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Review Article

Zinc(II)-porphyrin Receptors in Multi-point Molecular Recognition: Recent Progress

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Abstract

The tremendous efforts made in order to control the coordination chemistry of hemoprotein models have considerably enhanced the synthesis of functionalized porphyrins, whose carefully designed architectures allowed for selective bindings of exogenic substrates. The common use of zinc(II) in place of pentacoordinated iron(II) has induced the use of zinc(II) porphyrins as building blocks for selective receptors. These receptors offer a convenient combination of multi-point recognition of substrates, and monitoring of the complexation due to the chromophoric nature of the tetrapyrrolic unit. This review is dedicated to recent progress made in the field of molecular recognition involving multi-point selective binding processes, in which the establishment of a strong coordination bond is finely tuned by one or more weak interactions adequately introduced in the architecture of a functionalized zinc(II)-porphyrin.

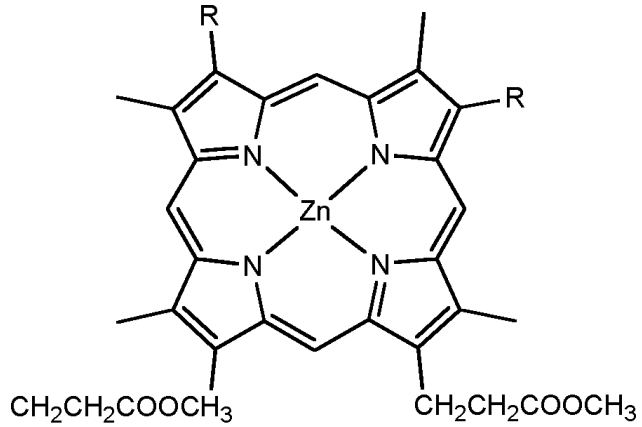
Introduction

Over the past forty years, the search for refined models of hemoproteins has led coordination chemists to incorporating the porphyrin skeleton in various architectures that mimic the peptide environment of the heme active sites in natural systems. Because of its diamagnetic character as a tetra- or penta-coordinated species, zinc(II) has been used very often as a substitute for iron(II) to investigate the coordination properties of metallo-porphyrins by NMR techniques. Selection of small exogenic substrates has been initially controlled by steric hindrance around the porphyrin core in picket-fence porphyrins, and has been further increased by the preparation of basket-handle, and strapped porphyrins, and a great deal of information and rationalization concerning substrate selection processes has been learned from both natural active sites and their models [1]. Owing to the aromaticity of the tetrapyrrolic macrocyle and the physical properties of this highly colored chromophore, zinc(II)-porphyrins rapidly appeared very attractive for the design of photo-active receptors in which spectrophotometric variations were used to monitor the coordination of axial auxiliary ligands. The inclusion of the zinc(II)-porphyrin moieties into carefully designed architectures has been generalized and multi-point recognition processes make extensive use of this relatively flat, and rigid building block which provide a strong ligand-metal interaction that can be associated with weak interactions located above the fifth coordination site of the zinc(II) or at the periphery of the porphyrin ring.

Scope of this review

Coordination chemistry of zinc(II) porphyrins is a field way too large to be covered in this paper. Several articles describing the use of axial coordination as an organizing tool in crystal engineering and new material preparation can be found in the literature and generally concern the covalent linkage of the base to the periphery of the porphyrin in order to obtain coordination polymers, or the formation of porphyrin monolayers on gold surfaces via immobilization of the axial base. An exhaustive review by Heitz *et al.* [2] concerning the non-covalent assemblies of multiporphyrins is available in the recently issued "Porphyrin Handbook", as well as an exhaustive review covering all aspects of molecular receptors involving porphyrins and metalloporphyrins by Ogoshi *et al.* [3]. Remote modifications of the photophysical properties of a porphyrin probe by the complexation of substrates in a covalently attached receptor have also been described and reviewed but generally do not involve a fifth coordination on the zinc(II)-porphyrins [3–5]. This review is dedicated to receptors involving a strong and undiscriminating axial coordination on the zinc(II) central atom acting in synergy with steric interactions, van der Waals interactions, aromatic stacking, and H-bonds as tools for fine tuning of the substrate selection.

After a short energetic quantification of the interactions that are involved in these processes, systems combining coordination to zinc(II) and weak interactions will be described, starting with receptors comprising one zinc(II)-



1: ZnHP, R=-XH(OCH$_3$)CH$_3$
2: ZnMP, R=-CH$_2$CH$_3$
3: ZnPP, R=-CH=CH$_2$

Figure 1. Zinc(II) protoporphyrin IX esters.

porphyrin unit, then multiple porphyrin receptors. Due to intrinsic properties, flexible porphyrin dimers are used for chiral recognition, and the development of chiral receptors and the stereoselective binding or detection of substrates will logically appear in a second part of this review.

Axial ligand coordination on zinc(II)-porphyrins

Coordination of axial bases arises from the interaction of the available lone pair from the base with the electron deficient 4p$_z$ and 4d$_{z^2}$ orbitals of the tetracoordinated square planar zinc(II). This interaction is the driving force for the formation of rather stable receptor substrate complexes. Relatively old studies of the simple Zn(II)-5,10,15,20-tetraphenylporphyrin (ZnTPP) provide a good estimation of the free energy associated with nitrogen containing ligands and model compounds have also been used for oxygen containing coordinates. When no additional interaction is present, the general trend of the association constants (Ka) with O and N containing axial bases is to follow the increasing order of pKa of the ligands. The overall binding process is considered to be enthalpy driven [3], and in organic solvents, quite drastic differences have been observed by calorimetric titrations [6] of zinc(II) protoporphyrin IX esters (**1**, **2**, and **3**, Figure 1) with pyridine in benzene and chloroform, benzene providing the strongest binding (Table I).

Oxygen binding can be considered as a much weaker interaction when compared to the axial ligation of nitrogen containing bases. For example, in benzene, ZnTPP binds pyridine with a Ka of 6.0×10^3 M^{-1} ($\Delta G^0 = -21.3$ kJ mol^{-1}) [7], and **4** binds tetrahydropyrane with a Ka of 3 ($\Delta G = -2.6$ kJ mol^{-1}), and hydroxymethylcyclohexane with a Ka of 7 ($\Delta G = -4.6$ kJ mol^{-1}) in chloroform at 288 K [8].

Even though oxygen coordination on zinc(II) is weaker than N coordination, it can be used as a non-selective anchoring point in a multi-point recognition process. Oxygenated axial ligands on Zn(II)-porphyrin are usually present in the solid state [9] but if present in solution in free receptors, their release affords a mean of compensating the entropy loss usually associated with the coordination of the base [10].

Primary amines also show moderate affinity for zinc(II) porphyrins that may serve as a non-selective driving force in recognition processes. For example, the energetic gains associated with the binding of amino-acid esters by an unfunctionalized receptor **5** are listed in Table 2 [11].

A first look at Table 2 shows that the ΔG values for primary amines are in the range of those observed with aromatic imines, slight variations illustrating again that the strength of the N binding is associated with the basicity of the lone pair.

The association of such strong non-selective interaction with one or more weaker interaction(s) provides a mean of fine tuning for the achievement of very selective recognition processes. The porphyrin skeleton offers many advantages besides its photochemical and photophysical interesting properties, especially owing to its moderate conformational flexibility. Rigid and semi rigid platforms like calixarenes, cyclodextrins, or cyclotriveratrylene are frequently used to achieve a topographic control on the orientation of coordinating sites. Zinc(II)-porphyrins may play the exact same role if adequately functionalized, providing an additional strong interaction along the 4p$_z$ and 4d$_{z^2}$ orbitals of the zinc(II). Due to the strong UV-visible absorption of the porphyrin ring, zinc(II) complexes may also act as a spectral probe for the binding of substrates [4, 5].

The spectrophotometric features of porphyrins are due to the conjugation of 18π electrons allowing energetically inexpensive π–π^* transitions. The diagram in Figure 4 shows the electronic transitions involved in the UV-visible absorption spectrum of a D_{4h} ZnTPP,

Typical molar extinctions are in the range of 250,000 M^{-1} cm^{-1} for the B band called the Soret band ($S_0 \rightarrow S_2$), and of 5,000 to 35,000 M^{-1} cm^{-1} for the Q bands ($S_0 \rightarrow S_1$). Axial base coordination on the zinc generally pulls the metal cation out of the porphyrin plane, thus changing the symmetry and the energetic distribution of molecular orbitals, and inducing significant red shifts for both the Soret and Q bands [12]. A compilation of red shifts induced by coordination of a series of selected axial bases in solution can be found in reference [13].

As shown in Table 3, the amplitude of the red shift tends to correlate with the pKa of the base, except when the coordinating lone pair is located near bulky substituents (entry 6). However, axial coordination on the central zinc(II) cation is not very sensitive to slight pKa variations which is expected for a non-selective interaction, but the spectral variations observed when a substrate is bound to the metal provide a very efficient tool for the detection of the binding. Pioneering works of Collman [14], and other bio-organic or bio-inorganic chemists have demonstrated that the introduction of bulkiness at the periphery of the porphyrin

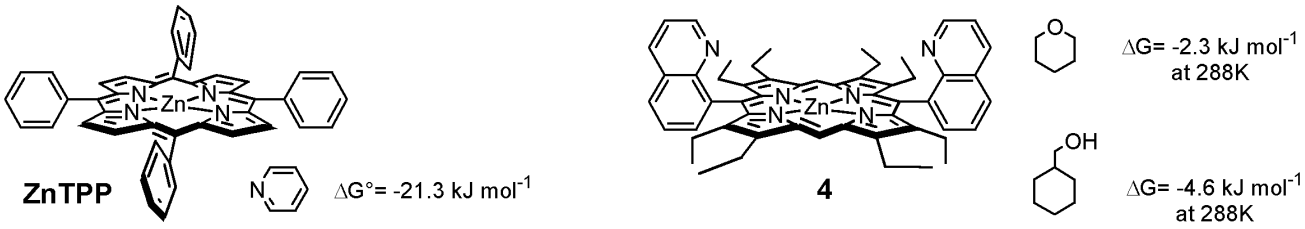


Figure 2. Reference values for binding free energies of N and O axial ligands.

Table 1. Comparative binding of pyridine by zinc(II)-protoporphyrin IX esters in chloroform and benzene [6]

Receptor	Solvent	Ka M^{-1}	ΔH^0 kJ mol^{-1}	ΔS^0 J mol^{-1} K^{-1}	ΔG^0 kJ mol^{-1}
ZnPP 3	Benzene	5795 ± 310	-45.7 ± 0.8	-81 ± 3	-21.5 ± 0.8
ZnMP 2	Benzene	5586 ± 339	-35.6 ± 0.4	-48 ± 2	-21.3 ± 0.4
ZnHP 1	Benzene	4694 ± 391	-33.1 ± 0.4	-41 ± 3	-20.9 ± 0.4
ZnPP 3	Chloroform	3267 ± 220	-25.4 ± 0.4	-18 ± 2	-20.0 ± 0.4
ZnMP 2	Chloroform	2590 ± 143	-29.2 ± 0.3	-33 ± 2	-19.4 ± 0.3
ZnHP 1	Chloroform	1136 ± 44	-24.6 ± 0.3	-24 ± 2	-17.4 ± 0.3

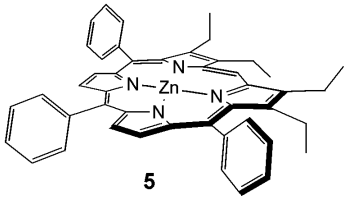


Figure 3. An unfunctionalized porphyrinic receptor.

core can be useful to control or modify the reactivity of the metallo-porphyrin [15]. Taking advantage of this bulk of information, porphyrins were rapidly incorporated in receptors to monitor and to achieve topographical control in the substrate binding. Thus, steric restrictions, or hydrogen bonds, as well as electrostatic interactions have been adequately positioned around the porphyrin skeleton. In addition, intrinsic chirality may exist in the porphyrin itself, or arise from the introduction of chiral groups around the ring in order to achieve chiral recognition.

Beside UV-visible spectrophotometry, various techniques may be used for the detection of the selective complexation. In particular, ^{1}H NMR provides excellent insights about the host/guest complex. Sanders and Hunter [16] did extensive conformational studies on the coordination of nitrogen ligands on zinc(II)-porphyrins dimers by ^{1}H NMR, and this technique is now routinely used to characterize inclusion complexes as the guest protons generally exhibit significant high field shifts when brought next to the ring current produced by the 18π e^- of the porphyrin.

Weak interactions contributing to the selection of guests range from -0.4 kJ mol^{-1} for London forces, van der Waals interactions, and steric requirements to -5.0 kJ mol^{-1} or more for hydrogen bonding. Electrostatic contributions will depend on the number of charges and the ionic strength of the medium but will be a function of (1/R) in the range of -10 kJ mol^{-1}. If a second coordination to a zinc(II)-porphyrin is present, its contribution will be in the same range as the first axial ligation (ca. -16 kJ mol^{-1}). Another type of non-covalent interaction has to be considered as π–π interactions may play a dual role. They will favor the binding but may also disfavor the binding if they are present in the free receptor (e.g., collapsible porphyrin dimers). The nature of these interactions has been very well investigated by Sanders and Hunter [17], giving an upper value of -65 kJ mol^{-1} for the enthalpic contribution to π-π interactions reinforced by strong electrostatic interactions.

Tuning zinc coordination with weak peripheral interactions

Introduction

The general features of receptors achieving multi-point recognition of organic substrates are summarized in Figure 5. These features will be the basic concept for the building of achiral as well as chiral receptors but the specificity of chiral porphyrins must be introduced at this point.

Chirality can be the consequence of introducing chiral groups on a symmetric porphyrin core, by simple substitution of the achiral porphyrin with chiral centers as shown in Figure 6a. Another way of rendering a tetra-aryl porphyrin chiral is to use the relative rigidity of the skeleton (Figure 6b), thus, breaking the D_{4h} symmetry by positioning two or more adequate substituents in the ortho positions of the phenyl group, and generate stable atropoisomers for which free rotation around the phenyl-meso link is no longer possible at room temperature. For example, the bottom left porphyrin will not racemize at room temperature if it bears substituents other than H in β positions. The anchoring of appropriate substituents in β positions of the pyrrole

Table 2. Association constants (Ka) and corresponding binding energies of amino-acid methylesters with porphyrin **5**

Entry	1	2	3	4	5	6	7	8
Substrate	Ile	Leu	Val	Pro	Phe	Ala	Leu*	Ser*
Ka M^{-1}	1 420	1 130	1 240	13 200	1 770	740	1 060	480
ΔG kJ mol^{-1}	−17.4	−16.8	−17.0	−22.7	−17.8	−15.8	−16.7	−14.8

At 288 K in $CHCl_3$. Standard deviations of Ka within 4%, adapted from reference 11, (*) as benzyl esters.

