

Porphyrins

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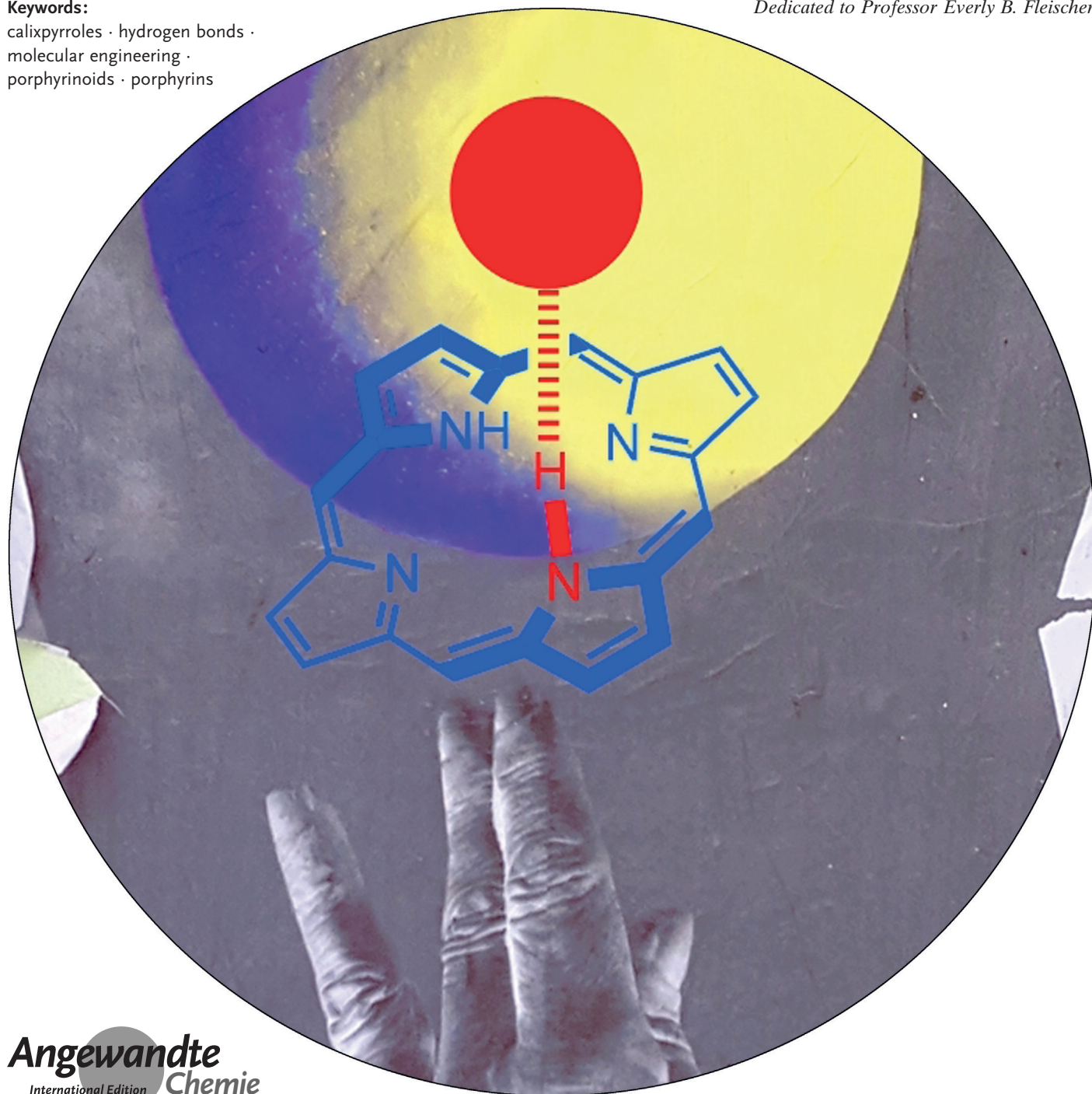
# Molecular Engineering of Free-Base Porphyrins as Ligands—The N–H...X Binding Motif in Tetrapyrroles

Marc Kielmann and Mathias O. Senge\*

**Keywords:**

calixpyrroles · hydrogen bonds ·  
molecular engineering ·  
porphyrinoids · porphyrins

*Dedicated to Professor Everly B. Fleischer*

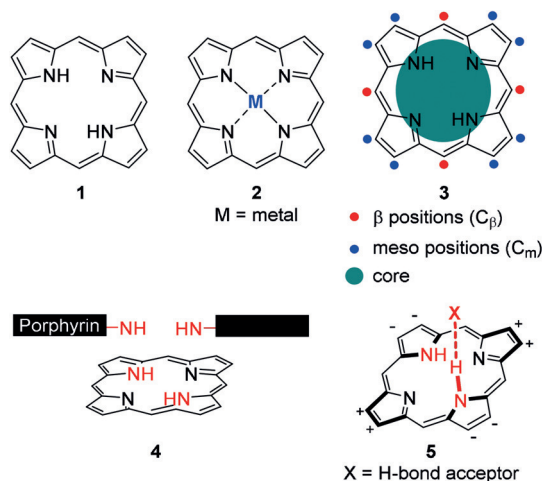


The core N–H units of planar porphyrins are often inaccessible to forming hydrogen-bonding complexes with acceptor molecules. This is due to the fact that the amine moieties are “shielded” by the macrocyclic system, impeding the formation of intermolecular H-bonds. However, methods exist to modulate the tetrapyrrole conformations and to reshape the vector of N–H orientation outwards, thus increasing their availability and reactivity. Strategies include the use of porpho-(di)methenes and phlorins (calixphyrins), as well as saddle-distorted porphyrins. The former form cavities due to interruption of the aromatic system. The latter are highly basic systems and capable of binding anions and neutral molecules via N–H⋯X-type H-bonds. This Review discusses the role of porphyrin(oid) ligands in various coordination-type complexes, means to access the core for hydrogen bonding, the concept of conformational control, and emerging applications, such as organocatalysis and sensors.

