein models by changing the size and nature of the hydrophobic cavity to achieve hydrosolubility and modulate the heme model environment.

Figure 7. The first self-organized porphyrin- β -CD scaffold assembled in organic medium.

Around the same period, the β -CD-induced dissociation of μ -peroxo dimers of water-soluble tetra-sulfonated iron porphyrins (FeTPPS) was reported with the possibility of using Fe^{III}TPPS in conjunction with β -CD as a paramagnetic contrast agent for in vivo imaging due to its particular relaxivity.³⁵ Although no evidence for a type E scaffolding was presented, the data suggest the binding of the CDs to the phenylsulfonate *meso* substituents of the porphyrin. Since the latter work, the trend has shifted to the use of phenylsulfonate substituents on the porphyrin macrocycle because these groups provide hydrosolubility to the starting iron porphyrin. Interesting association constants ($>10^4 \text{ M}^{-1}$) for both K_{11} and K_{12} , the respective first and second CD binding to the FeTPPS with

various β -CDs.^{36,37} For example, the iron(III) complex of FeTPPS showed moderate binding constants with per-O-methylated β -cyclodextrins (TMe- β -CD) with TMe- β -CD in pure water. The K_{11} and K_{12} values were $(2.8\text{--}3.5) \times 10^5$ and $(0.5\text{--}7.0) \times 10^4 \text{ M}^{-1}$, respectively, in buffer solution at 25 °C, where these values were pH-dependent.³⁸ For these stable 2:1 complexes, the axial binding to the iron core was extensively studied. It was shown that among a series of anions (F^- , Cl^- , Br^- and I^- , N_3^- and SCN^-), none except fluoride would coordinate to the Fe^{III} core in the absence of (TMe- β -CD). In addition, in the presence of (TMe- β -CD), bulkier anions such as ClO_4^- or NO_3^- for example, would not bind to the haemoprotein model.³⁸ Although the protonated polyamine substituents initially used in this field³⁰ might not be optimal to develop interactions with CDs, they are probably more than suitable to interact strongly with CDs and offer a greater versatility versus pH variations.

Figure 8. Porphyrin chelates obtained with bis- β -CD hosts.

Even though the association of CDs with TPPS is in general strong, the relative lability of the host-guest complexes quickly prompted the design of CD dimers to bind hydrosoluble porphyrins, taking advantage of a chelating effect of the cyclodextrin cavities.³⁹ A study using various linkers between two β -CDs and either tetra-phenylcarboxylate or tetra-phenylsulfonate porphyrin derivatives showed that the binding constants for the 1:1 complex were significantly enhanced ($>10^6 \text{ M}^{-1}$). As shown in Figure 8, depending on the length of the

linker between the CDs, type F *syn* and *anti* complexes were obtained.²⁵ For example, the **1:4** complex is exclusively *syn* with an association constant of ca. 10^6 M^{-1} , whereas the **2:4** complex is a mixture of *syn* and *anti* conformations. When the linker joining the two β -CDs was a bipyridine, a peculiar (**3**)₂(**4**)₂ entwined structure corresponding to a cross dimer (Figure 8) was observed in the presence of a zinc(II) template. Similar cage structures, obtained without the help of a metallic template, were reported later by the group of Kuroda.³⁰

Once the principles controlling the formation of self-organised porphyrin/ β -CD scaffolds were established, the notable breakthrough in applying these principles to the preparation of functional haemoprotein models was the design of cyclodextrin dimers in which the linker joining the two CDs bears a mimic of the axial ligand present in the natural enzymes. For many years, the group of Kano has developed functional haemoprotein models operating in water. This last section will focus on the functional scaffolds based on a type F structure, in which the link between the β -CDs contains an additional function (axial ligand) required for the haemoprotein activity.

Figure 9. Various CD dimers bearing a coordinating base in the linker joining the CD hosts.

Over the years, a wide range of functionalized CD dimers have been prepared and studied. These structures, summarized in Figure 8, mainly differ by the position of the CD to which the axial ligand is anchored or the nature of the latter. In association with FeTPPS, various haemoprotein functions were reproduced. The first evidence of a water-soluble type F scaffold mimicking myoglobin was reported in 2005.⁴⁰ In this functional model, a Fe^{III}TPPS is associated with the CD dimer Py3CD (Figure 9) and then reduced into its Fe^{II} derivative using sodium dithionite (Na₂S₂O₄). The Fe^{II}TPPS-Py3CD assembly was characterised by several physical methods, including Raman spectroscopy, and compares well with natural systems in terms of oxygen affinity and stability against auto-oxidation, unless anions are present to induce degradation.⁴¹ The same Fe^{II}TPPS-Py3CD scaffold was also

used to generate and characterise hydroperoxoferric (Fe^{III}OOH) derivatives, which are intermediates better known as Compound I in biological processes.⁴² Similarly, superoxide dismutase activity was reported with a Mn^{II} *p*-tetra(4-pyridinium)porphyrin quaternised with adamantyl derivatives and combined with a CD dimer joined by a Te-Te “linker”.⁴³

To enhance the bio-inspired character of the artificial myoglobin model, the pyridine moiety was replaced by an imidazole derivative in the Im3CD cyclodextrin dimer in Figure 9.⁴⁴ As a result of the enhanced pK_a of the imidazole axial ligand bound to the Fe^{II}, a much lower half-saturation pressure (P_{1/2}) of 1.7 torr was observed and was 10 times smaller than that of the Fe^{II}TPPS-Py3CD model.⁴⁵

Scheme 2. Assembling of a cytochrome c oxidase model using a terpyridine linker in a β -CD dimer.