Table 3. Soret and Q band displacements upon coordination of axial bases in porphyrin grids

Entry	Base	pKa	λ_{max} Soret (nm)	λ_{max} Q (nm)	λ_{max} Q′ (nm)
1	None		418	546	580
2	3,5-Dibromopyridine	0.82	426	550	584
3	Pyrimidine	1.31	426	550	586
4	Pyridine	5.21	429	552	586
5	3,5-Lutidine	6.14	430	554	586
6	2,6-Lutidine	6.62	422	548	578
7	4-*t*-Bu-pyridine	5.99	432	554	588
8	N-Me-Imidazole	7.30	430	556	588

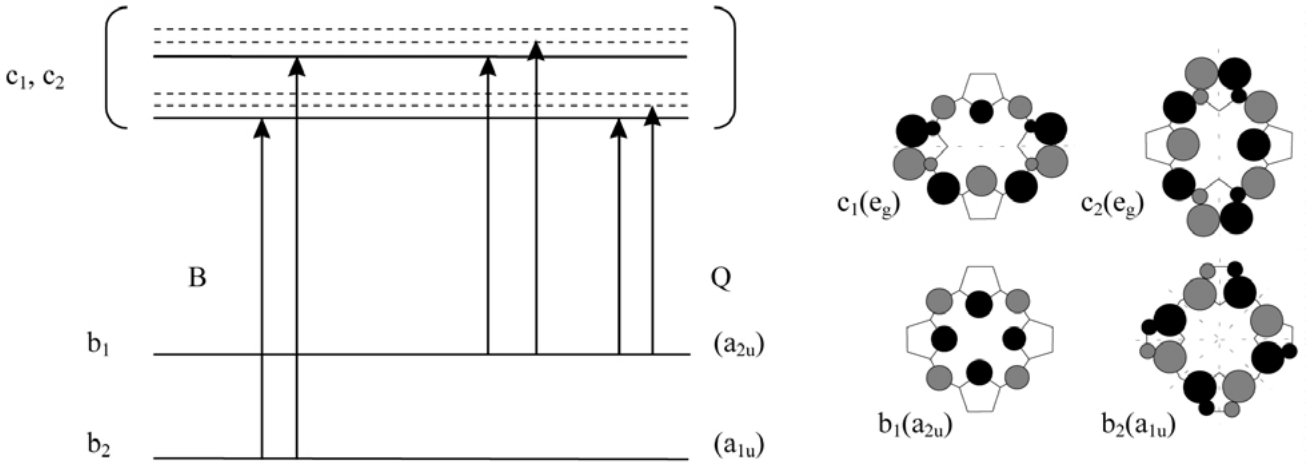


Figure 4. HOMO-LUMO electronic transitions for a D_{4h} porphyrin.

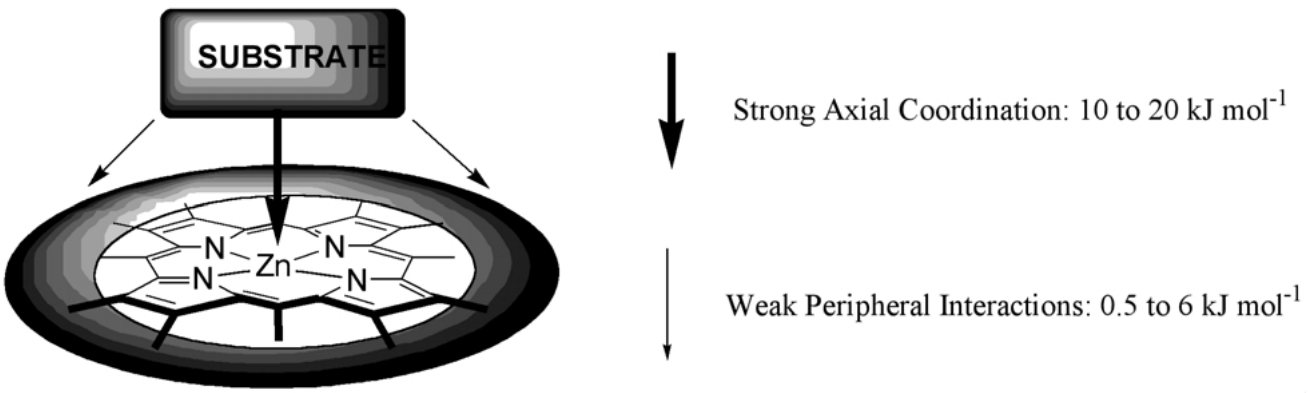


Figure 5. Generalized multipoint recognition with zinc(II)-porphyrin receptors.

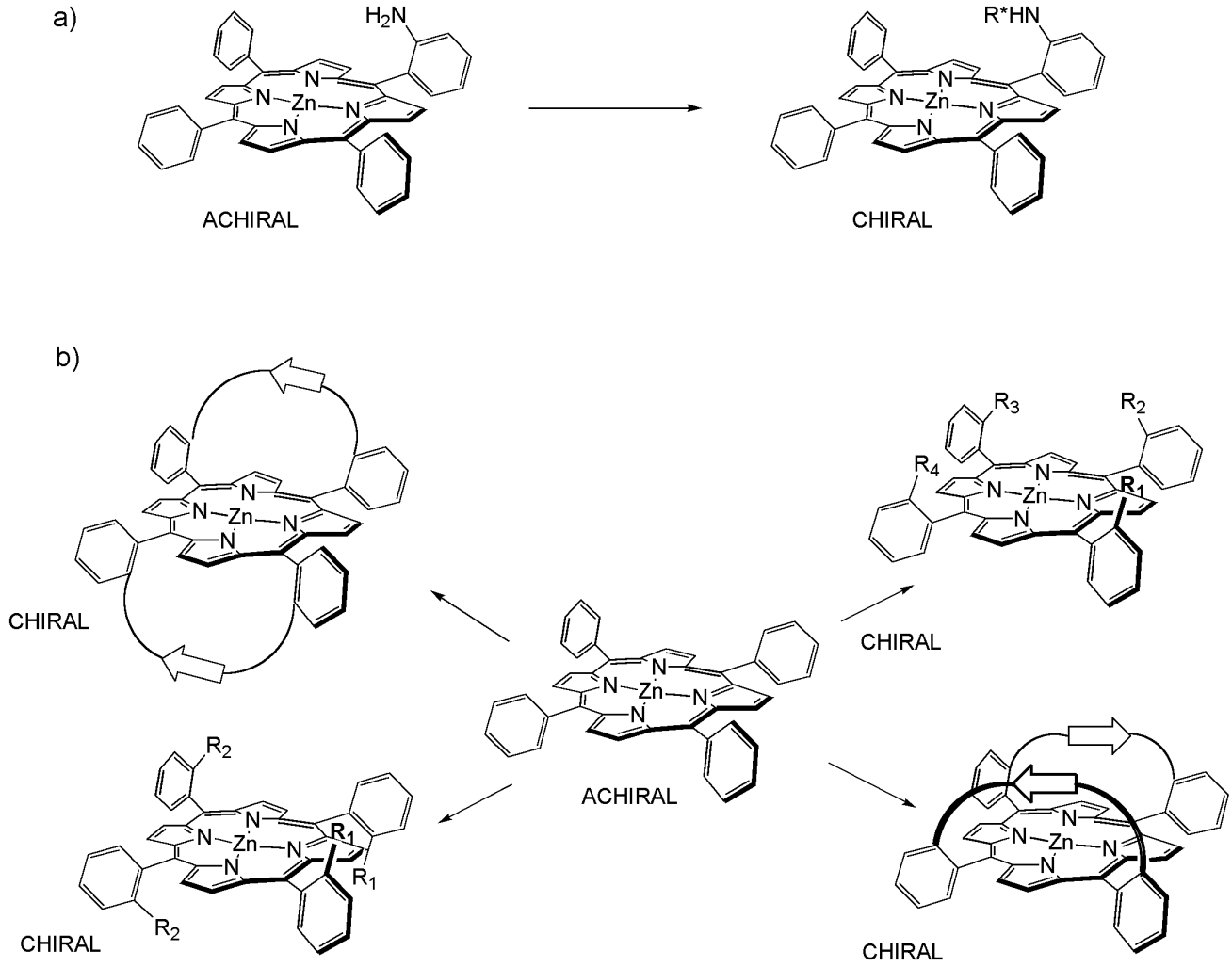


Figure 6. Five different ways of making a chiral porphyrin from an achiral porphyrinic core.

rings itself can also lead to intrinsic chirality [3, 18], but this method is seldom used and phenyl functionalization is usually predominant in the preparation of receptors.

Achiral recognition by zinc(II)-porphyrin receptors

In general, achiral receptors based on zinc(II)-porphyrins are involved in non stereo-selective recognition. However, examples in which chirality can be detected or generated with and from achiral porphyrin derivatives have been reported. Even though the receptors themselves are achiral, those examples will be treated later.

Steric and H-bonding discrimination of substrates by superstructured zinc(II)-porphyrins

Picket-fence type zinc(II)-porphyrins. The exhaustive review of Ogoshi *et al.* [3] provides an excellent coverage of this field up until the end of 1998, and only selected examples that are either complementary or introductory to more recent papers will be presented here. The term "picket-fence porphyrin" will apply to any porphyrin bearing functional peripheral groups, even though these groups are sometimes not bulky enough to be considered as pickets.

Several picket-fence zinc(II)-porphyrin derivatives have been studied by Imai and Kyuno [7], and their affinities for pyridine, piperidine, and quinoline have been determined in toluene and other non coordinating solvents. Their results illustrate the importance of the atropoisomerism in porphyrinic receptors as they have demonstrated that the trans-α^2 atropoisomer of various picket-fence zinc(II)-porphyrins have higher affinities with pyridine and quinoline axial ligands than the α^4 atropoisomer.

This study emphasizes two basic concepts. The first concept is the steric selection of the axial ligand. This is achieved with the α^4 atropoisomer for which some obvious steric repulsion directs the binding on the open face of the porphyrin. Consequently, as this side is lacking peripheral substitution, only non selective binding is observed, and the small variations may be attributed to distortions in the porphyrin skeleton. The second concept is that interactions as weak as CH—π interactions can contribute to enhance the affinity of the receptor for an aromatic axial ligand in the cases of trans-α^2 atropoisomers. Studies of the chemical shift variations (slight upfield shift of the alkyl protons) during complexation for both pyridine or isoquinoline adducts confirmed the insertion of the aromatic guest in between

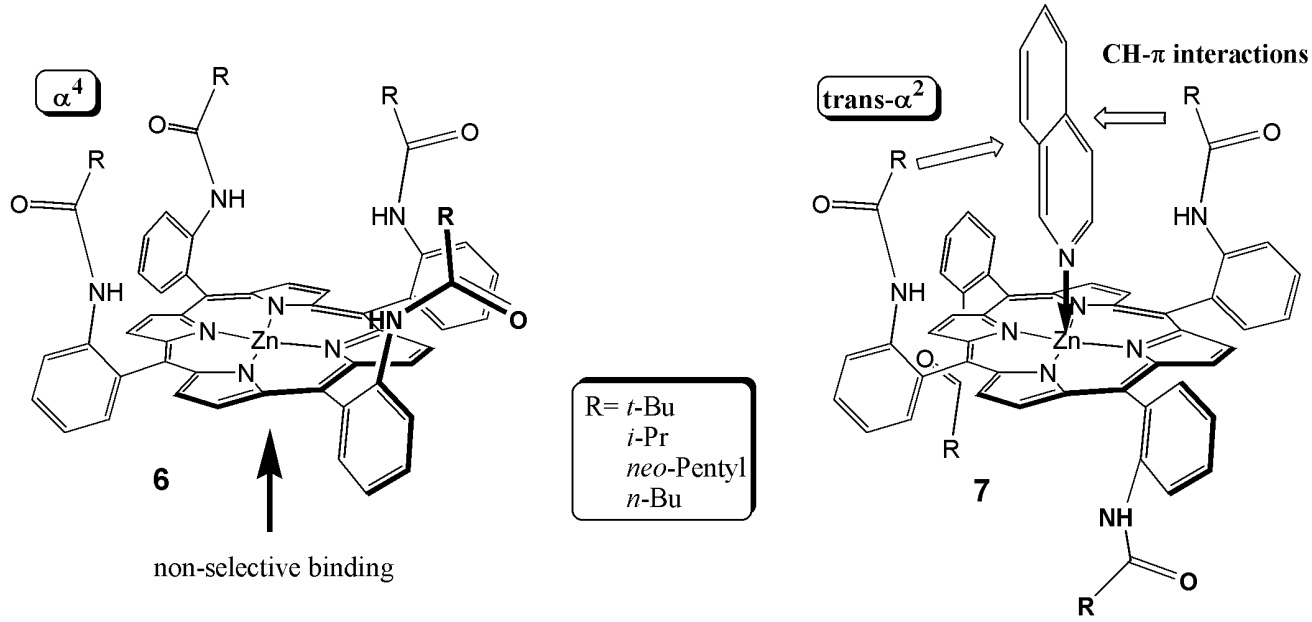


Figure 7. Two atropoisomers of picket-fence porphyrins (R = *t*-Bu, ZnTPPiv).

Table 4. Binding free energies of pyridine and isoquinoline with ZnTPPiv and analogues in toluene. (10% error)

Substrate	Atropoisomer	$\Delta G^0_{t\text{-Bu}}$ (kJ mol^{-1})	$\Delta G^0_{i\text{-Pr}}$ (kJ mol^{-1})	$\Delta G^0_{\text{neo-Pentyl}}$ (kJ mol^{-1})	$\Delta G_{n\text{-Bu}}$ (kJ mol^{-1})
	**6** (α^4)	−24.9	−26.2	−25.2	−25.9
	7 (trans-α^2)	−32.3	−30.0	−28.6	−28.4
	**6** (α^4)	−25.5	−26.9	−25.9	−26.7
	7 (trans-α^2)	−34.1	−32.2	−30.3	−30.0

Binding free energy of pyridine to ZnTPP in these conditions: $\Delta G^0 = -21.6$ kJ mol^{-1}.