## 1. Introduction

### 1.1. Porphyrins

Porphyrins **1** are often discussed as macrocyclic compounds par excellence. They are heteroaromatic systems with a rich metal coordination chemistry (**2**) and high functional versatility (**3**, Figure 1, top). As a result of their conformational flexibility, manipulation of the macrocycle conformation allows a fine-tuning of their physicochemical characteristics, including binding properties and chemical reactivity in general.<sup>[1]</sup> This manifests itself, for example, in tetrapyrrole-containing proteins, one of the most fundamental classes of enzymes in nature, where a multitude of chemically distinct reactions involves the same porphyrin cofactor, which is largely attributed to protein-induced macrocyclic distortion.<sup>[2,3]</sup> Enhancement of the capability of porphyrins to



**Figure 1.** Top: (Metallo)porphyrin macrocycles **1** and **2** and functionalities of a free-base porphyrin **3**. Bottom: N–H-orientation in a planar porphyrin **4** and the N–H⋯X-type H-bonding motif in a nonplanar porphyrin **5** (+ and – indicate displacements above and below the 24-atom least-squares plane ( $\Delta_{24}$ ), respectively).

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undergo non-covalent interactions (i.e. hydrogen bonding) in enzymes or artificial systems is to a significant extent an effect of macrocycle non-planarity. As such, nonplanar free-base

tetrapyrroles can form hydrogen-bonded complexes N–H⋯X (**5**) under participation of the pyrrolic N–H groups in the core and suitable substrates X while often, the planar counterparts (**4**) remain inert (Figure 1, bottom).<sup>[3]</sup>

Research on (nonplanar) porphyrins has exploded in recent decades and these days, they are used to test and illustrate advances in almost any area of chemistry, such as analytics,<sup>[4]</sup> physical chemistry,<sup>[5]</sup> biomedicine,<sup>[6]</sup> as well as optics and materials science.<sup>[7]</sup> Their organic chemistry has given rise to a bewildering multitude of porphyrinoid macrocycles, which are isomeric, expanded, or contracted in relation to the parent 18  $\pi$ -electron system.<sup>[8]</sup> Total synthesis of symmetrical porphyrins has finally made it to a scale suitable for practical applications and unsymmetrical substituted porphyrins are now available en gros in many cases via short syntheses or through functionalization reactions.<sup>[9]</sup> The size of oligoporphyrins has reached the realm of polymer chemistry<sup>[10]</sup> with the field coming to a point where more publications use scanning tunneling microscopy (STM) rather than classical CHN analysis for characterization.<sup>[11]</sup> As a result of the many papers in these areas, this cannot be a classic review; rather we will use illustrative examples to highlight the points we aim to make.

One could ask “what is left to do in porphyrin chemistry?” Well, one area, which has escaped significant attention relates

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to the coordination chemistry of porphyrins. Interest in porphyrins has been driven to a large extent by their ability to chelate almost any metal in the core. Many of the metal complexes are catalytically active and/or exhibit rich axial coordination chemistry.<sup>[12,13]</sup> This is most prominently exemplified in nature, recalling, for example, hemes (iron complexes)<sup>[14]</sup> and their role in respiration in the electron transport chain and in a plethora of catalytic reactions or the chlorophylls (magnesium complexes) as the photoactive pigments of photosynthesis.<sup>[15]</sup> Furthermore, the cobalt complex vitamin B<sub>12</sub> is essential for the functioning of the brain and nervous system and the formation of red blood cells.<sup>[16]</sup> As a result, there is a rich coordination chemistry involving the central metals and/or peripheral substituents.<sup>[12,17]</sup>

In this context, the pyrrole N–H units in the core of so-called free-base porphyrins often appear in discussions solely as the precursor for metal insertion (**1**→**2**). The pyrrole N–H moieties are most often thought of as “hidden” in the core and inaccessible for any meaningful use in supramolecular chemistry (e.g., as shown in formula **4**, Figure 1). Detailed studies involving these groups have mostly been physical organic chemistry investigations on the N–H tautomerism, that is, studies on the behavior of the N–H units *within* the porphyrin plane.<sup>[18]</sup>

While traditionally in chemistry, a ligand is considered an ion or neutral molecule that binds to metal centers, we will here specifically include and discuss scenarios more akin to the situation and definition of ligands and receptors used in biochemistry.<sup>[19]</sup> Therein, the tetrapyrrole is usually bound to a much larger unit, which qualifies all porphyrins in pigment protein complexes and metalloproteins as ligands. However, we will focus here mainly on an emerging functional porphyrin chemistry where the targeted use of weak interactions, that is, (out-of-plane) H-bonding (of the N<sub>4</sub> porphyrin core) is utilized.

