Side Selection of the Fifth Coordinate with a Single Strapped Zinc(II) Porphyrin Host: Full Characterization of Two Imidazole Complexes

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The complementarity of strong direct interactions with the metallic core of a porphyrin and weak interactions located at peripheral positions have received a lot of attention lately. Weak interactions such as steric, hydrophobic, or H-bond formation may be used to control the selectivity of the axial ligation on zinc(II) or iron (III/II) porphyrins.[1] As axial bases, imidazole derivatives have been widely used, in particular 2-methylimidazole (2-MeImH) with hindered hemes, because the position of the axial ligand[2] has been shown to be a determinant factor for the catalytic properties of hemes.[3] Discrimination between proximal and distal coordination based on steric criterions has been extensively used with strapped "basket handle" porphyrins.[4] Recently, peripheral H-binding sites have been introduced on porphyrins, leading to the recognition of carbohydrates[5] and chiral amino acids,[6] by zinc porphyrins. The combination of axial auxiliary binding on metalated porphyrins and peripheral interactions such as H bonds or hydrophobic π-stacking has resulted in an elegant approach of modeling heme-dependent proteins.[7] We have previously described the synthesis of a highly rigid phenanthroline (phen) strapped porphyrin,[8,9] and this paper reports how, for its zinc(II) complex, **1(Zn)**, the nature of the strap allows the selective binding of the fifth coordinate, either on the hindered strapped side or on the open unstrapped side.

The log values of association constants log K_{ass} have been determined, in CH_2Cl_2, for pyridine (Py), imidazole (ImH), *N*-methylimidazole (*N*-MeIm), and 2-MeImH with known spectrophotometric titration methods[10] on both **1(Zn)** and **TPP-(Zn)**. Red shifts observed for the Soret and Q bands during titrations confirm the known effects of axial auxiliary ligand coordination on zinc(II) porphyrins.[11] Axial ligation of *N*-donor ligands generally affords pentacoordinated zinc(II) ions,[12,13] and all data have been analyzed on the basis of a 1/1 stoichiometry controlled by Job's method for each substrate. ^{1}H NMR titrations have been used to localize the preferred binding site for each substrate with **1(Zn)** in $CDCl_3$.

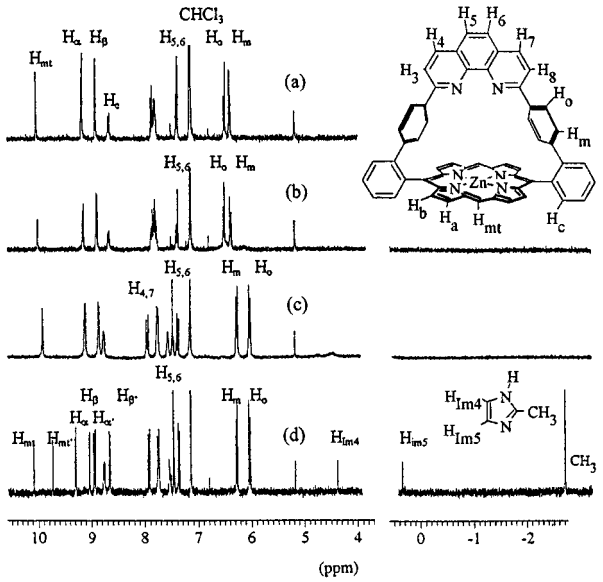

Figure 1. ^{1}H NMR ($CDCl_3$, 300 MHz) spectral changes after addition of 1 equiv of *N*-MeIm (b), ImH (c), and 2-MeImH (d) to **1(Zn)** (a).

During the titration of **1(Zn)** the phen bands in the UV region of the spectra are affected by the coordination of ImH and 2-MeImH while the binding of *N*-MeIm or Py induces no change in this region. From the log K_{ass} values obtained for each substrate, it is clear that ImH (log K_{ass} = 6.1 ± 0.2) and 2-MeImH (log K_{ass} = 7.3 ± 0.3) develop additional interactions with the host when compared to *N*-MeIm (log K_{ass} = 4.7 ± 0.2) or Py (log K_{ass} = 3.3 ± 0.2). Phen pocket type derivatives have been studied as concave bases and are considered H-bond acceptors, especially when hidden in a hydrophobic cavity.[14] The UV changes observed for the phen bands suggest that a hydrogen bond with the strap is responsible for the enhanced binding of ImH and 2-MeImH. To confirm this hypothesis, ^{1}H NMR titrations have been performed in each case. For 1 equiv of substrate added the spectra represented in Figure 1 shows that the guest induced variation of chemical shifts is