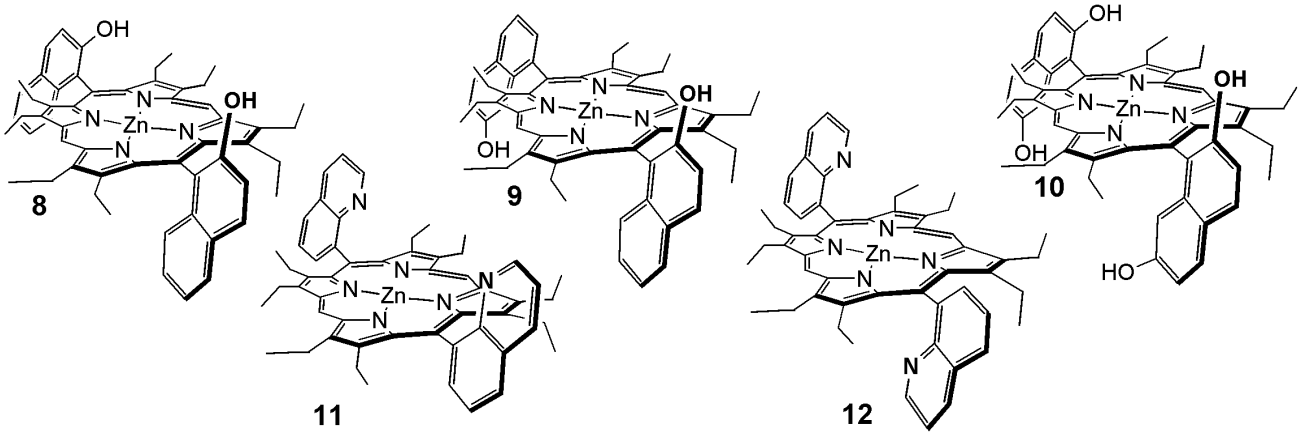


Figure 8. Five receptors for pyranosides and amino-acid esters [8, 20, 21].

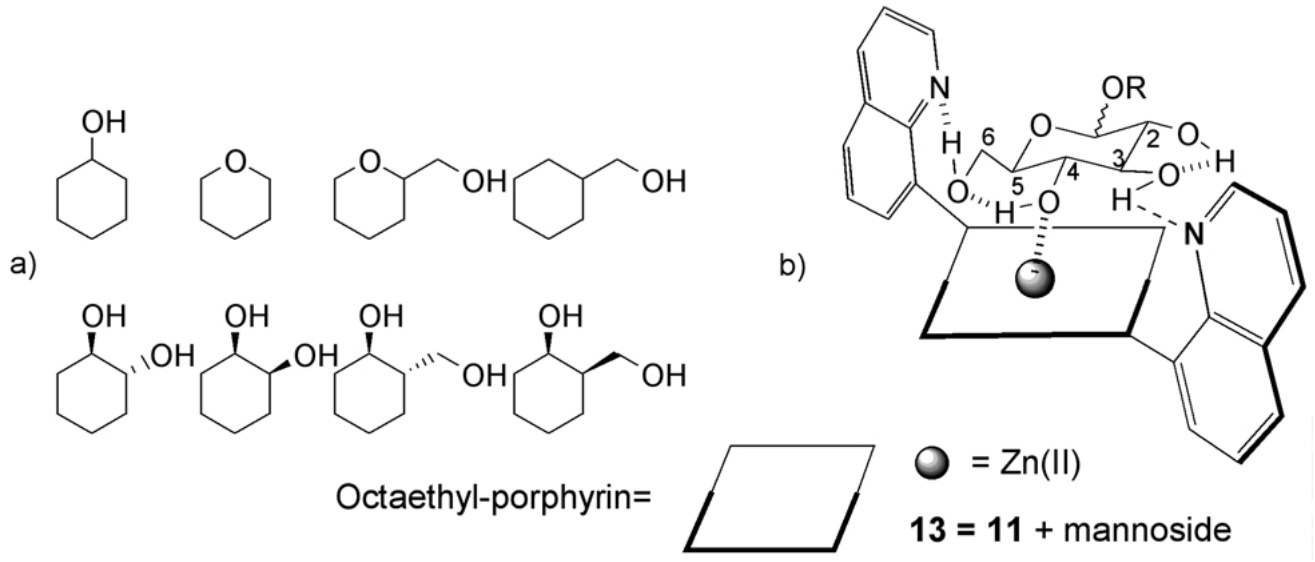


Figure 9. (a) Test substrate for pyranoside receptors; (b) proposed binding mode for β-mannoside.

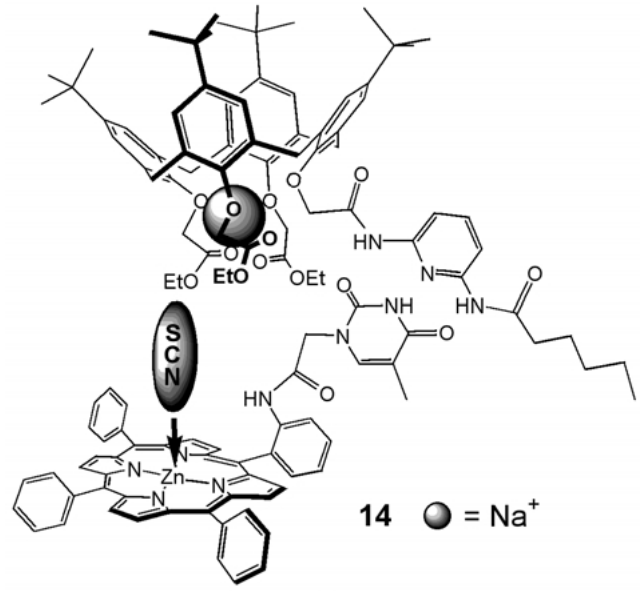


Figure 10. Simultaneous binding of cations and anions with a self-assembled receptor.

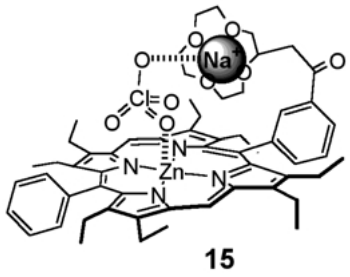


Figure 11. Simultaneous binding of cations and anions with a pre-assembled receptor.

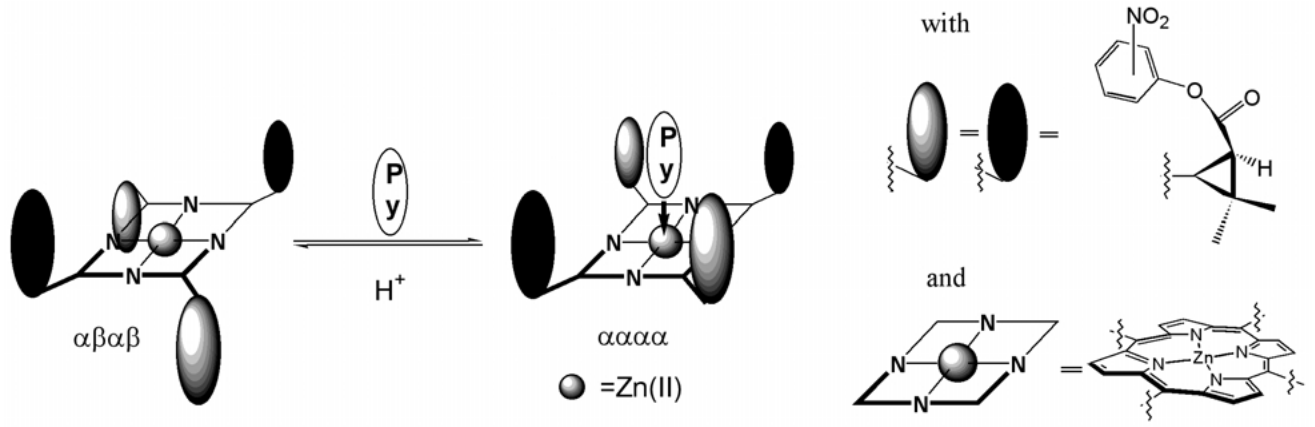


Figure 12. Venus-flytrap zinc(II)-porphyrin displaying reversible conformational changes [27].

the pickets. Even though CH—π interactions are not that energetic, the entropy loss during complexation is certainly compensated by the release of an axial solvent molecule (in coordinating solvents).

The use of peripheral interactions to select substrates has been efficiently applied to the recognition of pyranoside and to amino-acids by Ogoshi and Mizutani [19]. The receptors used (**8** and **9**) were initially designed for the binding of nucleobases by either H-bonding or coordination, but did not combine the two binding modes. Even though the receptors shown below are not chiral, some aspects will be discussed in more detail in the part of this manuscript that will describe stereoselective recognition.

Receptors **8**, **9**, and **10**, have been employed to demonstrate that the adequate positioning of two hydrogen bond donors or acceptors allows differentiation, in chloroform, of β-octyl mannopyranoside ($\Delta G = -27.2$ kJ mol^{-1} for **11**, and $\Delta G = -24.8$ kJ mol^{-1} for **12** at 303 K) [8, 20] and β-galactopyranoside ($\Delta G = -26.2$ kJ mol^{-1} for **11**) among other pyranosides derivatives, as well as aspartate dimethyl ester ($\Delta G = -26.5$ kJ mol^{-1} at 288 K for **10**) compared to the methyl ester of Leu ($\Delta G = -23.5$ kJ mol^{-1} at 288 K for **10**) [21].

Test substrates represented in Figure 9 have been used to demonstrate that for the example of mannoside, the recognition process involves both the coordination of the 4-OH to the zinc, and H-bond formation between the quinoline nitrogens and the hydroxyl group in position 3 and 6 (Figure 9b). The presence of a stabilizing interaction between the 2-OH group and the neighboring H-bound 3-OH has been controlled by comparison with the 2-OMe derivative. In addition, the binding of mannoside derivatives to **10** induced a biphasic CD spectrum, and this aspect will be discussed later when dealing with stereoselective recognition.

An interesting use of H-bonding sites located at the periphery of a porphyrin has been described by Rudkevich and Reinhoudt [22]. A thymine has been anchored to a Zn(II)-TPP derivative and bound to a complementary cone shaped calix[4]arene-triester bearing a diamido pyridine (Figure 10). Similar H-bonding sites had been previously attached to porphyrins but were used for spontaneous assembling of multi-chromophoric electron transfer systems [23]. In this elegant system, both the variations of chemical shifts (diamido pyridine and thymine) and the red shift of the Soret band can be used to monitor, by respectively ^{1}H NMR or UV-visible, not only the synergic binding of the cationic species in the calixarene moiety, and the anion axial coordination of the thiocyanate, but also the assembling of the complete receptor.

Recently, a similar example has been described by Tanaka *et al.* [24] and the receptor **15** (Figure 11) has been designed for the recognition of ionic substrates. Sodium thiocyanate surprisingly gives a 1:2 (host:guest) stoichiometry, a 3 nm red shift being assigned to anion coordination on the central zinc, while sodium perchlorate is captured with a ΔG^0 of -30.6 kJ mol^{-1}, and sodium iodide comprises a spherical anion too large to act as a bridge between the zinc and the sodium cation.

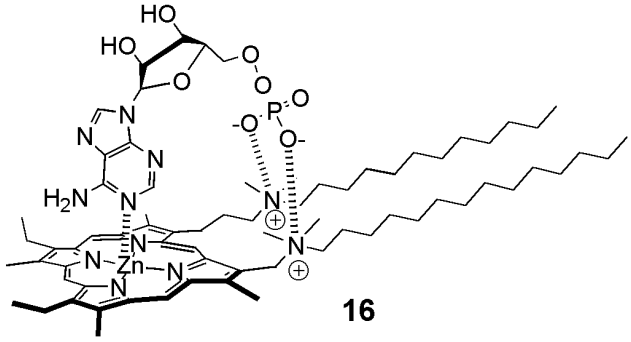


Figure 13. A zinc(II)-porphyrin AMP carrier.

In the latter example, it is obvious that the receptor has to be reshaped from the original free receptor, in order to achieve the recognition of the ion pair. Conformational changes due to complexation are not very common but extremely interesting with regards to information storage. This "induced fit" process was introduced a long time ago, and reviewed recently by Koshland [25], and an efficient "read and write" system involving a free base porphyrin based on this concept has been described by Aida *et al.* [26]. Around the same time, Marchon *et al.* [27] have reported a flytrap porphyrin that is intrinsically chiral but displays conformational changes upon pyridine complexation. The principle of the flytrap is summarized in Figure 12.

In this case, the peripheral interactions developed with the substrate are donor-acceptor interactions between the electron rich pyridine and the nitrophenyl substituted peripheral arylesters. Stronger bases, like 3,5-lutidine or 4-methyl pyridine are more efficient than pyridine. Indeed, the $\alpha\alpha\alpha\alpha/\alpha\beta\alpha\beta$ ratio in the presence of 10 equivalents of guest is >100 for lutidine and >2.0 for methylpyridine compared to 1.2 for pyridine.

Pure electrostatic interactions can also contribute to enhance the recognition and the binding of charged substrates. A zinc(II)-porphyrinic receptor bearing two ammonium groups on one side of the porphyrin plane (Figure 13) has been used by the group of Ogoshi [28] for the selective transport of nucleotides across an organic liquid membrane. Competition between AMP, GMP CMP, UMP, revealed that receptor **16** is highly selective for the transport of AMP.

A last example of a zinc(II) porphyrinic receptor with additional peripheral interactions has been recently described by Sanders, who used peripheral coordination sites to control the spatial arrangement of a porphyrin guest in a porphyrin receptor [29] as shown in Figure 14. In this case, the binding of Sn(IV) by the carboxylate moieties and the binding of Zn(II) by the pyridine are highly synergistic.

Additional coordination of the external pyridine can be used to control and lock the binding of the opposite pyridine to the zinc(II)-porphyrinic receptor, as shown by the solution structure established by bi-dimensional ^{1}H NMR.