## 1.2. Coordination Types in Porphyrins

### 1.2.1. Peripheral H-bonding

Hydrogen bonds are a type of attractive electrostatic interaction (weak interaction) between two polar groups, that is, covalently bound and polarized hydrogen atoms and electronegative atoms or groups.<sup>[20]</sup> They are common and

important non-covalent forces in biological systems, such as proteins, enzymes, and nucleic acids and utilized as structural and functional principles in biomolecules and to control the microenvironment around metal centers in tetrapyrrole-containing enzymes. Additionally, H-bonds are partly responsible for the secondary and tertiary structures of proteins and nucleic acids and play an important role in the structure of natural and synthetic polymers. Given the porphyrin motif's pronounced role both in nature and artificial systems, it is unavoidable to highlight the role of hydrogen bonding in porphyrin-based assemblies.<sup>[21]</sup>

In this context, it seems rational to define two major categories of H-bonds: those involving the tetrapyrrole core and those involving peripheral groups. Both types are vital but found often in substantially different contexts. Peripheral H-bonding is a major driving force in supramolecular chemistry since the resulting frameworks are usually highly organized and exploit the structural flexibility and diversity that lies in the tunable hydrogen-bonding strength.<sup>[22]</sup> On the other hand, hydrogen bonds of the tetrapyrrole core are often discussed where porphyrins act as ligands. While peripheral H-bonding will be introduced briefly at this point, central (N–H···X-type) hydrogen bonding is discussed later as the essential element of this Review. As we will show in this chapter, the former and the latter may also interplay, producing unique porphyrinic architectures.

Hydrogen bonds play an important role in the self-assembly and stabilization of porphyrin J-aggregates; for example, where peripheral hydroxyl groups interact with the central nitrogen atoms of an adjacent macrocycle (**6**, Figure 2).<sup>[23]</sup>

Further examples of the directing and reinforcing characteristics of hydrogen bonds are found in porphyrinic solids,<sup>[24]</sup> self-assembled monolayers (SAMs),<sup>[25]</sup> nanofibers and nanorods,<sup>[26]</sup> and nanochannels of 2,3,5,7,8,10,12,13,15,17,18,20-dodecaphenylporphyrin (H<sub>2</sub>DPP, **64**) derivatives.<sup>[27]</sup> It has also been shown that protoporphyrin IX (PPIX, **71**) adsorbed on a Cu surface at low temperature forms adlayers stabilized by tetragonal H-bonds between the nitrogen atoms of the macrocycle core and peripherally bound carboxyl groups.<sup>[28]</sup>

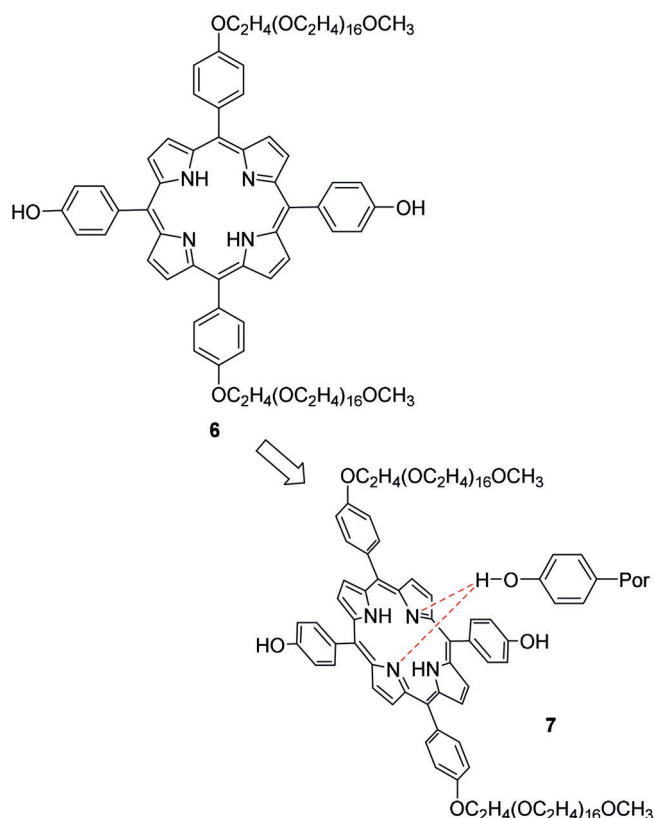
Looking at examples in nature, the malaria pigment hemozoin, a disposal product from the digestion of blood by malaria parasites, is an insoluble, peripherally hydrogen-



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**Figure 2.** Supramolecular porphyrin complexes formed through peripheral H-bonding and core interactions. J-aggregate of **6**, **7**, where the possibility of hydrogen bonds forming between the porphyrin core and the hydrogen of the O–H group of the adjacent macromolecule has been suggested by molecular mechanics (MM) calculations.<sup>[23]</sup>

bonded dimer of  $\beta$ -hematin.<sup>[29]</sup> And in chlorosomes, photosynthetic antenna complexes found in some anaerobic bacteria, hydrogen bonding can have a critical influence on exciton dynamics and as such, the light-harvesting process itself.<sup>[30]</sup> In the future, these findings may motivate new ventures into bionic supramolecular chemistry.

