Inorg. Chem. **2007**, *46*, 9534–9536

Recognition of Imidazoles by Strapped Zinc(II) Porphyrin Receptors: Insight into the Induced-Fit Mechanism

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Received August 9, 2007

Imidazole–porphyrin coordination has become an important tool in the design of self-assembled materials. A combination of spectrophotometric and stopped-flow techniques has been used to gain insight into the control of imidazole binding in the distal pocket of phenanthroline-strapped porphyrins. The binding studies of a variety of imidazole substrates in combination with both hindered and accessible receptors have permitted the determination of the thermodynamic and kinetic parameters associated with the imidazole binding.

The design of self-assembling multiporphyrin arrays and networks makes extensive use of axial base coordination to metalloporphyrins.[1] In particular, axial imidazole binding to zinc(II) porphyrins is an extremely powerful tool in the formation of self-assembled, linear, and cyclic multiporphyrin assemblies.[2] Although we have described self-assembled photodyads[3] and linear porphyrin arrays,[4] based on selective distal binding of imidazole substrates in phenanthroline (phen)-strapped porphyrins,[5] these architectures were initially designed as hemoprotein models.[6] For both research fields,[1] control over the fifth coordination of the metalloporphyrin is a key parameter, and the behavior of zinc(II) porphyrins versus nitrogen axial bases is commonly extrapolated to pentacoordinated iron(II).[7] Because of the labile nature of the fifth *N*−Zn coordination bond, kinetic data, which are essential to both deciphering the assembly mechanism[8] and understanding the distal site recognition process, are extremely scarce.[9]

Once established, the recognition of imidazoles offered an opportunity to gain insight into the self-assembly process, especially its thermodynamic and kinetic parameters. Thus, 2,9-diphenyl-1,10-phenanthroline-strapped porphyrins Zn**L**^{1} and Zn**L**^{2} and substituted imidazoles **S1**−**S5** were chosen to identify the key parameters controlling the proximal/distal[10] recognition of the substrates (Figure 1).[2] The resorcinol ether **L**^{2} was initially prepared as a synthetic intermediate and offered the opportunity to address the influence of

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10.1021/ic701590x CCC: $37.00 © 2007 American Chemical Society
Published on Web 10/12/2007

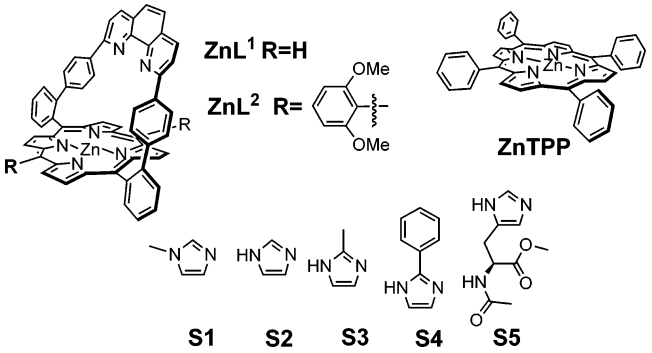

Figure 1. Chemical structures of the phen-strapped zinc(II) receptors Zn**L**^{1} and Zn**L**^{2} and of the imidazole substrates **S1**−**S5**.

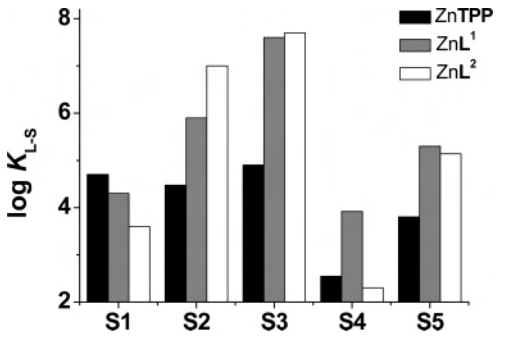

Figure 2. Stability constants (log K_{ZnL-S}) of imidazoles **S1**−**S5** with strapped receptors Zn**L**^{1} and Zn**L**^{2}. Solvent: 1,2-dichloroethane. $T = 25.0(2)$ °C. Stability constants determined from UV−vis absorption and fluorescence spectrophotometric titrations (see the Supporting Information). Uncertainties $= 3\sigma$.