Strapped and basket-handle zinc(II)-porphyrins. Following the path that led bioinorganic chemists from picket-fenced porphyrins to strapped porphyrins because it provided better control in the selection of exogenic substrates like O_2

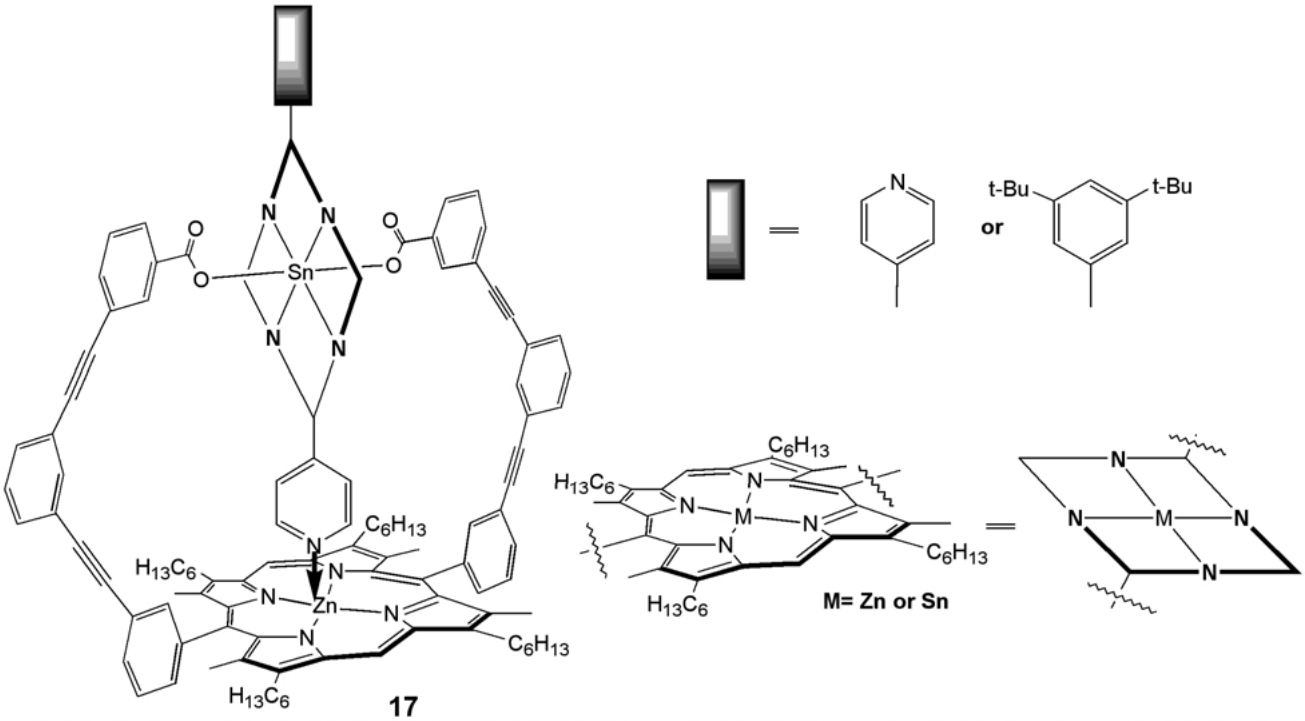


Figure 14. Rotaxane based on specific binding abilities of carboxylates for Sn(IV) and pyridine for Zn(II).

or CO [30, 31], supramolecular chemists have developed porphyrinic receptors bearing straps oriented either across the porphyrin plane (strapped), or along the side of the porphyrin plane (basket-handle). From both points of view, bioinorganic chemistry and molecular recognition, the starting point is a steric selection of the substrate, but very rapidly functionnalized straps have been introduced in order to use the strap(s) as a support for the proper positioning of H-bonding or coordinating sites. In natural systems, H-bonding is also involved in selective assembling processes like aggregate formation [32], and anchoring to proteins and membranes [33, 34]. Water molecules may play a crucial role in bridging H-bond donors and H-bond acceptors, leading to superstructures [35], and H-bonding may originate from a water molecule coordinated axially to a metalloporphyrin. A confirmation of the role of water in the three dimensional structure of a peridin-chlorophyll light harvesting complex has been reported by Hofmann and Welte [36]. In this case, the pigment is in contact via a H-bond (water coordinated to central Mg) with an imidazole ring from histidine, which is stacked with ring II of the chlorophyll. Thus, the use of straps brings a steric control of the approach of the substrate, plus, if needed, the possibility to precisely locate H-bond donors and acceptors, or lipophilic cavities above the plane of the porphyrin.

Hence, various straps have been attached to zinc(II)-porphyrins in order to control the binding of substrate. These straps may be quite complicated in order to achieve precise functions, and zinc(II) usually used for binding studies is further replaced by less inert species, such as iron(II), in order to perform chemical transformation of substrates. For example, Diederich *et al.* [37] have described the synthesis of porphyrin-cyclophanes **18** and **19** (Figure 15) which were designed to mimic cytochrome P-450 activity after replacement of zinc(II) by iron(II). When the nitrogens are not quaternarized, binding arises from metal coordination and typical lock and key features that are expected in organic solvents. When the nitrogens are quaternarized, binding of pyridine occurs in methanol with a $\Delta G = -11.2$ kJ/mol at 293 K, indicating competition between pyridine and methanol in the binding process. It should be noted that with this set of receptors, no variation of chemical shifts are observed with polyaromatic substrates, thus precluding the existence of lipophilic interactions between the substrate and the receptors [38]. Binding of polyaromatic substrates without zinc coordination [39a] takes place only when the strap contains a typical cyclophane receptor as already described in earlier papers by Diederich [39b].

Kyuno and Imai [10] have described a similar type of receptor and have prepared a "bis-roof" porphyrin **20** (Figure 16). Exhaustive binding studies with a variety of amines and imines provide evidence for very little discrimination among primary amine ligands, versus a shape selective recognition for secondary amines. A maximum selectivity is observed for substrate **az** ($\Delta G = -37$ kJ mol^{-1} in toluene at 293 K), while **pyr** and **py** in the same conditions are bound with respective ΔGs of -34 kJ mol^{-1} and -19 kJ mol^{-1}, which in the case of **py** is lower than what is observed for classical "picket fence" type porphyrins.

Although rigidity does not necessarily account for enhanced binding abilities, achieving selectivity by targeting specific functional groups of the substrate may result in both selective and enhanced binding. The phenanthroline strapped porphyrin **21** [40] represented in Figure 17 was initially prepared in order to allow the binding of imidazolates in its zinc(II)–copper(I), [41] and later on, its

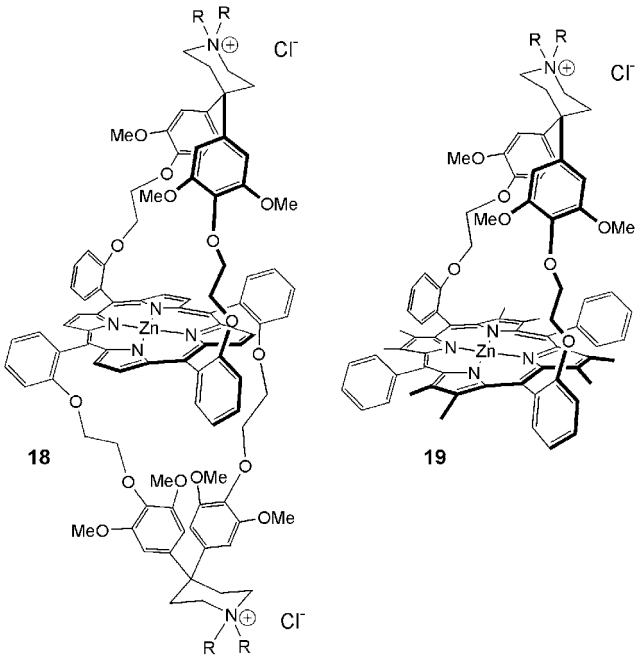


Figure 15. Porphyrin-cyclophanes as cytochrome P-450 structural analogs.

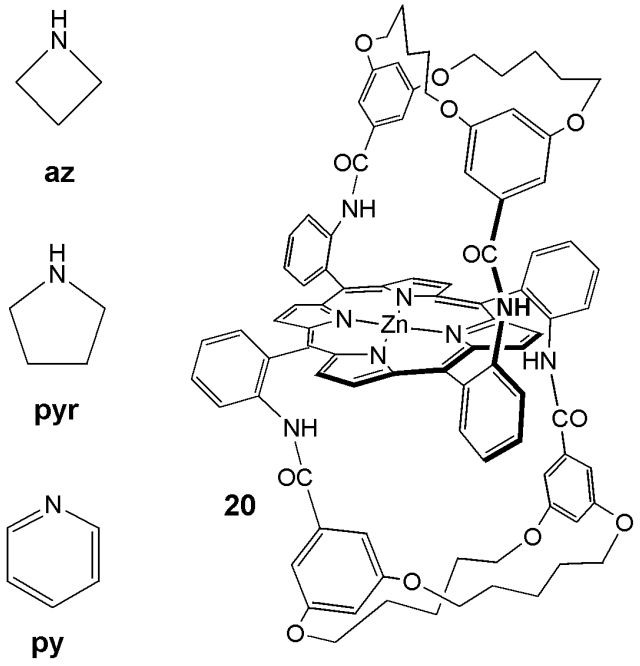


Figure 16. Bis-roof zinc (II)-porphyrins and their substrates.

iron(II)–copper(I) binuclear complex. The distance between the zinc(II) central metal of the porphyrin subunit and the phenanthroline coordinating site is well suited to provide an efficient and selective binding of *N*-unsubstituted imidazoles. In its structure, receptor **21** contains a rigid strap that usually accounts for selective binding of the substrates on the open face of the metalloporphyrin, but this segregation is efficient only when based on size exclusion, with no additional interactions present. In the case of **21**, the phenanthroline nitrogen atoms provide not only a second coordination site for a metal [42] but also two H-bond acceptors. In presence of *N*-methylimidazole and pyridine (excess), the

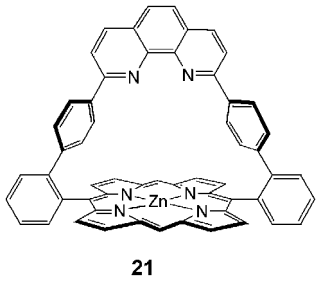


Figure 17. A highly rigid strapped porphyrin.

expected binding on the open face of the receptor occurs, whereas when *N*-unsubstituted imidazoles are used as substrates, the formation of very stable host-guest complexes is observed in methylene chloride and chloroform [43]. The stability constants of various inclusion complexes are summarized in Table 5, and it is remarkable that even with bulky substituents in the 2 position of the imidazole guest, efficient binding within the cavity is observed [44].

The estimated contribution of weak interactions to the strongest binding of imidazole derivatives in the phenanthroline pocket (2-methyl imidazole) can be obtained from comparison of the binding to Zn(II)-TPP in the same conditions ($\Delta G^0 = -30.7$ kJ/mol) and corresponds to a value of -9.7 kJ/mol. Considering that two equivalent hydrogen bonds are formed between the pyrrolic proton of the imidazole and both phenanthroline nitrogen atoms, this value corresponds to a ΔG of -4.8 kJ/mol per H bond.

Initially, the diphenyl-phenanthroline strap has been considered as "rigid", but a series of crystallographic structures have provided good evidence for its considerable flexibility which is partly responsible for allowing the recognition of bulkier substrates. Five ORTEPs are collected in Figure 18 and show the drastic modification of the dihedral angles between the porphyrin plane and the meso phenyl groups bearing the phenanthroline strap.

It should be noted that the very high constant observed for the binding of 2-methyl imidazole allows a precise determination concerning the solution structure of the inclusion complex. A very weak dissociation and a very slow exchange rate between the host–guest complex and free receptor/ligand is evident from simple ^{1}H NMR titration experiments [43], resolved peaks are also observed for both the host–guest complex and the free receptor below the 1:1 stoichiometry. In the case of the 2-methyl-imidazole guest, a ROESY experiment clearly shows respective correlations between the protons of the phenyl spacer, H_0, and the upper proton of the imidazole guest (H_5), and H_m and the methyl group of the guest shielded to -2.5 ppm.

The structure of the free receptor shows that two molecules of water are strongly held in the cavity by several H-bonds and CH—O interactions. The uncoordinated (to the zinc) water plays a crucial role in the solid state herringbone arrangement observed in the crystal [45]. The entropic contribution of their release during the complexation of the guests has yet to be established but the presence of very localized hydrates is important regarding the role of water in "pigment-protein" interactions for example [36]. Earlier re-

Table 5. Association constants and binding free energies of imidazole derivatives with receptor **21**

Substrate	Pyridine	*N*-Me imidazole	Imidazole	2-Me imidazole	2-Ph imidazole
K_{ass} (M^{-1})	1,990	50,100	1,259,000	19,500,000	2,550,000
ΔG^0 kJ mol^{-1}	−18.7	−26.7	−34.6	−41.4	−36.4

Error 5%. All data collected in CH_2Cl_2 and determined by UV-visible titrations according to the method described by Anzai *et al.* in reference [46].

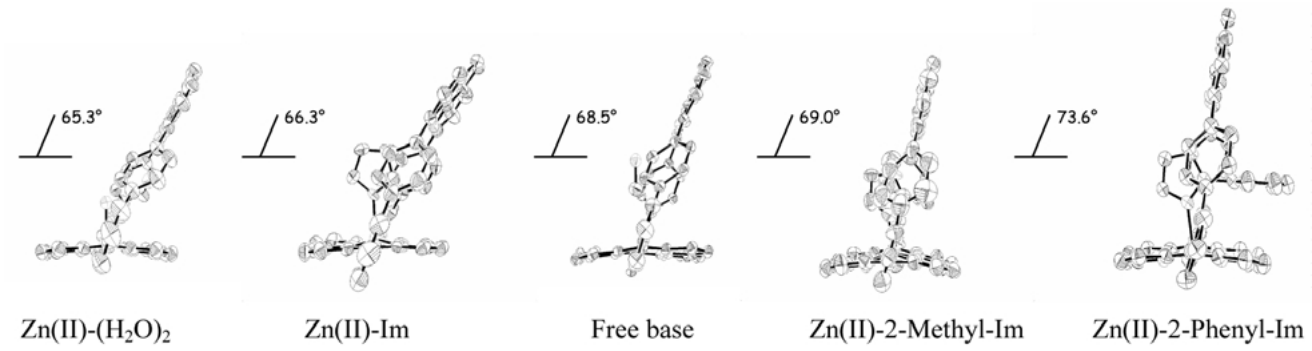


Figure 18. Induced-fit adjustment of the dihedral angle between the meso phenyl spacers and the porphyrin plane of receptor **21** observed by X-ray crystallography.

ports from Guilard and Smith [47a] have described receptors bearing crown-ethers as straps, one of them crystallizing in the presence of a water molecule guest bound to the zinc(II) and developing two H-bonds (1.93 and 1.83 Å) with oxygen atoms of the crown. Multiply bound water on a zinc(II)-porphyrin bearing Kemp's acid derivative have also been observed, along with imidazole binding by the free base by Chang *et al.* [47b].

