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meso-Tetrakis[*o*-(*N*-methyl)pyridinium]porphyrin ensembles with axially coordinated cyclodextrin-penetrating phenethylimidazole: reversible dioxygen-binding in aqueous DMF solution

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Received (in Cambridge, UK) 11th September 2002, Accepted 7th November 2002
First published as an Advance Article on the web 21st November 2002

α-Cyclodextrin (αCD)-penetrating 2-methyl-1-phenethylimidazole coordinates to the zinc(II) and iron(II) complexes of *meso*-tetrakis[*o*-(*N*-methyl)pyridinium] porphyrinate, giving non-covalently linked αCD-porphyrin ensembles; the iron(II) complex can reversibly bind and release dioxygen in aqueous DMF solution.

Modified porphyrinatoiron(II) complexes with a highly-complicated structure, which are prepared by general organic synthetic procedures, namely covalent bonding, have been extensibly studied to mimic the diverse reactivities of hemoproteins.[1,2] In particular, the designs of single-face or double-face encumbered models have been a topic of great interest for the preparation of dioxygen (O_2)-carrying hemes as hemoglobin and myoglobin analogues.[3,4] Based on these significant efforts, we now recognize that two crucial factors are necessary for the dioxygenation of the synthetic heme; (i) bulky-substituents on the porphyrin ring plane to prevent μ-oxo dimer formation, and (ii) a hydrophobic environment to exclude the protons, especially in aqueous media.[5] However, a great deal of labor is generally required to introduce the encumbrance on the porphyrin macrocycle and the total synthetic yields are rather low. If a suitable molecular structure, which provides the O_2-binding capability to the porphyrin platform, is constructed by non-covalent bond formations in water, a totally new class of porphyrin architectures will appear in this chemistry. We report herein for the first time the formation of *meso*-tetrakis[*o*-(*N*-methyl)pyridinium]porphyrinato-zinc(II) and -iron(II) ensembles with axially coordinated α-cyclodextrin-penetrating 2-methyl-1-phenethylimidazole (αCD-MPIm), and the reversible O_2 binding to the iron(II) complex in aqueous DMF solution (Fig. 1). We have employed an αCD to prepare the water-soluble bulky proximal base, and its binding to the flat tetracationic porphyrinato-iron(II) leads to a stable O_2-adduct formation. This is the first example of dioxygenation of a non-covalently linked supramolecular architecture of a cyclodextrin-heme complex.

meso-Tetrakis(*o*-pyridyl)porphine (TPyP), prepared by Adler's method,[6] was reacted with CH_3I in $CHCl_3$–EtOH solution to yield the quaternarized 5,10,15,20-tetrakis[*o*-(*N*-methyl)pyridinium]porphine tetraiodide (47%). The Zn(II) insertion was carried out using $Zn(OAc)_2$ in MeOH, affording the Zn(II) complex (**1a**). In the case of the iron complex (**1b**), the central metal was formerly introduced to TPyP by $FeBr_2$ in DMF, and then quaternarized using CH_3I. Both materials were finally passed through an ion exchange column (Dowex 1-2X) to convert their counter anions to Cl^-. Analytical data for all the compounds were satisfactorily obtained.

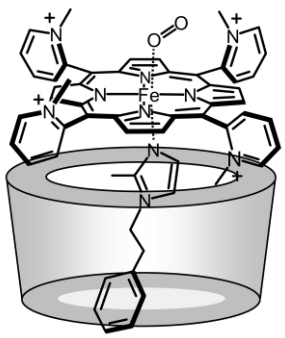

Fig. 1 The possible dominant ααaβ structure of the dioxygenated **1c**(αCD-MPIm) ensemble.