steric hindrance around the distal cavity, which was not possible with previously obtained systems bearing *meso*-xylyl substituents.[13] Prior to detailed studies, previous studies performed in dichloromethane were reproduced in 1,2-dichloroethane. The latter solvent was preferred because of its greater stability upon irradiation at high energies. Previous studies in dichloromethane confronted us with the protonation of free base porphyrins during UV−vis studies.[3] As stated hereafter, slightly higher stability constants were obtained in dichloroethane, and the trend remains unchanged in the case of **L**^{1} and valid in the case of **L**^{2}.

Thus, the stability constants of a series of N_1-unsubstituted imidazoles (**S2**−**S5**; Figure 2) with zinc porphyrin receptors Zn**L**^{1} and Zn**L**^{2} were determined using both absorption and emission spectrophotometry (see the Supporting Information).[11] The substrates were selected to examine the effect of substituent bulkiness in positions 2 and 5. Substrate **S1** is taken as an example of N_1-substituted analogues, whereas Zn**TPP** is a reference porphyrin receptor.

In agreement with previous reports, in the case of Zn**TPP**, the data collected in Figure 2 mostly reflect electronic effects of the substituents on the N_3-heteroatom, which binds to zinc(II). The association constants increase in the same order as the pK_a values.[12] Substrates **S3** and **S4** are representative examples because the electron-donating methyl group in **S3** enhances the stability of the corresponding Zn**TPP**−**S3** complex [log $K_{Zn\mathbf{TPP}-\mathbf{S3}} = 4.9(1)$]. The electron-withdrawing phenyl substituent of **S4** strongly destabilizes the Zn**TPP**−**S4** species [log $K_{Zn\mathbf{TPP}-\mathbf{S4}} = 2.54(6)$], confirming general trends in the stability constants of zinc porphyrins with N-axial bases.

Imidazole **S2** without a substituent either in position 2 or in position 5 and substrate **S5** with a bulky substituent in position 5 are both stabilized in their interactions with Zn**L**^{1} and Zn**L**^{2} compared to those with Zn**TPP** (Figure 2). Substrates **S3** and **S4**, which are substituted in position 2, also lead to more stable Zn**L**^{1} and Zn**L**^{2} complexes than with Zn**TPP** (Figure 2).

Clearly, N_1-unsubstituted imidazoles are strongly stabilized by at least 1 order of magnitude in the presence of the phen strap in both receptors Zn**L**^{1} and Zn**L**^{2} with respect to Zn**TPP**. The binding of **S2**−**S5** within the strap is shown by the spectrophotometric changes at about 250−370 nm, where the phen absorbs (see the Supporting Information).[5,13] On the other hand, the binding of **S1** by Zn**L**^{1} and Zn**L**^{2} does not affect the electronic spectra of the phen subunit (see the Supporting Information). These data confirm the proximal recognition of the N_1-methyl derivative that is unable to establish bifurcated hydrogen bonds with the phen nitrogen atoms in the strap. The global trend is a significant decrease in the stability of the complexes formed between **S1** and Zn**L**^{1} or Zn**L**^{2} in comparison to that of the **S1**−Zn**TPP** complex (Figure 2).