More recently, diphenylglycouril clips extensively used by the group of Nolte [48] have been introduced into two porphyrinic architectures **22** and **24** [48]. These clips combine lipophillic interactions, directed H-bonds, and donor-acceptor "π inter-actions" to complex various guests even in the absence of a porphyrinic core, which provides an excellent opportunity to identify the contribution of weak interactions in the presence, and absence of zinc(II) coordination. The two zinc(II) porphyrin receptors in Figure 19 can bind guests in their clefts via a combination of π interactions, H-bonds, and electrostatic interactions (with charged guests), and differ mainly by the size and the flexibility of the cavity. The binding free energies of hosts **22**–**25** with the series of guests **G1**–**G7** compared with those of the diphenylglycouril unit alone **26** are collected in Table 6.

Clearly, the more flexible hosts **24** and **25** display weaker binding than strongly preorganized hosts. The enhancement of the binding for guests small enough to fit the rigid cavity (**G6** in **23**) shows that the precise orientation of additional H-bonds plus π interactions between the guest and the lipophillic cavity greatly enhance the binding of axial bases.

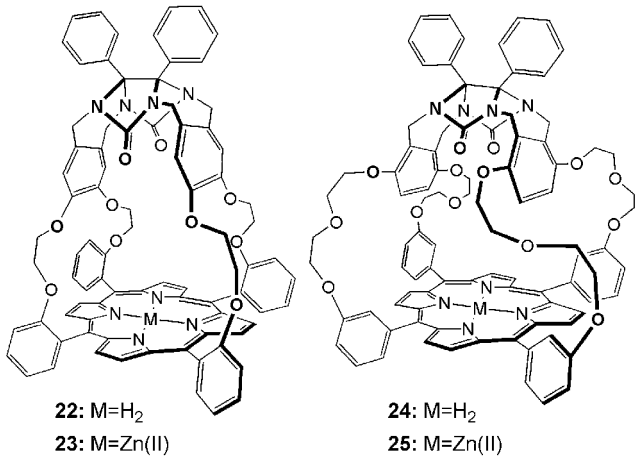


Figure 19. Two glycouril zinc(II)-porphyrins receptors.

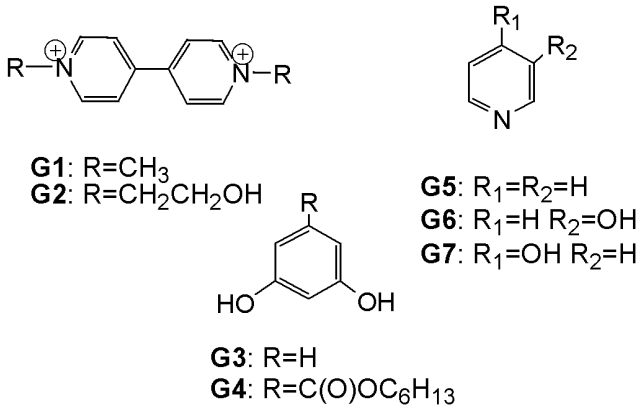


Figure 20. Guests for diphenylglycouril capped zinc(II)-porphyrin receptors.

Multiple zinc coordination in porphyrin oligomers

The existence of additional H-bonds is not necessarily directly related to the enhanced binding of the guest but may also provide an assembling tool for a more adequately complexing species, as the formation of porphyrin dimers by

Table 6. Binding free energies of hosts **22–25** with guests **G1–G7** [48]

Guest	**22**	**23**	**24**	**25**	**26**
G1[a]	−32.9[e]	−33.8[e]	−17.4[d]	−20.2[d]	
G2[a]	−39.2[f]		−20.2[d]	−22.8[e]	
G3	−19.1[d]	−17.9[d]	−17.9[d]	−15.1[d]	−19.5[d]
G4	−15.5[d]	−16.6[d]	−19.0[d]	−20.8[d]	−24.1[d]
G5		−28.8[e]		−23.6[e]	
G6		−42.7[f]		−38.1[f]	
G7		−25.1[e]		−28.0[e]	

[a] In $CHCl_3/CH_3CN$ (1/1 in volume).
[b] In $CDCl_3$.
[c] In $CHCl_3$.
Estimated error:
[d] 10%.
[e] 30%.
[f] 50%.
Values for host **26** from ref. [49].

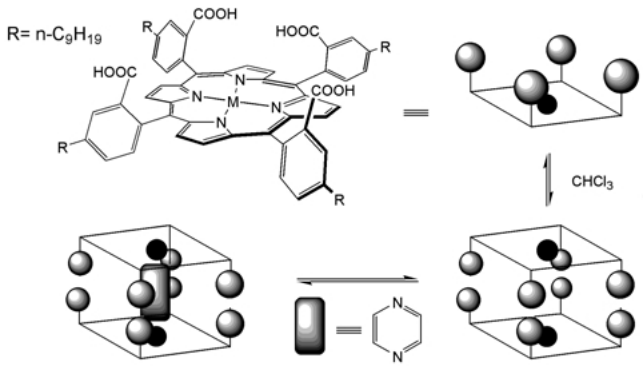


Figure 21. A self-assembling of a receptor induced by pyrazine.

induced-fit processes has been described by Ogoshi *et al.* [50].

In this case, α^4 atropo-isomers of 5,10,15,20-tetra (*o*-carboxy-phenyl) porphyrinatozinc derivatives are brought together by the binding of pyrazine in chloroform with constants up to 10^7 M (approx. $\Delta G^0 = -40$ kJ/mol in $CHCl_3$). This corresponds roughly to an additive interaction of two zinc(II) coordinations by the nitrogen atoms of the pyrazine ligand, but demonstrates that due to the spontaneous assembling of the dimeric species, no binding energy is "wasted" in the organization of the receptor. Earlier examples by Sanders [51] allow for comparison with systems in which assembling of the dimer species is not a prerequisite to the binding of a bidentate base. In this case the conformation of a cyclic dimer is changed by the addition of diazabicyclooctane. Entropy is necessarily gained from the use of a covalently linked dimeric receptor and high stability of the host–guest complexes is obtained with a high $\Delta G^0 = -44.7$ kJ/mol for receptor **27** (Figure 22). Less flexible receptors and reference monomeric species have also been used in order to estimate the energetic parameters controlling the release and the exchange rates of diaza-bicylo[2,2,2]octane (DABCO) guests by variable temperature ^{1}H NMR.

More flexible links between potentially cofacial architectures have been described, and among these a peptidic chain has been used as spacer by Voyer and Maltais [52].

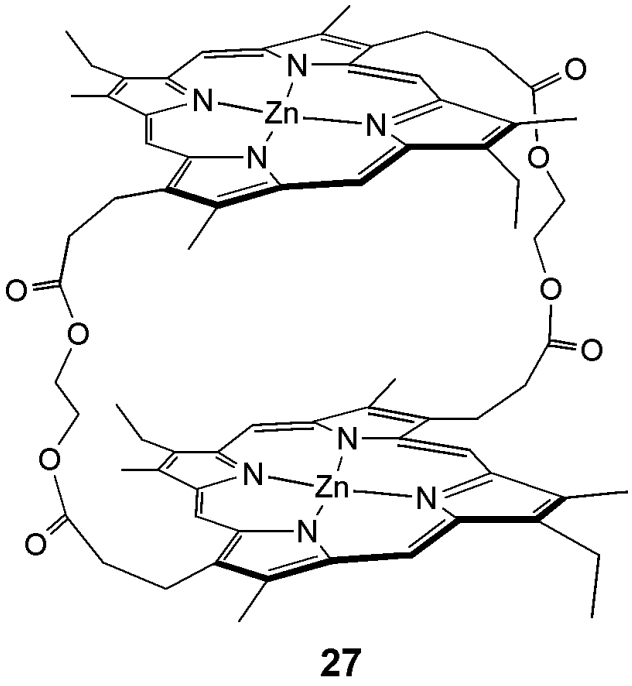


Figure 22. A flexible porphyrin dimer.

The conformation of the peptidic chain did not preorganize the ditopic receptor for complexation as no excitonic coupling (blue shift for cofacial structures) has been observed, but addition of diamines provoked the rearrangement of the structure, and in the case of short diamines, self-induced a cofacial arrangement of the porphyrin dimer. Contrary to the case of the assembling dimers (*vide supra*), part of the binding energy is probably consumed in the reorganization of the receptor when a short interchromophore distance is required (entry 1 and 2 Table 7). In the case of short diamines, the association is in the same order of magnitude as for a monomeric reference compound and propylamine. A better match of the diamine length and the Ala-Ala spacer provides the highest binding constant but weak energetic coupling between the two chromophores (2 nm blue shift).

Very rigid dimers for which almost no receptor rearrangement could account for an energy consumption have been described quite recently by Sanders [53]. In this case, the unexpected binding of the guest in the cavity of the receptor **28** has been observed. The most remarkable result is the binding of 4-*t*Bu-pyridine in the cavity of the receptor in a 1/1 stoichiometry with $\Delta G^0 = -33.3$ kJ mol^{-1} in toluene while the monomer binds the same substrate with a $\Delta G^0 = -23.5$ kJ mol^{-1} in the same conditions. Assuming that a coordinated solvent molecule may be present on each zinc inside the cavity in the free ligand state, the ΔG^0 gain may be due to entropy gained during the complexation process.

A very similar approach leads to inclusion of C_{60} within the cavity of receptor **29**, taking in account that the length of 4,4′-bipyridine is similar to the diameter of C_{60} [54]. The reported ΔG^0 is −33.1 kJ mol^{-1} and chromatographic separation of the inclusion complex is possible. The flexible nature of the linker is in part responsible for allowing strong π interactions between the surface of the porphyrin

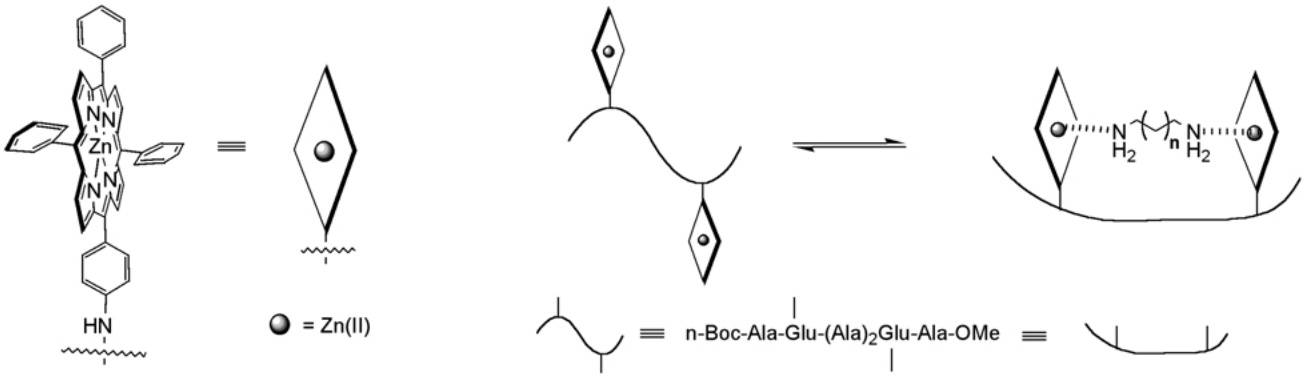
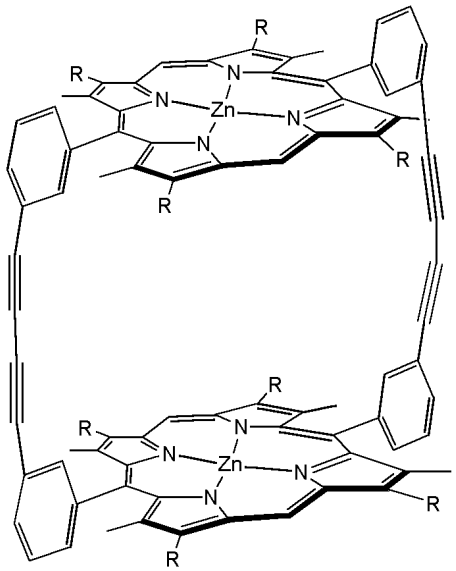


Figure 23. Conformational changes in porphyrin dimers appended to a polypeptide backbone upon complexation of diamines.

Table 7. Binding free energies of diamines in a porphyrin dimer with peptidic backbone

Entry	1	2	3	4	5	6	7
n	0	1	2	3	4	5	6
Kass (M^{-1})	6.2×10^5	7.6×10^5	3.3×10^8	1.0×10^9	1.3×10^7	2.2×10^8	4.7×10^7
$\Delta G^{)}$ (kJ mol^{-1})	−32.9	−33.4	−48.4	−51.1	−40.4	−47.3	−43.6

5% error. In CH_2Cl_2. Binding constants to monomer reference in the range of 1.1 to 2.9×10^5 M^{-1}.



28 R= $CH_2CO_2(CH_2)_2CH(CH_3)(CH_2)_3CH(CH_3)_2$

Figure 24. A rigid dimer displaying unexpected binding of guests within its cavity.

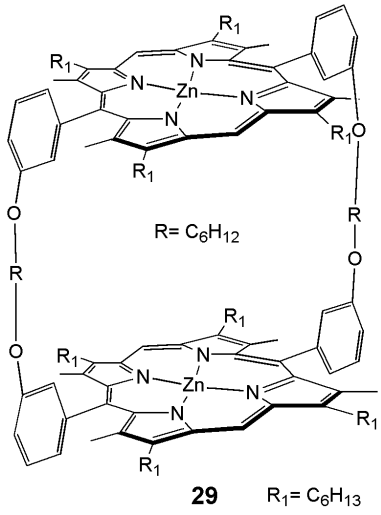


Figure 25. A flexible host for C_{60}.

rings with the surface of C_{60} as the corresponding rigid acetylenic precursor (R = CH_2-C_4-CH_2) did not lead to complex formation with fullerene.