Applications of peripherally hydrogen-bonded tetrapyrroles are found in material science, molecular electronics, nanotechnology, and solar technology. Representative examples are hydrogen-bonded organic frameworks (HOFs) based on porphyrins for selective gas separation<sup>[31]</sup> and H-bonding mediated reversible self-assembly of porphyrin on a surface for the construction of dye-sensitized solar cells (DSSCs).<sup>[32]</sup>

### 1.2.2. Peripheral Covalent Bonding/Porphyrin Ligands in Biochemistry

In addition to weaker non-covalent bonds, nature also utilizes covalent bonding to fix and regulate porphyrin cofactors in defined arrangements. The archetypical case is heme proteins, an indispensable class of porphyrin cofactors involved in a wide range of functions in nature, such as oxygen storage and transport, electron transfer, catalysis, gas sensing, and gene regulation.<sup>[33]</sup> Moreover, they pose an interesting case study to deduce the effects of different coordination types (covalent linkage to proteins: e.g., heme c in cyto-

chrome c<sup>[34]</sup> vs. axial coordination: e.g., heme a in cytochrome c oxidase, heme b in hemoglobin and myoglobin) in tetrapyrroles.

A comparison of hemes in various binding situations underlines the functional and physicochemical differences originating from the several binding modes, for example, robustness,<sup>[35]</sup> fine-tuning of reduction potentials over a wide range,<sup>[36]</sup> interaction with proximal amino acids, metal–ligand interactions, metal spin state<sup>[37]</sup> and oxidation state,<sup>[38]</sup> and, potentially, kinetics and thermodynamics of electron transfer reactions itself. Notably, covalent attachment of a protein often results in heme c undergoing conformational changes (i.e. nonplanarity),<sup>[36b,39]</sup> which effects, for example, the tetrapyrrole's redox properties (see Section 3.3).<sup>[37,40]</sup> As such, nature highlights the critical role of binding types in porphyrins and provides one of the most interesting case studies on molecular engineering of tetrapyrroles.

Historically, many tetrapyrroles were involved in studies on the biological role of nonplanar porphyrin/porphyrinoid conformations<sup>[41]</sup> and conformational control in enzymes.<sup>[3a,42]</sup> To date, numerous protein crystal structures were solved in which the tetrapyrroles exhibit distorted macrocycles<sup>[43]</sup> along with considerable movement and flexibility.<sup>[44]</sup> As such, a rich landscape of structural studies, including our own,<sup>[45]</sup> revolves around porphyrin–protein complexes with a focus on weak interactions and tunable properties.

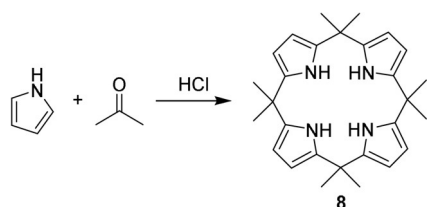
## 2. Nonaromatic Porphyrinoids

Before focusing on “true” porphyrins, a look must be taken at a number of nonaromatic tetrapyrroles in which the N–H units have been utilized extensively to bind ions and small molecules through hydrogen bonds.<sup>[46]</sup> Macrocyclic conjugation in such systems is interrupted due to  $sp^3$ -hybridized *meso*-carbon atoms, giving rise to macrocycles with isolated pyrrole units that form what can be considered as cavities. The isolated pyrrole units can easily tilt out of the mean-plane and are therefore accessible as hydrogen-bond donors, as opposed to the situation in more rigid and often planar porphyrins. Overall, this is a main prerequisite for the rich coordination chemistry that revolves around these ligands.

### 2.1. Calix[4]pyrroles

Since their first description by Baeyer (“acetonepyrrole”) in which a tetrapyrrole with four  $sp^3$ -hybridized *meso*-carbon atoms, octamethylcalix[4]pyrrole (**8**), was synthesized from acetone and pyrrole (Figure 3),<sup>[47]</sup> calix[4]pyrroles (porphyrinogens) and their analogues, including metal complexes, have been extensively studied and stand now as versatile and often used ligands for the complexation of ions and neutral molecules through H-bonding with the central pyrrole moieties.<sup>[48]</sup>

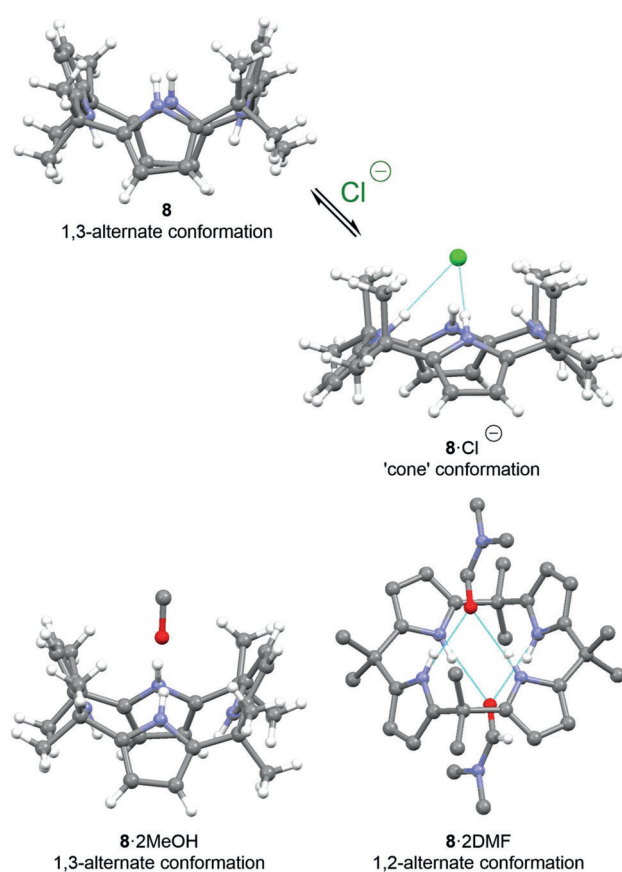
However, it was more than a century after the initial discovery that a “gold rush” of using calixpyrroles and related compounds in ligand-based applications emerged, which



