

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

Jeremy Brandel,[†] Ali Trabolsi,[†] Frédéric Melin,[‡] Mourad Elhabiri,[†] Jean Weiss,^{*,‡} and Anne-Marie Albrecht-Gary^{*,†}

Laboratoire de Physico-Chimie Bioinorganique, ULP-CNRS (UMR 7177), Institut de Chimie, ECPM, 25 rue Becquerel, 67200 Strasbourg, France, and Laboratoire de Chimie des Ligands à Architecture Contrôlée, ULP-CNRS (UMR 7177), Institut de Chimie, 4 rue Blaise Pascal, 67000 Strasbourg, France

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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 photodyads³ 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 mechanism⁸ 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 ZnL¹ and ZnL² and substituted imidazoles S1–S5 were chosen to identify the key parameters controlling the proximal/distal¹⁰ recognition of the substrates (Figure 1).² The resorcinol ether L² was initially prepared as a synthetic intermediate and offered the opportunity to address the influence of

* To whom correspondence should be addressed. E-mail: jweiss@chimie.u-strasbg.fr (J.W.), amalbre@chimie.u-strasbg.fr (A.-M.A.-G.).

[†] Laboratoire de Physico-Chimie Bioinorganique.

[‡] Laboratoire de Chimie des Ligands à Architecture Contrôlée.

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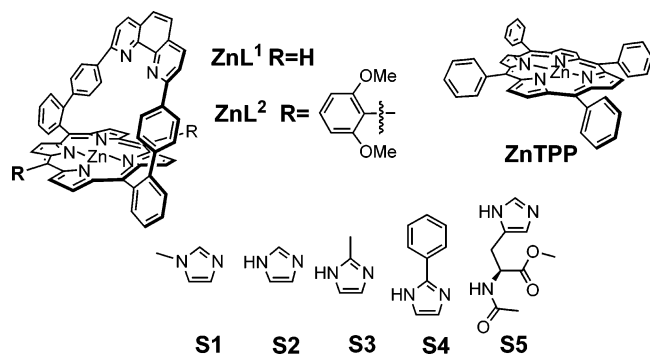


Figure 1. Chemical structures of the phen-strapped zinc(II) receptors ZnL^1 and ZnL^2 and of the imidazole substrates **S1**–**S5**.

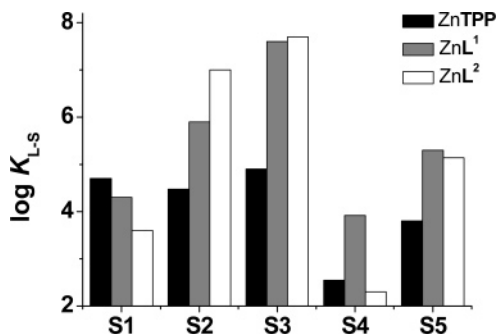


Figure 2. Stability constants ($\log K_{L-s}$) of imidazoles **S1**–**S5** with strapped receptors ZnL^1 and ZnL^2 . Solvent: 1,2-dichloroethane. $T = 25.0(2)^\circ\text{C}$. Stability constants determined from UV–vis absorption and fluorescence spectrophotometric titrations (see the Supporting Information).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

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 ZnL^1 and ZnL^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 ZnTPP is a reference porphyrin receptor.

In agreement with previous reports, in the case of ZnTPP , 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 $\text{p}K_a$ values.¹² Substrates **S3** and **S4** are representative examples because the electron-donating methyl group in **S3** enhances the stability of the corresponding ZnTPP –**S3** complex [$\log K_{\text{ZnTPP-S3}} = 4.9(1)$]. The electron-withdrawing phenyl substituent of **S4** strongly destabilizes the ZnTPP –**S4** species [$\log K_{\text{ZnTPP-S4}} = 2.54(6)$], 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 ZnL^1 and ZnL^2 compared to those with ZnTPP (Figure 2). Substrates **S3** and **S4**, which are substituted in position 2, also lead to more stable ZnL^1 and ZnL^2 complexes than with ZnTPP (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 ZnL^1 and ZnL^2 with respect to ZnTPP . 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 ZnL^1 and ZnL^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 ZnL^1 or ZnL^2 in comparison to that of the **S1**– ZnTPP complex (Figure 2).

Interestingly, comparison of the stabilities of ZnL^1 and ZnL^2 imidazole complexes shows that the smallest substrate **S2** is more stable by about 1 order of magnitude with ZnL^2 compared to ZnL^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 ZnL^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 ZnL^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 ZnTPP , ZnL^1 , and ZnL^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 ZnL¹ and ZnL²^a

sub- strate	receptor					
	ZnL ¹			ZnL ²		
	log <i>K</i>	<i>k_f</i> (M ⁻¹ s ⁻¹)	<i>k_d</i> (s ⁻¹)	log <i>K</i>	<i>k_f</i> (M ⁻¹ s ⁻¹)	<i>k_d</i> (s ⁻¹)
S3	7.6(4) ^b 6.2(3) ^c	2.2(9) × 10 ⁷	16(8)	7.7(5) ^b 7.6(4) ^c	3(2) × 10 ⁶	0.07(3)
S4	3.92(7) ^b 3.2(2) ^c	2.0(7) × 10 ⁴	1.4(2)	2.3(3) ^b 2.1(3) ^c	4.9(1) × 10 ²	4.3(3)
S5	5.3(4) ^b 4.04(7) ^c	1.54(8) × 10 ⁵	14(2)	5.14(4) ^b 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 ZnL¹ and ZnL² 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 elsewhere⁹ for ZnTPP and **S2** (*k_f* = 3.2 × 10⁹ 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 ZnL²–**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 ¹H 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 ZnL¹ 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 ZnL¹ than 1*H*-imidazole did because of the additional π–π 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 (ZnL²) 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 ZnL¹ because of the stopper effect of the 2,6-dimethoxyphenyl substituents.

Substrate **S4** exhibited the most striking behavior; therefore, the activation parameters for the ZnL¹–**S4** and ZnL²–**S4** complexes will be presented. For ZnL², the activation enthalpies for the formation and dissociation are comparable with Δ*H*[‡]_f = 74(4) kJ mol⁻¹ and Δ*H*[‡]_d = 71(3) kJ mol⁻¹, whereas the activation entropies are significantly different [Δ*S*[‡]_f = 53(12) J mol⁻¹ K⁻¹ and Δ*S*[‡]_d = 4(9) J mol⁻¹ K⁻¹]. The reaction is therefore entropically driven with ΔΔ*S*[‡] = 49(15) J mol⁻¹ K⁻¹. An opposite and interesting situation is found for the ZnL¹–**S4** complex, for which the formation [Δ*H*[‡]_f = 42(2) kJ mol⁻¹ and Δ*S*[‡]_f = –26(6) J mol⁻¹ K⁻¹] and the dissociation [Δ*H*[‡]_d = 65(4) kJ mol⁻¹ and Δ*S*[‡]_d = –28(12) J mol⁻¹ K⁻¹] activation parameters lead to an enthalpically controlled reaction [ΔΔ*H*[‡] = –23(2) kJ mol⁻¹]. In the absence of strong steric interactions between **S4** and ZnL¹, the reaction proceeds through an associative and enthalpic mechanism. In contrast, the steric hindrance in ZnL² imposes drastic desolvation and significant conformational changes of both substrate **S4** and receptor ZnL². 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.

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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>.

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