An interesting approach to allosteric receptors recently described by Kubo [55], concerns a flexible dimer possessing a peripheral crown ether binding site for Ba^{2+}. The dimer **30** (Figure 26) displays relatively high affinity for its diamine guest ($\Delta G^0 = -33.5$ kJ mol^{-1} in CH_2Cl_2/CH_3CN, 9:1) but progressive release of the latter is observed in the presence of barium perchlorate. Reciprocally, the extraction efficiency versus barium in biphasic systems is reduced when the represented diamine is added to the organic phase.

Oligomer species are also able to achieve multipoint recognition, as they provide more than two coordinating sites and allow for the formation of several strong interactions. In that case, rigidity of the species strongly controls the binding of the substrate as demonstrated by the comparative properties of trimers **31** and **32** [56]. The floppy receptor **32** displays induced-fit properties and atroposiomerisation in the presence of rigid bidentates like DABCO (diazabicyclo[2,2,2]octane) and tris-pyridyl-triazine. In the case of **31** the latter conformational change is not possible and the cavity is extremely rigid, as previously shown by the promotion of a stereoselective Diels-Alder reaction within the cavity between coordinating dienes and dienophiles [57].

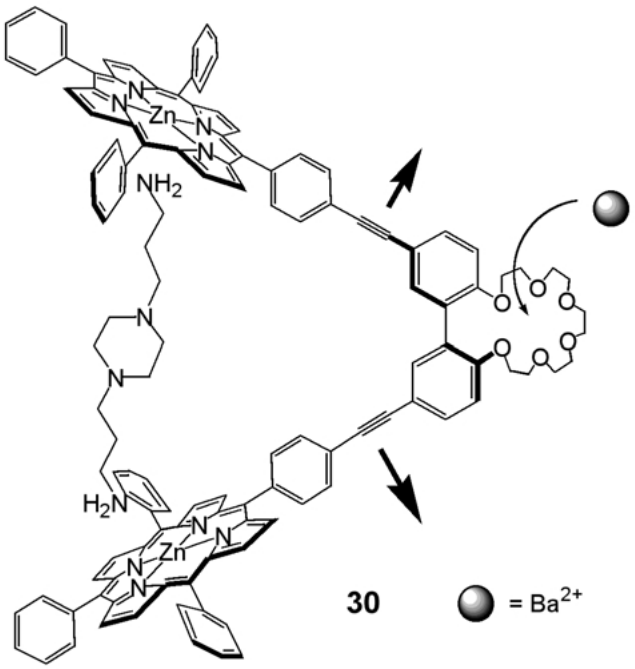


Figure 26. Allosteric control of the binding of diamines.

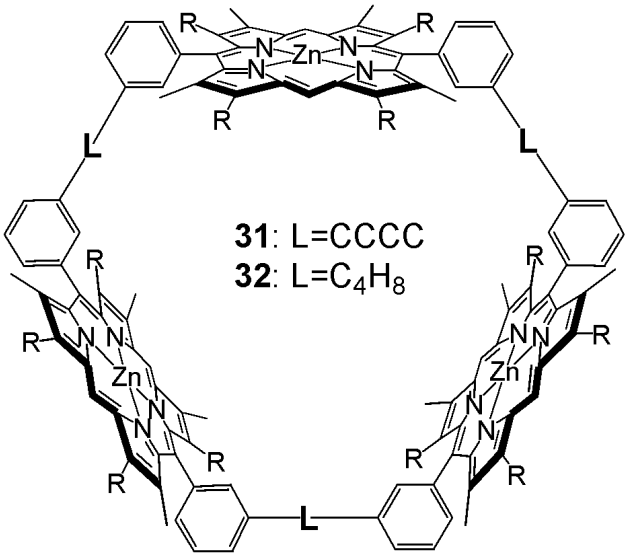


Figure 27. Porphyrin trimer receptor with variable flexibilities.

Stereoselective recognition by zinc(II)-porphyrin receptors

This section will be divided into three main subsections, the first and second will be devoted respectively to the use of peripherally substituted, and strapped porphyrins that are intrinsically chiral and therefore designed to bind selectively chiral substrates. The last section will cover the more recent use of achiral receptors for chirality sensing due to selective induction of circular dichroism (ICD).

Steric and H-bonding discrimination of substrates by chiral superstructured zinc(II)-porphyrins

Although asymetric catalysis had been reported with rhodium(III)-porphyrins during the 80s [58], early attempts of multi-point stereo discrimination with this type of receptors appeared to be limited due to too strong interactions of Rh(III) with nitrogen bases. This has the disadvantage of slowing down the dissociation rate of the host guest complex, therefore limiting the thermodynamic guest selection [59]. It also tends to minimize the role of additional weak interactions, thus stereo-inductive catalysis with Rh(III) porphyrin is essentially limited to reactions involving olefins. The use of chiral superstructured porphyrins in stereoselective molecular recognition was started by two main research groups [60] in the beginning of the 90s, when reports from Sanders and Ogoshi described two synthetic approaches leading to chiral receptors built on zinc(II) porphyrins.

In the first set of studies, chirality based on isolation of atropoisomers was described by Ogoshi *et al.* [61], and porphyrins presenting two identical faces with a C_2 symmetry were isolated. Due to the presence of the ortho hydroxy groups of the 5, 15 substituents on the receptor, the two atropoisomers represented in Figure 28 cannot interconvert at room temperature. Those mirror images display chiral recognition of amino acids esters in chloroform. Values obtained for ΔGs collected in Table 8 may be compared with those listed in the first part of this paper (see Table

Table 8. Binding energies of receptor **33**(R,R) with aminoacid enantiomers in CH_2Cl_2 at 288 K (4% standard deviation).

Amino acid ester		Ile	Leu	Val	Ala	Ser
ΔG	D	−19.1	−18.9	−18.9	−15.9	−15.6
(kJ mol^{-1})	L	−16.9	−16.9	−16.9	−15.7	−17.2

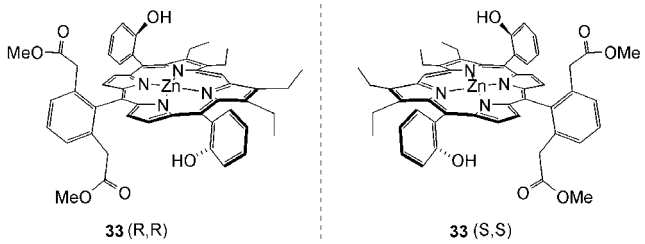


Figure 28. Chirality in two atropoisomers for the selective recognition of amino acids esters in chloroform [11, 61].

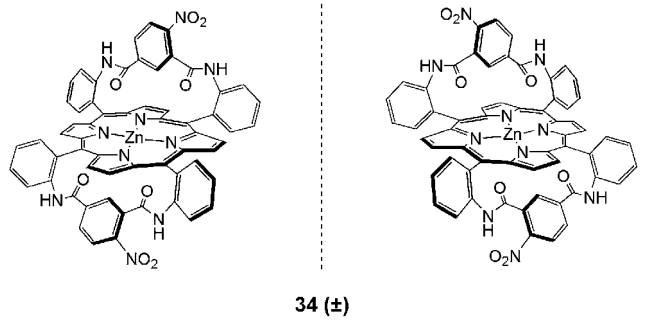


Figure 29. Chirality in two strapped receptors for the selective recognition of amino acids esters in chloroform [62, 63].

Table 9. Stereoselective binding of L-aminoacid esters in chiral receptor **34**

L-Amino acid ester		Val	Leu	Phe	Ala	PheG[a]
ΔG	(−)34	−33.6 ± 0.1	−33.4 ± 0.2	−32.4 ± 0.1	−29.9 ± 0.1	−30.1 ± 0.1
(kJ mol^{-1})	(+)**34**	−28.6 ± 0.1	−28.0 ± 0.2	−27.6 ± 0.1	−26.4 ± 0.1	−29.6 ± 0.1

[a] Phenyl-glycine ester. At 293.5 K in methylene chloride.

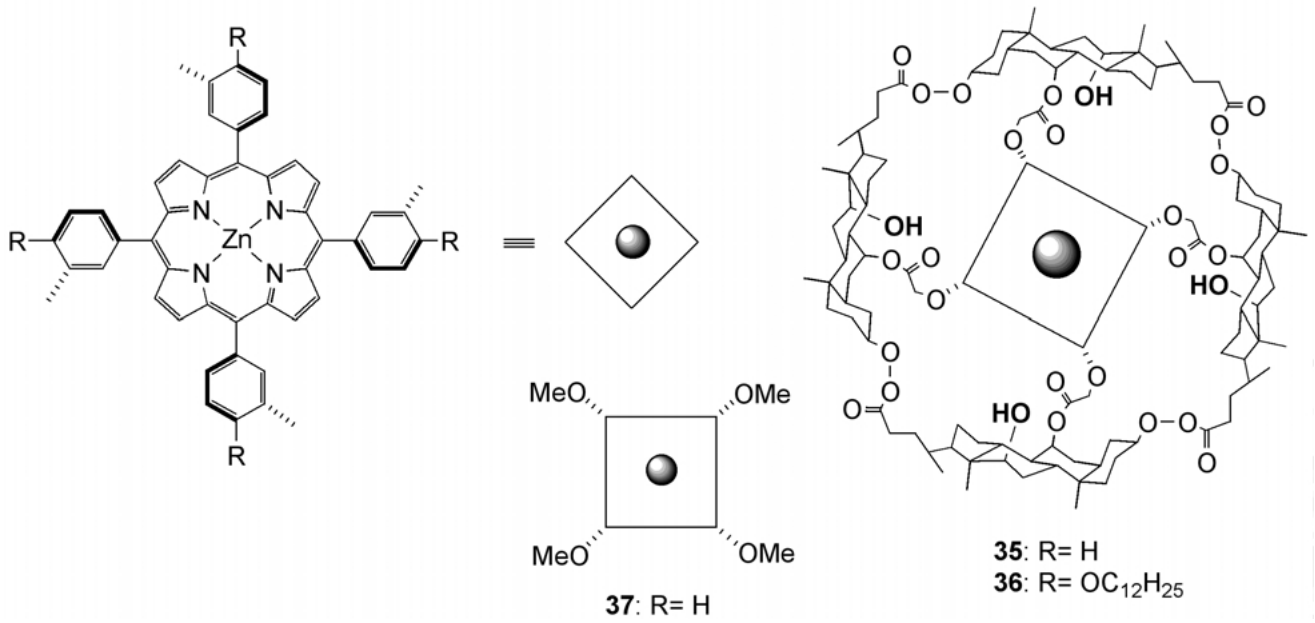


Figure 30. Porphyrin-cyclocholate bowls bearing four convergent hydroxyl groups (bold), and reference **37** [65].

2) with similar receptors bearing no H-bonding sites on the periphery (compound **5**).

The segregation of enantiomers arises from a stepwise process. First, the two point fixation of the substrate occurs due to the coordination of the substrate to the zinc, and the formation of a H bond between the C=O group and the phenolic OH group. This process defines the orientation adopted by the side chain of the amino-acid. If the resulting orientation is towards the bulky ester present on both sides, the host–guest complex is less stable than if the side chain is oriented towards the open meso position [11, 61]. The larger Leu and Ile side chains provide the greater selectivity while reverse selectivity is observed for Ser which may be due to the formation of an additional H bond between the OH group of the side chain and the ester group on the receptor. The parent receptor in which the two ester groups are absent displays larger ΔGs, with a highest value of -20.7 kJ mol^{-1} in the same conditions for D-Ile.

Another type of chirality has been introduced by Ogoshi and Kuroda [62, 63] by using unsymmetric basket-handles. The chirality is produced according to the representation on the top-left in Figure 6b. The two enantiomers represented in Figure 29 have been used for the chiral recognition of amino acid esters already mentioned above. The binding energies are listed in Table 9 and demonstrate that significant selection can be made for L-Val methyl ester for which a ratio of 7.5 is found between the binding constant of L and D isomers with the **(−)34** isomer (left, Figure 29).

The selectivity has been assigned to a preferential formation of a H bond between the carbonyl group of the ester with the NH proton located on the same side of the nitro group. For steric reasons, the conjugation of this nitro group may perturb the coplanarity of the amide link on the "nitro side" of the strap, therefore subsequently enhancing the acidity of the NH proton which explains the preferential orientation of the substrate for H bond formation. Bulkiness may also disfavor the formation of H bonds, as shown by the weak selectivity observed with phenyl-glycine ester. An exhaustive analysis of the parameters controlling the segregation of enantiomers with these receptors has been accounted for quite recently by Mizutani and Ogoshi [64].

Blocked atropoisomerism and unsymmetric straps are not the only means of providing tools for molecular recognition. The capping of zinc(II)-porphyrins with "chiral cavities" may also allow for an efficient substrate discrimination based on multipoint recognition. The shape selectivity is then preponderant as shown by the preparation of zinc(II)-porphyrins capped with cyclocholate bowls by Sanders and coworkers [65, 66]. The initial preparation of the cyclocholate bowl prior to the cyclization of the porphyrin [65] has been replaced by an elegant stepwise strategy which involves the preparation of a tetracholate porphyrin derivative in which atropoisomerisation is still possible followed by a tetra lactonisation of the four peripheral cholic acid [66]. High affinity for morphine and codeine derivatives show that

Table 10. Binding of N-containing axial bases in a cyclocholate-capped zinc-porphyrin

Substrate	Morphine	Codeine	Codeine Methyl ether	N-Methyl-piperidine	Pyridine	Brucine
Bowl **35**	−30.0	−23.0	−13.3	−19.0	−23.2	−27.7
37	−9.9[a]	−11.4	−12.5	−18.5	−22.4	−29.3

Binding energies (in kJ mol^{-1}) within ±10% of various substrates with the cyclocholate bowl porphyrin **35**. At 293 K in methylene chloride.
[a] 20% error.

formation of H bonds with the four converging hydroxyl groups of the bowl is crucial.

Additionally, size discrimination is also an important factor as shown by the binding affinities reported in Table 10 [67].