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(15) Crystals have been obtained by slow diffusion of hexane into a methylene chloride solution of **1(Zn)** containing 1 equiv of imidazole. Crystal structure of [**1(Zn)**-ImH](CH_2Cl_2): $C_{59}H_{36}N_8Zn$, CH_2Cl_2 formula weight 1005.24, red rectangular plate, monoclinic, $P2_1/c$, a = 8.883(2) Å, b = 28.110(5) Å, c = 18.733(4) Å, β = 90.99(3)°, V = 4677.2(3) Å^3, Z = 4, R_1 = 0.066, wR_2 = 0.090, GOF on F^2 = 2.52, max/min residual density 0.68 to −0.75 e/Å^3. Crystal structure of [**1(Zn)**-2-MeImH]0.5(CH_2Cl_2): $C_{60}H_{38}N_8Zn$, 0.5(CH_2Cl_2), formula weight 976.8, red orange plates, monoclinic space group Cc, a = 30.573(6) Å, b = 21.732(4) Å, c = 16.330(3) Å, β = 110.19(3)°, V = 10182.9(6) Å^3, Z = 8, R_1 = 0.0963, wR_2 = 0.2360, GOF on F^2 = 1.48, max/min residual density 1.13 to −0.60 e/Å^3. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Structural Data Centre as supplementary publication No. 100341. Copies of the data can be obtained free of charges on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: Int. code +(1223) 336−033; e-mail: teched@chemcrys.cam.ac.uk).

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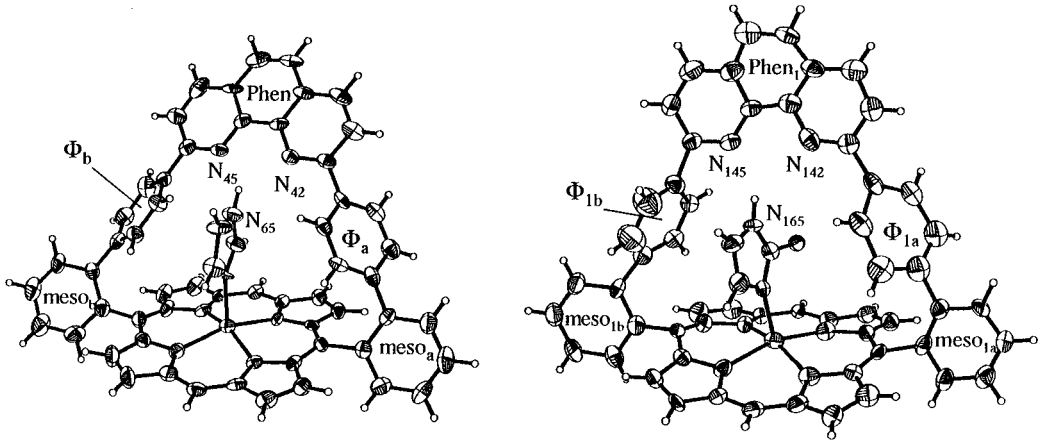

Figure 2. Molecular structures of **1(Zn)**-ImH (left) and **1(Zn)**-2-MeImH (right). Bond lengths, angles, and atomic coordinates available.[15]