Interestingly, comparison of the stabilities of Zn**L**^{1} and Zn**L**^{2} imidazole complexes shows that the smallest substrate **S2** is more stable by about 1 order of magnitude with Zn**L**^{2} compared to Zn**L**^{1}. This result accounts for an enhanced inertness due to the bulky stoppers in meso positions (Figures 1 and 2). The low stability constant for Zn**L**^{2}−**S4** clearly indicates that the fitting of the strapped porphyrins is reduced when bulky 2-phenyl-1*H*-imidazole (**S4**) is combined with the Zn**L**^{2} receptor. Although previous attempts to modulate the affinity of the phen-strapped porphyrins for exogen substrates were unsuccessful,[13] destabilization by a factor of nearly 50 is therefore observed when bulkiness is increased both at the receptor's meso position and at the imidazole's 2 position. Thus, for the first time, the proximity of the bulky resorcinol meso substituents, which control access to the distal site, tunes the influence of the bifurcated hydrogen bond established between the imidazole N_1−H and the phen strap. In the Zn**TPP**, Zn**L**^{1}, and Zn**L**^{2} series, tools to control the imidazole binding are gradually introduced with N-coordination, hydrogen-bond positioning, and steric hindrance, all of which provide insight about their respective role in the molecular recognition process.

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Table 1. Stability and Rate Constants Relative to Pentacoordinated Complexes with Zn**L**^{1} and Zn**L**^{2} [a]

substrate	receptor					
	Zn**L**^{1}			Zn**L**^{2}		
	log ***K***	k_f (M^{-1} s^{-1})	k_d (s^{-1})	log *K*	k_f (M^{-1} s^{-1})	k_d (s^{-1})
S3	7.6(4)[b]			7.7(5)[b]		
	6.2(3)[c]	2.2(9) × 10^7	16(8)	7.6(4)[c]	3(2) × 10^6	0.07(3)
S4	3.92(7)[b]			2.3(3)[b]		
	3.2(2)[c]	2.0(7) × 10^4	1.4(2)	2.1(3)[c]	4.9(1) × 10^2	4.3(3)
S5	5.3(4)[b]			5.14(4)[b]		
	4.04(7)[c]	1.54(8) × 10^5	14(2)	4.5(1)[c]	2.0(3) × 10^4	0.65(9)

[a] Solvent: 1,2-dichloroethane. T = 25.0(2) °C. Uncertainties = 3σ. See the Supporting Information for detailed experiments. [b] Titrations. [c] Kinetics.

This prompted studies on the formation kinetics for complexes formed between receptors Zn**L**^{1} and Zn**L**^{2} and substrates **S3**−**S5** (see the Supporting Information). For substrates **S1** and **S2**, the reactions were too fast to be measured by the stopped-flow technique, in agreement with kinetic data reported elsewhere[9] for Zn**TPP** and **S2** (k_f = 3.2 × 10^9 M^{-1} s^{-1}) in chlorobenzene. However, a single rate-limiting step was observed for **S3**−**S5** and led to the determination of the bimolecular formation rate constant k_f and of the monomolecular dissociation constant k_d. It is noteworthy that the ratio k_f/k_d agrees well with the stability constants of the corresponding complexes (Table 1).

For both receptors, k_f drastically decreases with increasing bulkiness of the substituents in position 2 of the imidazoles (**S3** and **S4**). Differences of about 3−4 orders of magnitude are indeed observed between **S3** and **S4**. More moderate effects are observed for substrate **S5** substituted in position 5. The k_f sequence for the various substrates with the two porphyrin hosts is **S1**, **S2**[9] > **S3** > **S5** > **S4**.

Moreover, it should be noted that the increase of the bulkiness of the meso substituents of the receptors has a moderate effect on k_f for **S3** and **S5** (less than 1 order of magnitude), whereas a decrease of about 2 orders of magnitude is observed for **S4**. A strong steric hindrance in the formation of Zn**L**^{2}−**S4** quite drastically decreases the corresponding rate constant k_f (about 2 orders of magnitude). Regarding substrate **S5**, it is remarkable that, out of the two possible tautomers that can exist in solution, the least stable 3*H* tautomer is bound to the zinc-strapped receptor.[14] ^{1}H NMR data (see the Supporting Information) obtained are in agreement with this tautomeric change, which also accounts for the decrease in the formation rate of **S5**.