As shown by the comparison of morphine (2 OH groups) binding with **37** and **35**, the extra H-bonds present in **35** can contribute up to 20 kJ mol^{-1} to the binding free energy [65]. Etherification of one OH group on the substrate leads to codeine and binding is consequently reduced, but still enhanced versus the reference receptor **37**. Complete etherification leads to codeine methylester and the rather weak binding confirms the role of the converging OH groups towards the inside of the bowl. Size discrimination is obviously a very selective parameter as shown by the brucine binding outside of the bowl.

The steroid part can also be introduced as a cap on one or both sides of the porphyrin. The preparation of the steroid capped porphyrins **38** and **39** have been described by Sanders, Bonar-Law *et al.* [67], and the various properties of these elaborate receptors have been studied in several papers. The binding free energies associated with the recognition of a selection of axial bases with **39** are collected in Table 11.

Advantage has been taken of the affinity of **39** for functionalized pyridine (e.g., 3-hydroxypyridine) to react **39** with the anhydride of 3-carboxypyridine and 2,6-dichlorobenzoic acid, producing very efficiently and selectively a monoacylated derivative of the steroid bis-capped zinc(II)-porphyrin. Subsequently, the capped receptor was incorporated in micelles in the presence of SDS (sodium dodecyl sulfate) in water to achieve similar strong selective binding of various pyridine derivatives. When both H-bonding and solvophobic (hydrophobic in this case) effects are combined, micellar recognition is effective and can be fine tuned by the use of adequate co-solvents [68].

The binding properties of the capped receptor **38** has been studied versus various substrates bearing one or more hydroxyl groups. In the case of diols displaying relative flexibility, an intramolecular H-bond (within the diol chain) between the two hydroxyl groups of the diols is favored leading to a cyclic conformation. In methylene chloride, for butanediol and pentane diol, a 20 fold increase of the amount of cyclized form present in solution has been estimated from careful analysis of thermodynamic data [69]. An overview of this approach has been published, covering the progress towards synthetic enzymes based on porphyrins and steroids [70].

Table 11. Binding of N-containing axial bases in a bis-capped zinc-porphyrin **39**

Substrate	**39**	Porphyrin-tetramethylester
Pyridine (py)	−19.5	−22.6
4-Ethylpy	−15.3	−24.5
3,5-Dimethylpy	−26.2	−23.2
3-Hydroxypy	−28.8	−22.8
4-Hydroxypy	−26.0	−17.4
Pyrazine-N-oxide	−22.6	−16.0
Imidazole	−27.1	−25.2
Purine	−35.4	−20.2
Tropine	−14.2	−9.5

Binding energies in kJ mol^{-1} at 293 K in chloroform. Error 10% [67].

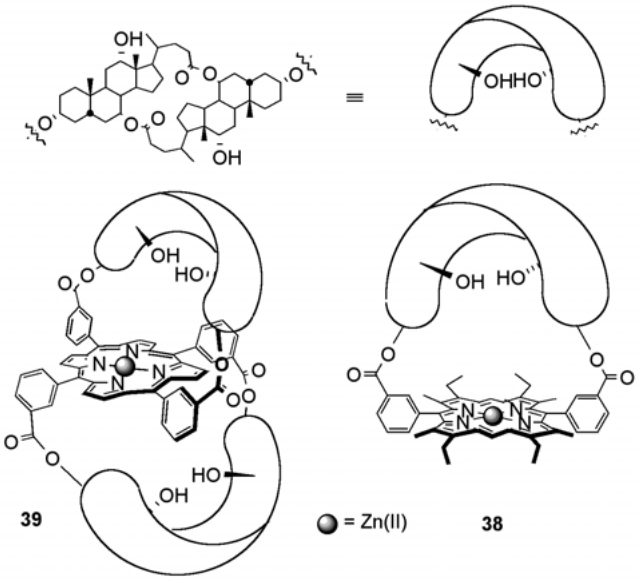


Figure 31. Steroid capped zinc(II)-porphyrinic receptors.

Detection of chirality by chiral and achiral hosts

Particular properties of monomeric and dimeric zinc(II)-porphyrin receptors will be considered in this section. First, for achiral monomer species, the multipoint fixation, and multipoint only, of a chiral aminoacid on the central atom of the receptor induces an anisotropy in the electronic transitions involved in the Soret band. This is due to a coupling between the electric transition (π–π^* transition: $B_\perp$, $B_\parallel$ Soret band) moments μ_x and μ_y, and both magnetic (n–π^*) and electric (π–π^*) transition moments of the aminoacid carbonyl group.

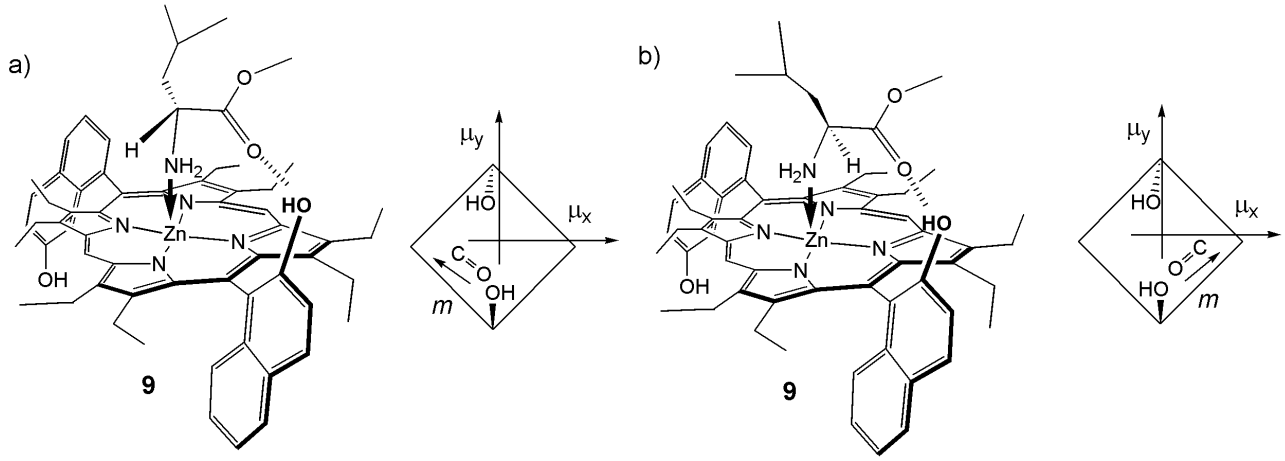


Figure 32. Two unique orientations of the magnetic transition moment (m) of the carbonyl group of Leu-methyl ester with respect to the electric transition moments μ_x and μ_y of the receptor.

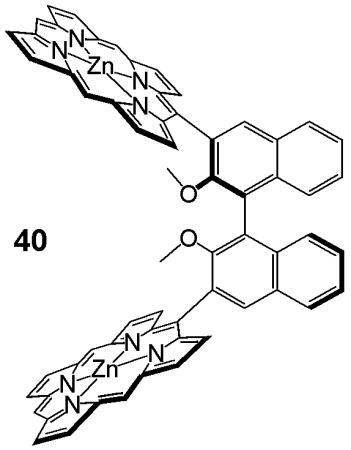


Figure 33. A chiral dimeric receptor built on binaphthol.

The stronger and the more directed the additional interactions are, the more precise the orientation of the C=O bond is, and the stronger the coupling between the porphyrin and the carbonyl transition will be. Thus, a higher induced circular dichroism (ICD) amplitude ($\Delta\epsilon$ between the positive and the negative absorption) is observed when the recognition is efficient. It should be noted that the splitting observed in the ICD and the positioning of the two absorptions do not vary much from one substrate to another, but the amplitude of the ICD absorption is considered as the significant parameter. Thus, this easily observable band can be used as a probe of chirality, as the achiral receptor will now display a specific ICD. As shown by the schematic representation in Figure 32, the absolute configuration of the amino acid determines the sign of the ICD, and all L amino-acid esters give a positive peak at shorter wavelength and a negative peak at longer wavelength [71].

Amplification effects are observed with chiral dimers because the existing CD due to chiral exciton coupling [72–75] between the two chromophores can be tuned by the presence of a guest. Ogoshi *et al.* [76] have reported that, for the chiral dimeric receptor **40** in Figure 33, an amplified CD is observed in the presence of bridging dialkylamines of adequate length, for which the amplitude is a function of the length of the diamine, and the strength of the binding. In order to assign the origin of the amplified CD, a chiral dimer receptor **42** has been recently reported and was prepared by linking two zinc(II) porphyrins with an enantiomerically pure amino acid in order to provide a better understanding of the reason for observing amplified CDs. The monomer **41** (Figure 34), displays no CD in the Soret region, and the dimer **42** displays a CD generated by chiral exciton coupling, the signs of the CD spectra being tuned by the configuration of the bridging amino acid, while the amplitude is regulated by steric factors [77]. These dimers have been further used for generation of chiral supramolecular assemblies using bridging ethylene-diamines too short to form inclusion complexes, thus forming linear self assembled porphyrin arrays [78].

These considerations lead to the use of porphyrin dimers with flexible links, or spacers, as chromophoric chirality sensitive hosts for amines. The probing of chirality using ICD has been recently reported in several papers, with similar porphyrins but with either short or long alkyl chains as spacers.

Long spacers have been introduced between tetra-aryl zinc(II) porphyrins by Nakanishi *et al.* [79] to produce the dimer **43**. The ability of this compound to bind diamines of various lengths and to display ICD in the presence of chiral diamines and chiral monoamines has been studied. While short simple diamines like diethylamine generate noticeable changes in the ^{1}H NMR spectrum and the UV-visible spectrum of the receptor due respectively to reciprocal ring current interactions between the two tetrapyrrolic units, and excitonic coupling, long diamines have about the same influence as isopropylamine [80]. The binding of chiral diamines, or chemically modified amino acids and amino alcohols with the same receptor occurs according to the process depicted in Figure 35, with a variation of amplitude directly related to the steric bulk of the large group, and a sign of ICD directly related to the absolute configuration of the substrate [79]. These considerations are still valid for determining the absolute configuration of primary amines if they are properly

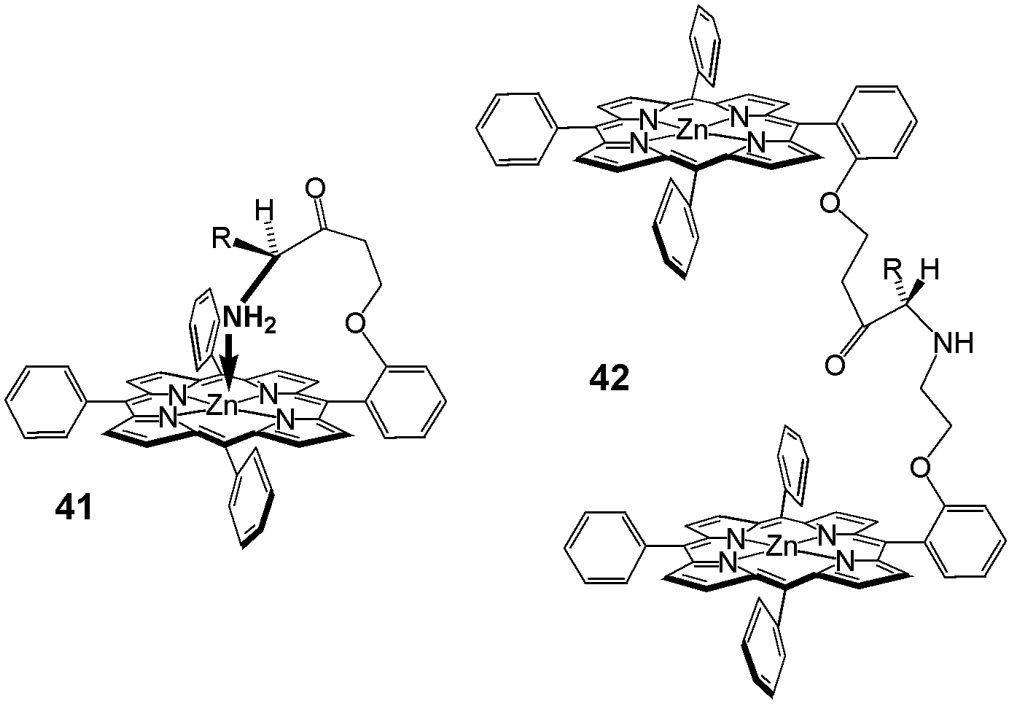


Figure 34. Chiral monomer (no CD) and chiral dimer displaying CD due to chiral excitonic coupling [77].

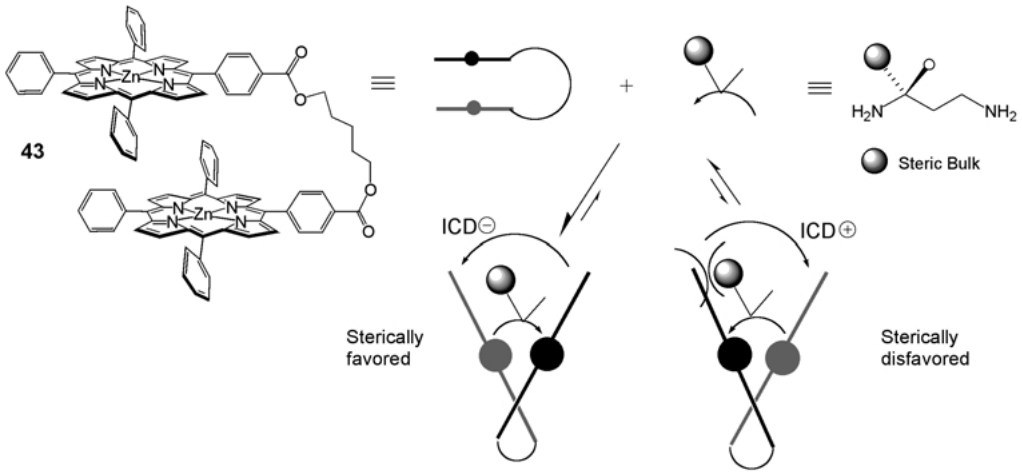


Figure 35. Schematic representation of the influence of the absolute configuration of a chiral diamine on the sign of ICD.