drastically different for the two substrates. Comparing plots a to d in Figure 1, it is clear that the addition, in a solution of receptor **1(Zn)** (plot a), of 1 equiv of *N*-MeIm (plot b) induces only small changes in the chemical shifts of the protons located on both the phen and the porphyrin moieties. Only a slight broadening is observed, which is consistent with the formation of a weak complex with fast exchange of the axial ligand bound to the zinc(II). On the contrary, the addition of 1 equiv of *N*-unsubstituted imidazole (plots c and d) strongly affects the resonances of specific protons of the receptor, providing valuable information concerning the site of ligation. The upfield shift of the H_o and H_m signals and the presence at 12.3 ppm of a broad signal corresponding to the imidazole N−H proton are in agreement with the coordination of ImH in the pocket of the receptor. It should be noted that H_o protons are drastically affected (−0.45 ppm) while H_m protons are only slightly shifted upfield (−0.10 ppm). The protons H_5 and H_6 are deshielded, which confirms the binding of the substrate in between the phenyl spacers, the imidazole ring current inducing the deshielding of these protons. Concerning the protons of the substrate, the methyl group of 2-MeImH provides an efficient probe for investigating the topography of the host−guest complex (plot d, Figure 1). The resonance signal of this CH_3, usually expected around 2.4 ppm, is observed at −2.5 ppm in the ternary complex, which is consistent with a proximity of this group to the porphyrin ring current. In addition, the signals (β pyrrolic H_a and H_b, and methene H_{mt}) of porphyrinic protons are split (Figure 1). This is necessarily due to the coordination of the 2-MeImH within the pocket of the receptor. For a 2-MeImH axial ligand bound on the unstrapped side of the receptor, the free rotation of the substrate would not be prevented and could not lead to a disymmetrical porphyrin. Thus, from ^{1}H NMR data, it is possible to determine the site of ligation for ImH, 2-MeImH, and *N*-MeIm. Confirmation of our hypotheses came from X-ray measurements,[15] and diffraction of single crystals allowed for the unambiguous location of the imidazole and the 2-MeImH on the strapped side of the receptor. Both porphyrin cores are slightly ruffled and the zinc−[24-atoms core] distances are identical (0.38(1) Å). The N---N distances between the phen part and the imidazoles ($N_{42}-N_{65} = 3.051$ Å, $N_{45}-N_{65} = 3.080$ Å, and $N_{142}-N_{165} = 2.818$ Å, $N_{145}-N_{165} = 2.869$ Å) are representative of the strong H bond. Besides the fact that two molecules are observed in the asymmetric unit for **1(Zn)**-2MeImH (only one will be considered in a first analysis), three main differences are observed between the two structures. First, the orientation of the imidazole ring in the pocket is almost perpendicular to the phen plane ($\angle$Im−phen = 85°), whereas in the case of 2-MeImH the dihedral angle between the phen and the Im plane is only 75°. This is the first consequence of the steric requirements for the accommodation of the CH_3 group of the 2-MeImH guest. The second consequence is the less important tilt of the phen strap in the case of 2-MeImH. Indeed, the dihedral angles between both the phen and the meso phenyls with the porphyrin [24-atoms core] are less important in the case of ImH than for 2-MeImH. For example, the meso-porph angles in the case of 2-MeImH are higher than 67°, but for ImH these angles are lower than 67°. Interestingly, the tilt of the strap already exists in the free base structure with a meso-phenyl−porph dihedral angle of 67°.[16] The last difference concerns the orientation of the phenyl spacers. The phenyl spacers (Φ_a and Φ_b) for the ImH structure are almost perpendicular (84°), which is again comparable with the value observed in the free base (82°)[16] while these spacers (Φ_{1a} and Φ_{1b}) tend to line up with the 2-MeImH guest (Φ_{1a} and Φ_{1b} angles with the 2-MeImH plane: 31 and 35°). Higher electron density on the 2-MeImH guest and increased $\pi-\pi$ interactions, despite some distortions, in the structure of **1(Zn)**-2MeImH are in agreement with the binding selectivity observed in the series of stability constants. No disymmetry has been observed in ^{1}H NMR for the ImH complex, which is consistent with fast free rotation of the ImH substrate around its N−H, N−Zn axis. The use of 2-MeImH blocks this rotation and induces the splitting of the resonances observed for the porphyrin ring protons. The stronger binding of the substrate allows a NOEMULT experiment to be run on an equimolar solution of **1(Zn)** and 2-MeImH in $CDCl_3$. The irradiation of the CH_3 signal at −2.5 ppm gives a positive NOE for the signal corresponding to one of the methene protons (H_{mt}) and for the doublet assigned to the H_o protons. The same process confirms the spatial proximities between H_o and $H_{3,8}$, H_o and H_{ImH4}, H_m and H_b, and H_m and $H_{b'}$. The disymmetry of the porphyrin with respect to the phen plane, while the AB spectrum of the phenyl spacers remains unchanged, suggests that the 2-MeImH substrate is in a fixed position with respect to the phen plane while the two phenyl spacers are still freely rotating around the phen−porphyrin link. Further thermodynamical investigation of this complexation process is in progress in order to estimate the entropic contribution to the binding free energy.

Thus, in the case of a phen strapped porphyrin, the strap behaves as the proximal site in the presence of *N*-unsubstituted imidazoles, due to the presence of a single H bond.[16] This provides insight for the combination of strong and weak interactions for modeling of active sites involving metalloporphyrins which are under way as well as the magnetic properties of topographically frozen **1(Fe^{II})-2-MeImH** species.

Supporting Information Available: NOE results and separate irradiations (6 pages). See any current masthead page for ordering and Internet access instructions.

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(16) Experimental details of titrations, 2D ^{1}H NMR of the ternary complex **1(Zn)**-2-MeImH, and X-ray structures of the free base and the zinc(II) porphyrins will be published elsewere.