**Figure 3.** The first synthesis of a calixpyrrole **8** by Baeyer via acid-catalyzed condensation of acetone and pyrrole.<sup>[47]</sup>

yielded hundreds of analogues and a multitude of sensing methods.<sup>[49]</sup> Given the presence of pyrrolic hydrogen-bond donor groups, they were considered as “old yet new” anion-binding agents and have been found to frequently complex halides, dihydrogen phosphate, carboxylate, and others, both in solution and in the solid state.<sup>[50–52]</sup> This is accompanied by a preference towards complexation of small fluoride anions over other guests, which is attributed to the spatial demands of the central cavity (i.e. size exclusion).<sup>[51,53]</sup> Notably, ligation can occur even in the solid state.<sup>[54]</sup>

Unlike most porphyrins where conformational flexibility is limited,<sup>[55]</sup> calix[4]pyrroles modify their shape to accommodate guests. They often adopt a 1,2-alternate conformation

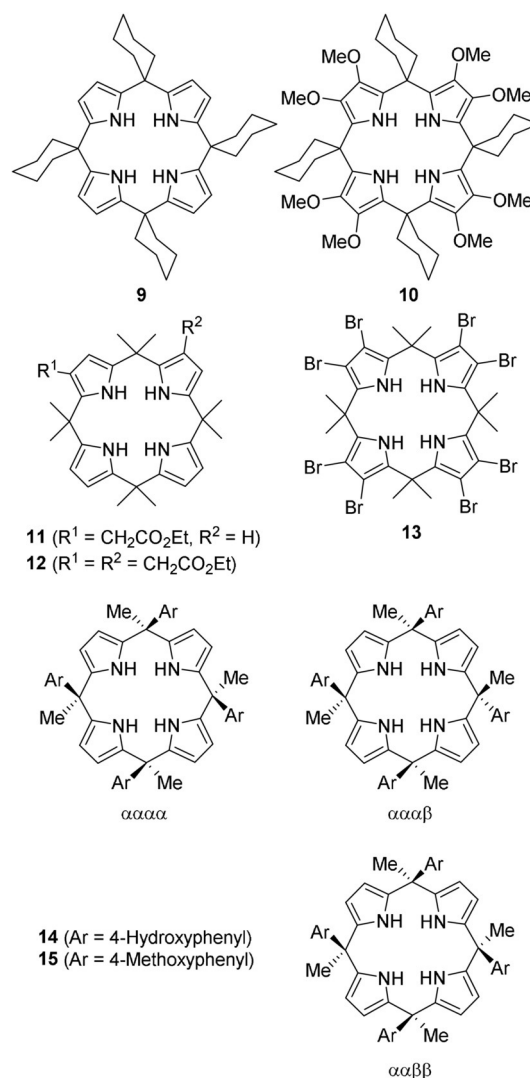


**Figure 4.** Typical conformations of calix[4]pyrroles and their crystal structures. Top: while the discrete ligand **8** (CCDC: VUSFIY01) is 1,3-alternate with regard to the pyrrole rings, the tetrapyrrole switches to a “cone” in **8-Cl<sup>-</sup>** (CCDC: TEQKI1) to accommodate anions.<sup>[51a]</sup> Bottom: the complexes **8-2MeOH** (RECPEU) and **8-2DMF** (RECIPIY; noncritical hydrogen atoms omitted) with neutral ligands are 1,3- and 1,2-alternate, respectively.<sup>[58,56a]</sup> DMF = dimethylformamide.

( $\uparrow\uparrow\downarrow$ ) in the absence of substrates and switch to cone-like shapes ( $\uparrow\uparrow\uparrow$ ) when bound to anions<sup>[51a]</sup> or 1,3- ( $\uparrow\downarrow\uparrow\downarrow$ ) and 1,2-alternate forms with neutral substrates (Figure 4).<sup>[56]</sup> The result is the formation of aromatic voids defined by the four pyrrole rings within the host molecules and may be considered as a conformational response towards substrates.<sup>[57]</sup>