Finally, the most interesting feature concerns the inertness of the imidazolyl complexes. The sequence of k_d for Zn**L**^{1} is **S3** > **S5** > **S4**. The inertness increases when the substrates are able to develop intramolecular interactions with the metalloporphyrin receptors. For example, **S4** and **S3** were found to form more inert edifices with receptor Zn**L**^{1} than 1*H*-imidazole did because of the additional $\pi-\pi$ stacking or CH−π interactions, for which evidence was obtained from NMR or X-ray data with *meso*-xylyl substituents.[5,8] When the bulkiness of the meso substituents (Zn**L**^{2}) increases, strong steric interactions between **S4** and the 2,6-dimethoxyphenyl groups lead to more labile complexes. In contrast, the complexes formed with **S3** and **S5** are 1−2 orders of magnitude more inert than those formed with Zn**L**^{1} because of the stopper effect of the 2,6-dimethoxyphenyl substituents.

Substrate **S4** exhibited the most striking behavior; therefore, the activation parameters for the Zn**L**^{1}−**S4** and Zn**L**^{2}−**S4** complexes will be presented. For Zn**L**^{2}, the activation enthalpies for the formation and dissociation are comparable with $\Delta H^{\ddagger}_f$ = 74(4) kJ mol^{-1} and $\Delta H^{\ddagger}_d$ = 71(3) kJ mol^{-1}, whereas the activation entropies are significantly different [$\Delta S^{\ddagger}_f$ = 53(12) J mol^{-1} K^{-1} and $\Delta S^{\ddagger}_d$ = 4(9) J mol^{-1} K^{-1}]. The reaction is therefore entropically driven with $\Delta\Delta S^{\ddagger}$ = 49(15) J mol^{-1} K^{-1}. An opposite and interesting situation is found for the Zn**L**^{1}−**S4** complex, for which the formation [$\Delta H^{\ddagger}_f$ = 42(2) kJ mol^{-1} and $\Delta S^{\ddagger}_f$ = −26(6) J mol^{-1} K^{-1}] and the dissociation [$\Delta H^{\ddagger}_d$ = 65(4) kJ mol^{-1} and $\Delta S^{\ddagger}_d$ = −28(12) J mol^{-1} K^{-1}] activation parameters lead to an enthalpically controlled reaction [$\Delta\Delta H^{\ddagger}$ = −23(2) kJ mol^{-1}]. In the absence of strong steric interactions between **S4** and Zn**L**^{1}, the reaction proceeds through an associative and enthalpic mechanism. In contrast, the steric hindrance in Zn**L**^{2} imposes drastic desolvation and significant conformational changes of both substrate **S4** and receptor Zn**L**^{2}. The self-assembly mechanism is consequently dissociative and entropically driven.

In conclusion, this study provides important kinetic and thermodynamic insight on the modulation and control of imidazole coordination with zinc porphyrins. In the perspective of porphyrin-based materials, high binding affinities usually required for the cohesion of self-assembled material should be paradoxically associated with moderate inertness, which allows self-correction and thermodynamically controlled assembling processes in solution and then further transfer of self-assembled material from the solution to the solid state. In this regard, this work distinguishes the specific influences of steric hindrance requirements on the receptor and the substrate. Steric hindrance ultimately determines the associative or dissociative character of the imidazole binding process. The bulkiness of the substituents slows down the rate of the recognition process, while the inertness of the imidazole−zinc(II) porphyrin species reflects additional intramolecular interactions.

Acknowledgment. This work has been supported by the Centre National de la Recherche Scientifique (UMR 7177), the Faculté de Chimie, and the Université Louis Pasteur (Strasbourg, France). A.T., J.B., and F.M. thank the Ministère de l'Enseignement Supérieur et de la Recherche for Ph.D. fellowships. Thanks are expressed to Dr. J. A. Wytko for fruitful discussions.

Supporting Information Available: Experimental data, stability constants, UV−vis spectrophotometric titrations, luminescence titrations, kinetic studies, activation parameters, and histidine complexation. This material is available free of charge via the Internet at http://pubs.acs.org.

IC701590X

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