As Miskelly *et al.* reported, four rotational atropisomers of **1a** could be separated on silica gel using an eluent of 2-butanone–conc. aq. NH_3–NH_4PF_6–*N*-methylimidazole (MIm).[7] However, attempts to separate these isomers without PF_6^- counter anions and axially coordinated MIm were unsuccessful. Anyhow, it is true that the ααaβ isomer is the most dominant species of **1a** (*ca.* 50%) at thermal equilibrium.[8]

From the aqueous suspension of αCD and MPIm (20-fold molar excess), the equivalent inclusion compound, αCD-MPIm, was isolated as a white solid. The ^{1}H NMR spectrum, where all signals were carefully assigned by ^{1}H–^{1}H COSY, showed that (i) it exactly consists of a 1 : 1 complex of the host and guest molecules, and (ii) MPIm is incorporated into the apolar cavity of the αCD on the basis of the upfield shifts of the proton signals for the 3- and 5-positions inside the αCD ring; Δppm = +0.075 and +0.049 for 3H and 5H, respectively. However, the magnitudes of these shifts were relatively small compared to the previously reported examples.[9] The molecular length of MPIm (9.5 Å) is longer than the depth of the αCD (6.7 Å), therefore, the ethylene moiety of MPIm may be located in the middle of the cyclic hexaglucopyranose. Hence, the ring current shift observed in the inner-H of αCD by the phenyl and imidazolyl groups is somewhat small. The FAB-MS also demonstrated a molecular-mass ion peak of αCD-MPIm at 1159.9 [M^+]. The hydrophobic and dipole–dipole interactions are probably responsible for the driving force of this inclusion.[10] The MOPAC calculations suggested that the conformer, in which the phenyl ring of MPIm (4.2 Debye) is oriented to the secondary hydroxyl side (the narrower rim) of αCD (9.4 Debye), is energetically more favorable than the reverse one.

The addition of this αCD-MPIm ligand to the aqueous solution of **1a** gave a five-*N*-coordinate Zn(II) complex (λ_{max}: 430, 559, 594 nm). Although anionic tetraarylporphyrins are known to form 1 : 2 complexes with β-cyclodextrin, the cationic porphyrins have no interaction with any cyclodextrin family.[11] The binding constant of αCD-MPIm (K_B = 1.0 × 10^2 M^{-1} in water) to **1a** was nearly the same as that of the 1,2-dimethylimidazole (DMIm) (K_B = 0.9 × 10^2 M^{-1}), indicating that the αCD-complexation produced no effect on the axial imidazole association constant. The most remarkable observation in the αCD-MPIm binding to the Zn(II) center is inducing the rotation of the C–C bond between the *meso*-C and the pyridinium 1-C. In the ^{1}H NMR spectrum of **1a** itself in D_2O, the signals of pyrrole β-H and the pyridinium 6-H appeared as a singlet at 8.85 and 9.25 ppm, respectively. On the contrary, after the αCD-MPIm coordination, they both became doublets and the pyridium 3-H signals significantly shifted upfield (Δppm: −0.12 ppm). Since the DMIm binding to **1a** did not induce such

DOI: 10.1039/b208882g

dramatic changes, we concluded that the bulky αCD-MPIm coordination influences the atropisomer equilibrium of **1a** in statistical distribution.[12] The chemical shifts for 2-CH_3 hydrogens of the pyridinium groups in **1a**(αCD-MPIm) might be more informative on which isomers exist,[7] but they were interfered with by the αCD signals.

The ferric **1b** was reduced to the corresponding ferrous complex (**1c**) in water by adding a two-fold molar excess of aqueous $Na_2S_2O_4$ under an N_2 atmosphere with αCD-MPIm. The UV-vis absorption spectrum showed the typical five-*N*-coordinate high-spin Fe(II) complex (λ_{max}: 431, 533, 562 nm).[3,4] However, upon exposure to O_2 gas, **1c**(αCD-MPIm) was oxidized to the ferric state even at low temperature (5 °C).