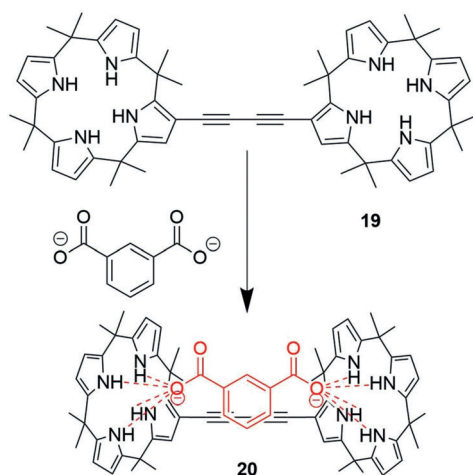
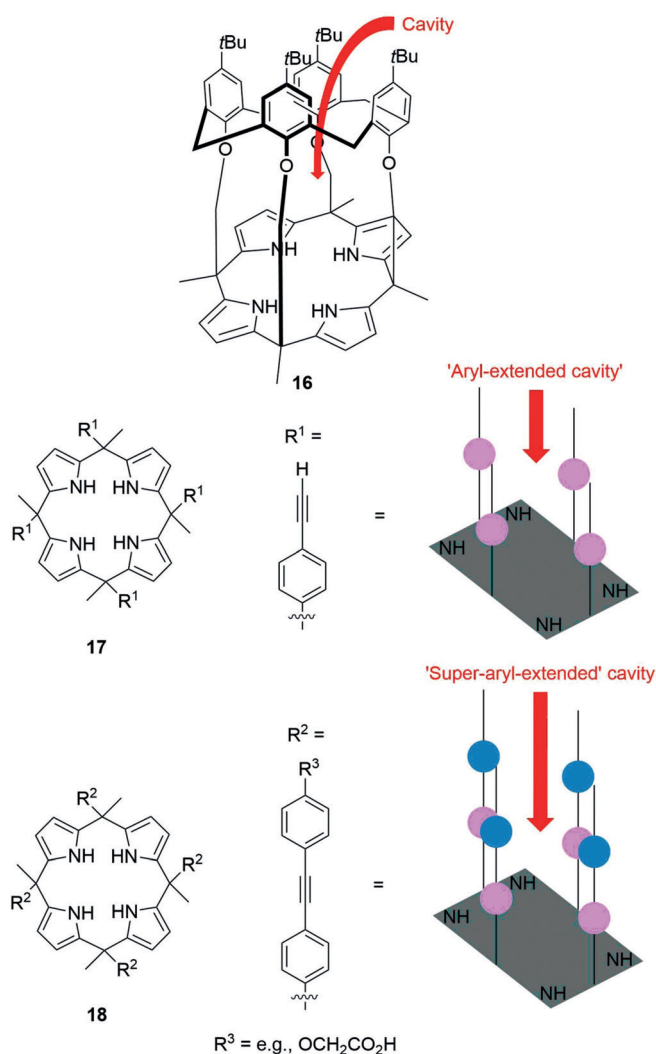
Many qualitative, quantitative, and theoretical studies have been performed on such tetrapyrroles. Examples include compounds **9–15** to compare binding constants and their dependence on electronic properties and the stereochemistry, resulting in a better mechanistic insight into the host–guest chemistry involved (Figure 5).<sup>[51a,59]</sup>

At the same time, complexation of neutral molecules is usually more challenging due to modest association constants.<sup>[56a]</sup> Nevertheless, a large number of neutral receptor–substrate H-bonded complexes of calix[4]pyrroles were described; for example, with alcohols, amides, a broad range of oxygen-containing species, and pyridyl-*N*-oxides.<sup>[56,60]</sup> Based on relatively simple calix[4]pyrroles, numerous more



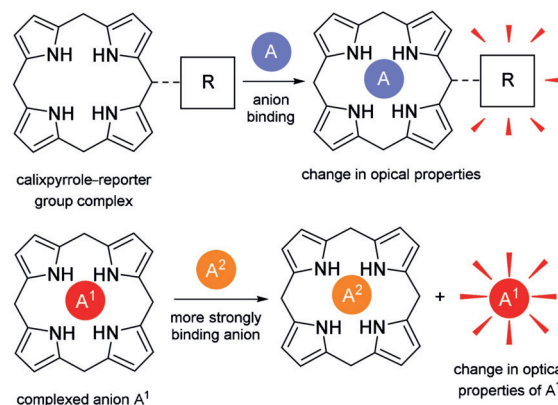
**Figure 5.** Some functionalized and stereoisomeric calix[4]pyrroles used in binding studies to compare the effects of both  $C_m$ - and  $C_\beta$ -substitution.<sup>[51a,59]</sup> The tags  $\alpha$  and  $\beta$  describe the orientation of the aryl substituents (“up” or “down”).

sophisticated receptors have been prepared through an ever-growing toolbox of functionalization techniques (e.g., **16–19**, Figure 6).<sup>[53b,c,56b,60–64]</sup>



**Figure 6.** Selected examples of structurally advanced tetrapyrrole receptors: calix[4]arene-calix[4]pyrrole pseudo dimer **16**,<sup>[64]</sup> “aryl-extended” and “super-aryl-extended” systems **17** and **18**,<sup>[60]</sup> and the dimeric anion-binding complex **19** when binding an isophthalate dianion to form **20**.<sup>[62c]</sup>