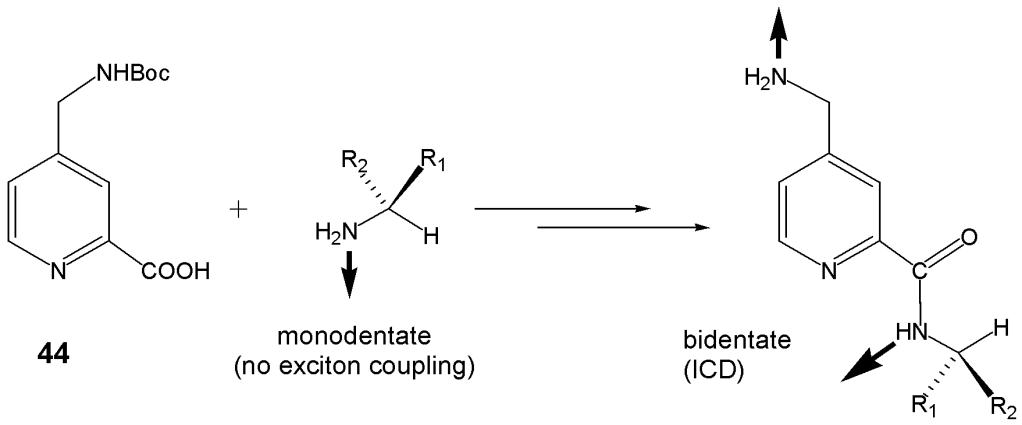


Figure 36. Making an optically active bidentate from an optically active monodentate and a "carrier" [81].

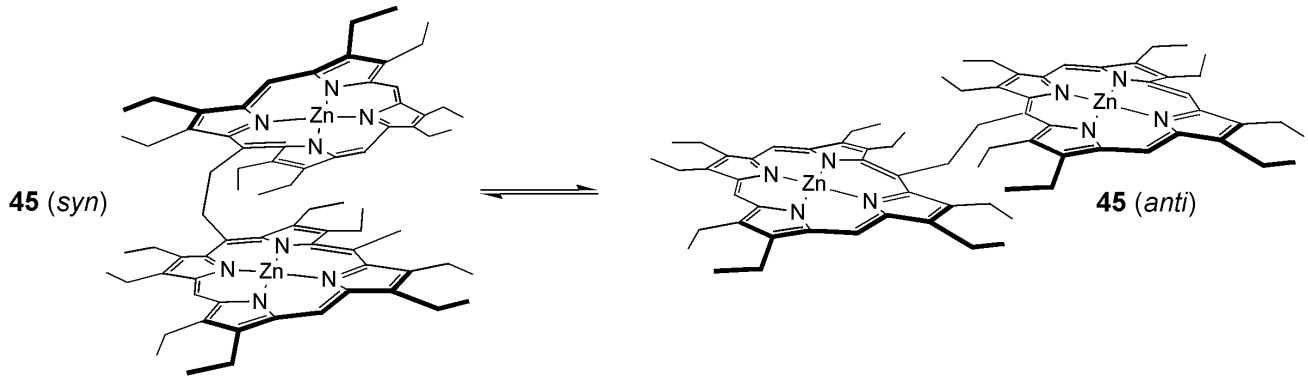


Figure 37. Two conformers of the achiral receptor **45**.

attached to a "carrier" that converts the monodentate substrate into a bidentate substrate, thus allowing the generation of exciton coupled CDs according to the general reaction in Figure 36 [81].

A bis-zinc(II) receptor based on a porphyrin dimer **45** presenting a much shorter bridge has been prepared by Inoue *et al.* [82], along with several other homo- and hetero-dimetallic complexes [83].

Blue shifted Soret bands (up to 398 nm) indicated that in various solvents the syn arrangement is adopted, even at high temperature [83, 84]. However, solvent may influence the conformation of the dimer and exhaustive studies of the influence of both solvents and temperature have been performed [85, 86]. Even poorly coordinating solvents (for zinc(II) in porphyrins) like ethanol displace the syn-anti equilibrium to the right while temperature may be used for a fine tuning of the alcohol coordination on the zinc(II) [86].

Receptor **45** (Figure 37) also displays ICD in the presence of chiral guests. The advantage of the smaller spacer between the two chromophores is to provide a chirality probe which does not require a second recognition point. The steric interactions developed with the second chromophore, and the consecutive changes in the orientations of the $B_{\square}$, $B/_{||}$ associated with Soret absorptions of each chromophore are sufficient to generate non ambiguous ICDs whose shape is directly related to the configuration of, for example, R-(+)-1-(1-naphthyl)ethylamine (R ligands giving a positive CD at shorter wavelength) [87].

Again, temperature changes have proven to be a useful tool for controlling the binding of enantiopure amine or alcohol guest molecules [88].

Outlook

What has been learned from bioinorganic approaches and discovered during many studies of enzyme models and their refinement, is a comprehensive data bank that helps the development of specific hosts and sensors based on zinc(II)-porphyrins. The fine tuning of recognition via multipoint interactions serves in turn as an input into the design of new catalysts with tailor-made properties based on more reactive (e.g., iron, ruthenium, or manganese) porphyrin metal complexes. Attempts at modeling cytochrome P-450 activity led many research groups to use peripherally substituted iron porphyrins as oxygenation catalysts [89]. Again, a great deal of literature coverage will be found in the review of Ogoshi *et al.* [3], but a few major papers have appeared since and will be briefly covered.

Concerning oxidation of substrates, due to the importance of epoxides as intermediates in organic synthesis, the catalytic oxidation of olefins has been often used as a test reaction for activity and chiral induction. Using bis-strapped porphyrin **46**, or bis basket-handle porphyrin **47** and **48** (Figure 38) containing controlled chirality on both sides of the porphyrin plane, Collman and Rose [90–92] have described very efficient catalytic asymetric epoxidation of terminal olefins with enantiomeric excesses ranging from 54 to 89% for *o*-nitrostyrene.

Although tentative studies were unsuccessful two decades ago [58], enantioselectivity in epoxidation may also be achieved with chiral pickets as reported recently by Salvadori and Guilard [93]. The atropoisomers of the tetra-binaphthol porphyrin derivative **49** (Figure 39) with iron(III)-, or manganese(III)-chloride display chemoselectivity or enantioselectivity in catalytic epoxidation of olefins. The properties of the catalysts vary depending on the atropoisomer used, with a maximum efficiency (57% *ee*) observed for **49**(Fe-Cl)$\alpha\alpha\beta\beta$ represented in Figure 39, and the lowest induction (21% *ee*) is reported for the α^4 atropoisomer.

Gross [94] has recently described the enhancement of the selectivity provided by more sophisticated architectures **50–52** represented in Figure 40. A series of ruthenium(II) catalysts with a gradual increase of the steric bulk comprised in the four straps of a double face protected porphyrin have been prepared and tested. The increase of the bulk allows for a better selection and orientation of the substrate which is oxidized by an aromatic N-oxide. Typical enantiomeric excesses obtained with **52** range from 38% for *trans*-stilbene, to values around 80% for styrene derivatives (maximum 83% for *p*-chlorostilbene). It should be noted that achiral ruthenium porphyrins like (TPP)Ru(CO) also catalyze cyclopropanation of alkenes and ethyl diazoacetate with regio-and enantio-selectivity, due to the prochiral nature of the reactants [95].

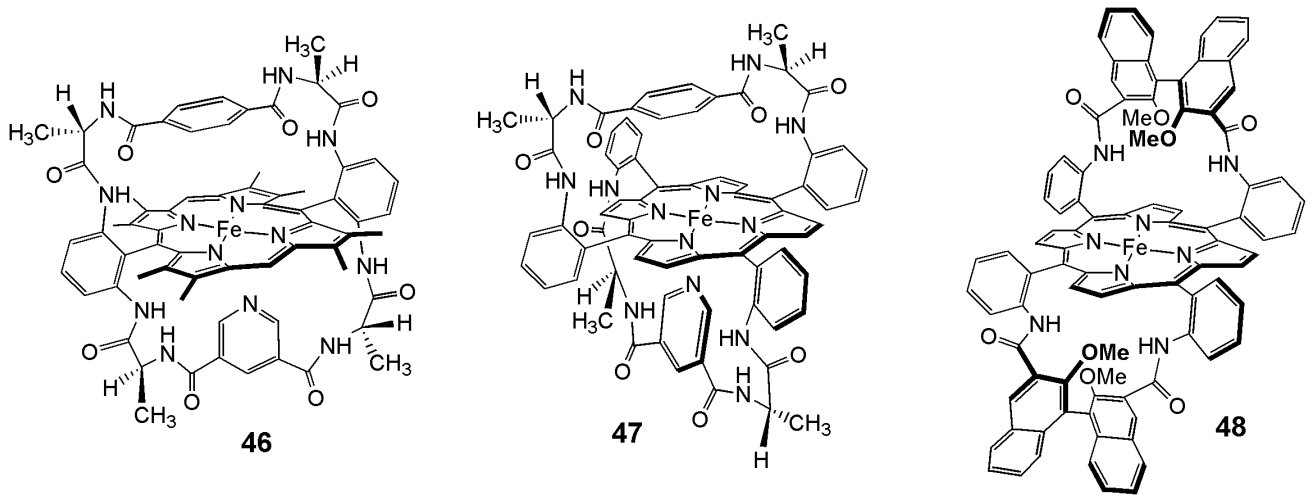


Figure 38. Three chiral iron(III) porphyrins allowing enantioselective epoxidation of olefin.

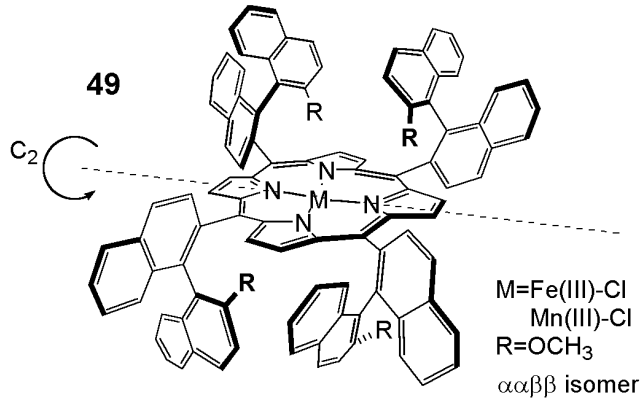


Figure 39. A tetra-binap epoxidation catalyst.

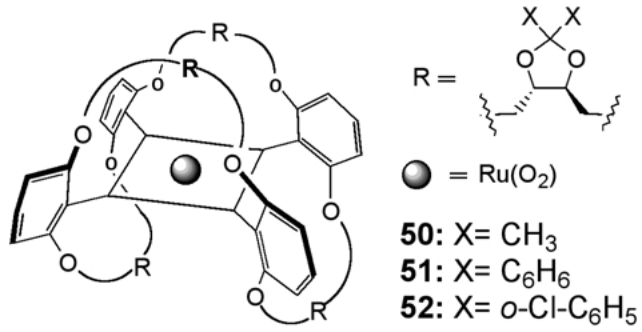


Figure 40. Three four-strapped Ru(II) porphyrins for the epoxidation of alkenes.

The last two examples described hereafter have been chosen because they illustrate the diversity of the approaches to efficient catalytic systems. Zinc(II) coordination may be associated with the enhancement of the activity of manganese(III) porphyrins by using Mn(III) porphyrins that are substituted with pyridine rings. The ternary complex **53** (Figure 41) reported by the group of Hupp [96] introduces bulk around the active Mn(III) center by the coordination of two zinc(II) porphyrins on its periphery.

Finally, these catalysts may be bound to surfaces via imidazole binding in order to control the open face co-

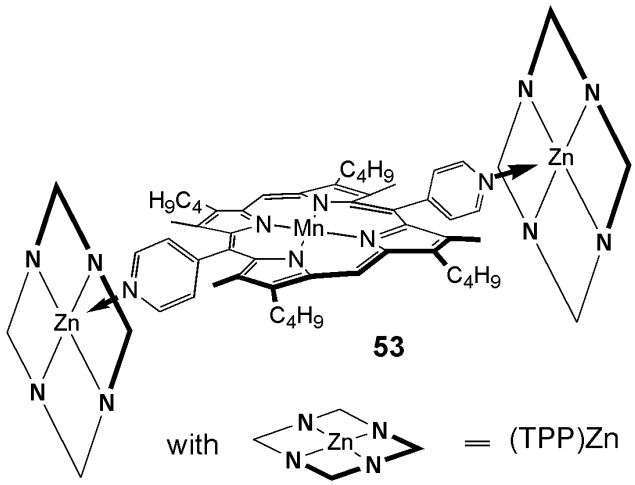


Figure 41. A "supramolecular" peripherally encumbered catalyst.

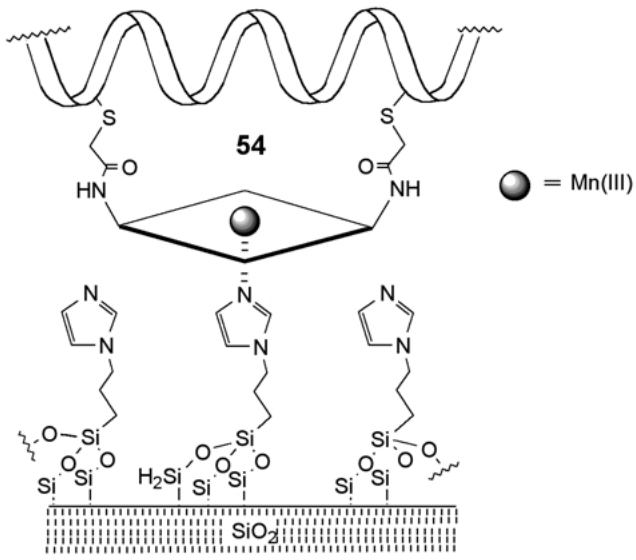


Figure 42. A Mn(II) porphyrin-peptide conjugate immobilized on a silica gel matrix.

ordination, and in particular to prevent the formation of bridged species. The peptide strapped manganese(III) porphyrin **54** has been attached to a silica surface previously coated with imidazole derivatives, as represented in Figure 42. The catalytic properties of this immobilized catalyst have been studied with a wide range of stilbene and styrene derivatives to demonstrate good selectivity in the formation of epoxides versus the production of higher oxidation products (e.g., aldehydes), and the peptidic pocket appears to have a significant influence on the cis/trans ratio of the formation of epoxides [97].

Conclusion

What is learned from studying the mechanisms of molecular recognition is indeed very useful in the development of new materials displaying either new or enhanced properties. This area of research all started from efforts to understand and reproduce biological function, and will continue in the building of sophisticated architectures around a simple tetrapyrrolic macrocycle whose properties are finely tuned by the imagination of synthetic chemists.

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