In a DMF–water (3/2, v/v) solution, the identical five-*N*-coordinate complex (λ_{max}: 435, 538, 564, 621 nm) of **1c**(αCD-MPIm) was formed under an N_2 atmosphere as well, and the obtained complex was stable in the range of 10 μM–1 mM at 5–40 °C (Fig. 2). After bubbling O_2 gas through this solution, the UV-vis absorption immediately changed to that of the O_2-adduct complex [λ_{max}: 422, 542, 570 (sh.) nm] at 5 °C.[3–5] This dioxygenation was sufficiently kinetically stable, and reversibly observed depending on the O_2 partial pressure. After the addition of CO, **1c**(αCD-MPIm) produced a very stable carbonyl complex [λ_{max}: 420, 535, 564 (sh.) nm]. The resulting O_2 and CO adduct species are both diamagnetic and the ^{1}H NMR spectra showed characteristics of $S = 0$.[13] Oxidation to the Fe(III)porphyrin slowly took place; the final product was the Fe(III)OH complex with a λ_{max} at 415 and 589 nm.[14] It is quite remarkable that the oxidation process obeyed first-order kinetics (half-life was *ca.* 40 min at 5 °C) even under a relatively low O_2-partial pressure (*ca.* 20 Torr) (Fig. 2 inset). The positively charged pyridinium groups at the porphyrin periphery could prevent μ-oxo dimer formation by an electrostatic repulsion. Neutral 5,10,15,20-tetraphenylporphyrinato-iron(II)(αCD-MPIm) [FeTPP(αCD-MPIm)] rapidly oxidized after the O_2 bubbling under the same conditions. We considered that the αCD-MPIm coordination to the αααβ and αααα isomers of **1c** took place from the β-side of the porphyrin plane by steric hindrance to the 2-CH_3 groups of the pyridinium rings. As a result, there were at least two pyridinium cations surrounding the O_2-coordination site of **1c**(αCD-MPIm), and then the proton driven oxidation was retarded.

The three-dimensional structure of the dioxygenated **1c**(αCD-MPIm) ensemble was simulated by molecular dynamics calculations.[15] The significant properties of the architecture are: (i) MPIm penetrates the cavity of αCD and half of the imidazole- and phenyl-rings are forced out from the cyclic hexaglucopyranose, which supports the ^{1}H NMR spectral data, (ii) the *meso*-pyridinium groups and the rim of the αCD bucket contact within the van der Waals distance, and (iii) the imidazole coordination angle does not distort and is identical to that observed in the same calculation for other dioxygenated FeTPP derivatives.

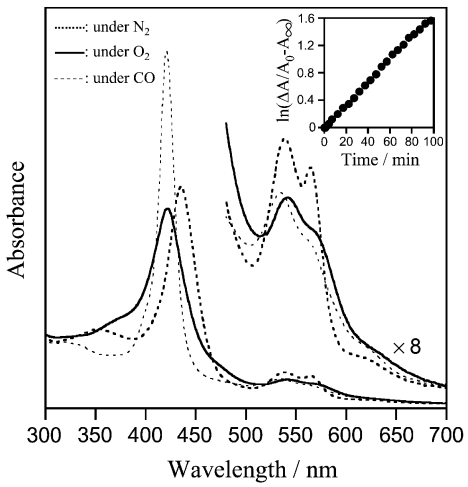

Fig. 2 Visible absorption spectra of the **1c**(αCD-MPIm) ensemble and its O_2-, CO-adduct complexes in DMF–H_2O (3/2 v/v) solution at 5 °C. The inset demonstrates the first-order plots of the absorption decay at 542 nm (O_2-adduct species).

In conclusion, the non-covalently linked αCD-porphyrin ensemble consisting of the simple flat tetracationic-porphyrinato-iron(II) and αCD-penetrating proximal imidazole showed the following unique characteristics. (i) The synthetic yield of the architecture based on the porphyrin is in principle ≈ 100%. (ii) The O_2-adduct complex of **1c**(αCD-MPIm) is the first example of a new class of synthetic O_2-carrying hemoprotein models which is constructed by non-covalent bond formations. The molecular O_2 can bind from the aqueous side to the flat porphyrinato-iron(II) and no oxidation occurs in polar environment, because protons cannot reach the dioxygen active site. (iii) The obtained ensemble was easily dissociated by the addition of methanol, and each building block was withdrawn by gel column chromatography. Further investigations to evaluate the O_2-binding behavior of these porphyrin architectures are now underway.

This work was partially supported by a Grant-in-Aid for Scientific Research (No. 13650938, 13031072) and COE Program 'Practical Nano-Chemistry' from MEXT, Japan.

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