At the top of the list of possible applications of water-soluble oxygen carriers, red blood cell substitutes are extremely motivating. The drawback of small molecular species like cyclodextrin dimers is their size, which will not prevent their excretion from living organisms. To address this problem, porphyrin-CD scaffolds have been associated with dendritic polyethylene glycol (PEG) derivatives to increase significantly their size while maintaining their hydro-solubility.⁴⁶ Depending on the generation of the dendrimer wrapping, the half-lives of the myoglobin models in the blood stream could be significantly enhanced from 0.5 hours to 5 and almost 13 hours for the respective 1st and 2nd generations of PEG dendrimers.

The rapid excretion of the porphyrin-CD scaffolds may become advantageous if the aim is to remove small diatomic molecules (CO, CN[•]) from a living organism. Two such applications have been developed. One utilized the fixation of a cyanide anion to the ferric centre of the Fe^{III}TPPS-Im3CD complex.⁴⁷ In this case, administration of the porphyrin-CDs species completely reversed KCN toxicity *in vitro*. *In vivo* studies also showed that pre-treatment of mice with the

porphyrin-CDs scaffold enhanced the rate of survival after KCN administration and that post-treatment led to complete recovery, thus qualifying the Fe^{III}TPPS-Im3CD model as an antidote for KCN poisoning. More recently, a tool for *in vivo* CO depletion was designed, taking advantage of the very high binding affinity of carbon monoxide for the ferrous state of Fe^{II}TPPS-Py3CD.⁴⁸ The ability of this scaffold to trigger a pseudo-knockdown of endogenous CO in animals offers a possible means of mediating biological functions of endogenous CO.⁴⁹

As a last example of the significant progress in the design of functional haemoprotein models, a chelating terpyridine (terpy) was chosen to link two CDs, as depicted in Scheme 2.⁵⁰ This strategy aims at investigating the class of heterodimetallic enzymes such as cytochrome c oxidase (CcO). CcO is the terminal enzyme in the mitochondrial respiratory chain and its active site contains an iron porphyrin (heme a₃) and a copper ion (Cu_B). In the enzyme, the Fe^{II}-Cu^I state binds dioxygen to generate a Fe^{III}-O-O⁻/Cu^I superoxo intermediate corresponding to a formal two electron reduced state of dioxygen. This intermediate is then further reduced to two water molecules. With the scaffold containing the terpyridine strap, Raman spectroscopy characterisations of the oxygen adduct on the Fe^{II}-Cu^I complex provided evidence for a model that mimics the superoxo state observed in natural systems.

Figure 10. Optimized molecular structures of the FeTPPS/CuTerpyCD2 inclusion complexes in the Fe/Cu oxo-bridged form. Hydrogens are omitted. a) the front-facing phenylsulfonate group is omitted. c) thioether bridges are omitted and cyclodextrins are colored in light blue. Molecular mechanics calculations were carried out using CONFLEX/MM3 (extensive search) parameters in Scigress version 2.2.1 software program (Fujitsu).

The model depicted in Scheme 2 mimics the function of the enzyme and catalyses the four-electron reduction of molecular

dioxygen in water, whereas all previous models were operative in organic solvents or deposited onto electrodes. The spectroscopic studies performed on this model suggest that the terpy-Cu^I and the methoxy groups of the secondary face of the cyclodextrin stabilise a water molecule at low pH, or a hydroxide anion at higher pH, in the proximity of the superoxo adduct, contributing to its enhanced stability. Whereas in most models of CcO the oxygen adducts are readily converted to CO adducts upon exposure to carbon monoxide, the superoxo complex of the model, for which the μ -hydroxo derivative modelled structure is represented in Figure 10, is only converted to its CO analogue after ca. 30 minutes. These encouraging results currently stimulate the exploration of other bridging linkers between the two cyclodextrins in order to modulate and control the catalytic and electrocatalytic events on the iron centre of the porphyrin.

Conclusion

This non-exhaustive overview of research oriented towards enzyme mimics using porphyrins and cyclodextrin derivatives is intended to demonstrate the advantages of using concave hydrophobic hosts in combination with a catalytically active iron- or other metallo-porphyrin and, more generally, with any catalytically active molecule. In haemoproteins, Nature, which achieves most processes at the most refined energy economy level, has embedded the heme catalytic sites into hydrophobic environments in which the reactivity is finely tuned by the distant environment of the ferric/ferrous ion core of the porphyrin. Cavitands, whether they are calixarenes, cyclodextrins or cucurbiturils, provide a unique chance to reproduce at the molecular scale what Nature achieves with globular proteins. In this regard and considering their intrinsic hydrosolubility, CDs and CBs appear to be perfect tools in the supramolecular toolbox to design new eco-friendly catalysts. Whereas a great deal of research in this direction concerns the use of CDs, CBs seem to have been underrated, probably due to legendary solubility and functionalisation issues. Several seminal recent papers have reported various methods for the functionalization of CBs,⁵¹⁻⁵⁶ and the difficult functionalisation of CBs is about to become a legend. As shown by the success of international conferences on CBs, this chemical structure appears to be more and more versatile in terms of functionalisation and uses. This contribution hopes to point out opportunities of combining CBs and porphyrins that should not be missed.

Conflicts of interest

There are no conflicts to declare.

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