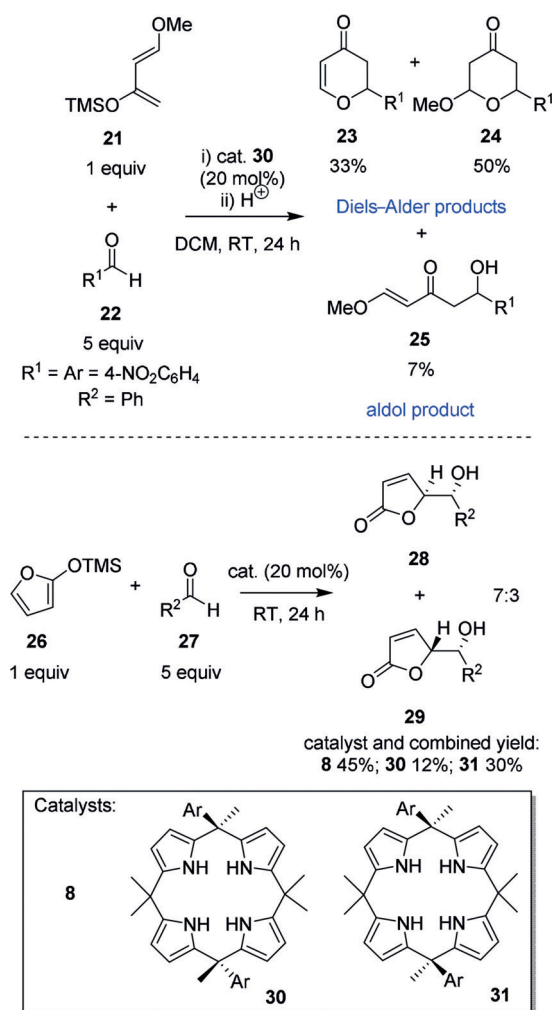
The various calixpyrrole-dependent recognition techniques were reviewed extensively by Gale and Sessler.<sup>[65]</sup> Optical sensors are often based on covalently linked colorimetric or fluorescent reporter groups where perturbation of the electronic properties upon complexation results in a visual or fluorescence-based signal (fluorescence quenching/“turn off” or “turn on”).<sup>[52,66]</sup> A second approach involves a displacement-assay where an initial host-guest complex dissociates upon addition of a more strongly coordinating analyte, which results in a color change (Figure 7).<sup>[53a]</sup> On the other hand, electrochemical sensing utilizes ion-selective electrodes,<sup>[67]</sup> discrete redox-active molecular receptors,<sup>[68]</sup> and chemically modified electrodes.<sup>[69]</sup>



**Figure 7.** Illustration of common calixpyrrole-based optical sensors. Top: covalently attached tetrapyrrole-reporter conjugate; bottom: displacement assay.

H-bonding calix[4]pyrroles have also been utilized as solid high-performance liquid chromatography (HPLC) supports in the form of modified silica gels for the separation of anions and neutral substrates such as amino acids and (oligo)nucleotides.<sup>[70]</sup> As potent Lewis acidic multi-hydrogen bond donors, they possess organocatalytic properties and activate substrates, as illustrated by Diels–Alder reactions and diastereoselective vinylogous additions (Figure 8).<sup>[71]</sup> Furthermore, calix[4]pyrroles can aid regioselective *O*-alkylations and -acylations.<sup>[72]</sup>

A recent Review by Kim and Sessler discusses calix[4]pyrroles as molecular containers for ion transport, recognition, and molecular switching functions<sup>[73]</sup> that are often based on weak interactions. Used in this capacity, they stand as selective receptors and extractants for anions and ion pairs across phase boundaries and membranes and as building blocks for stimulus-responsive materials.<sup>[74]</sup> Due to their remarkable non-covalent binding properties and their ability to form dimers, trimers,<sup>[62b,75]</sup> and aggregates of higher order for selective encapsulation<sup>[76]</sup> and allosteric binding of guests, such as nitroaromatic explosives and fullerenes,<sup>[77]</sup> they are now well-established in the realms of supramolecular chemistry (Figure 9A). Furthermore, calix[4]pyrroles were transformed into drug-delivery vehicles, enzyme mimics, and made an entry as potential anti-tumor agents when it was observed that such synthetic ion carriers can trigger cell death by



**Figure 8.** Calix[4]pyrrole organocatalysts. Top: hetero Diels–Alder reaction of Danishefsky’s diene **21** and aromatic aldehyde **22** in the presence of **30**, yielding a mixture of **23–25**.<sup>[71a]</sup> Bottom: synthesis of  $\gamma$ -butenolides **28** and **29** via vinylogous addition of **26** and **27** in the presence of calixpyrroles **8**, **30**, and **31**, respectively.<sup>[71b]</sup> DCM = dichloromethane; TMS = trimethylsilyl.

facilitating chloride anion transport into cells.<sup>[78]</sup> Even the simple calix[4]pyrrole **8** has been shown to act as an agonist to the G-protein-coupled estrogen receptor (GPER-1).<sup>[79]</sup>

## 2.2. Calix[4]pyrroles: Phlorins, Porphomethenes, and Porphodimethenes

Formal two-, four-, or six-electron oxidation of these nonaromatic macrocycles leads to calix[4]pyrins, which bear analogy to both porphyrins and calix[4]pyrroles by containing a mixture of  $\text{sp}^2$ - and  $\text{sp}^3$ -hybridized *meso*-like positions. The partial interruptions in the conjugation introduce a number of unique structural features since the  $\text{sp}^3$ -carbon atoms perturb the  $\pi$ -system and significantly modify the molecular shape and flexibility. Likewise, far-range electronic induction effects still exist so that functional groups may be used for fine-tuning of conformational and chemical properties.<sup>[80]</sup>

Early examples of rational calixpyrin syntheses include acid-catalyzed cyclization reactions between ketones and pyrrolic precursors followed by partial oxidation (Figure 9B)<sup>[81]</sup> and Buchler’s reductive methylation to yield metalloporphodimethenes<sup>[82]</sup> or substitution reactions.<sup>[83]</sup> The products are usually distorted and feature structural cavities and accessible inner nitrogen atoms (Figure 9C), which may aid the binding of substrates.

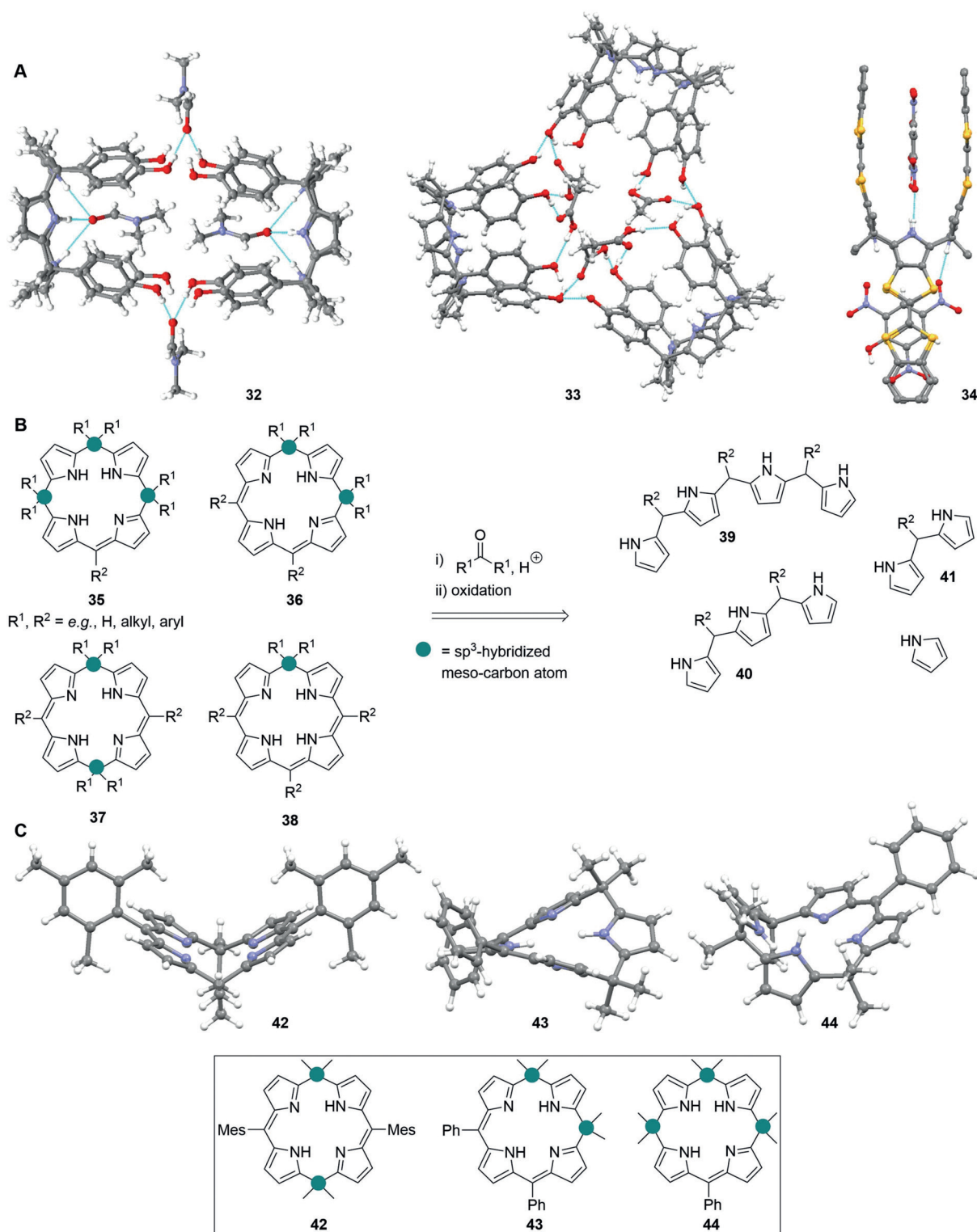
However, it should be noted that the calixpyrin core, like porphyrins, consists of both amine and imine groups and effectively has a lower number of N–H units to interact with guest molecules as compared to the analogous calixpyrroles. This may account for a less pronounced receptor chemistry revolving around this class of macrocycles, leaving the option of core protonation to introduce more N–H motifs and to increase the anion-binding capabilities.<sup>[84]</sup> Nevertheless, a number of H-bonding complexes between (expanded) calixpyrins and various substrates has been observed (Figure 10).<sup>[85]</sup> As such, they provide a potential avenue towards a rich—but as of yet underdeveloped—receptor chemistry up to enantioselectivity.<sup>[86]</sup>

Much like porphyrins, calixpyrins are basic and bind protons at their imine functions but, intriguingly, the corresponding dications are more conjugated and thus more stable than the neutral species.<sup>[86b]</sup> This again highlights the diverse character of calixpyrins as macrocycles with partial traits of both calixpyrins and porphyrins. In practical terms, core-protonated calix[4]pyrins form in the presence of acids where acid anions are subsequently hydrogen-bonded to the (protonated) core. In such complexes, for example, **46**, the pyrrole cycles are tilted significantly out of the mean-plane and, depending on the molecular geometry, the *meso*-hydrogen atoms can participate in further stabilization of those salts (Figure 11).<sup>[87]</sup>

This identifies tetrapyrrole core protonation as an opportunity to enhance the molecules’ receptor potential through out-of-plane distortion and exposure of the central nitrogen atoms. Hence, hereafter we will discuss in detail how this promising strategy has been utilized to exercise conformational control on porphyrins.

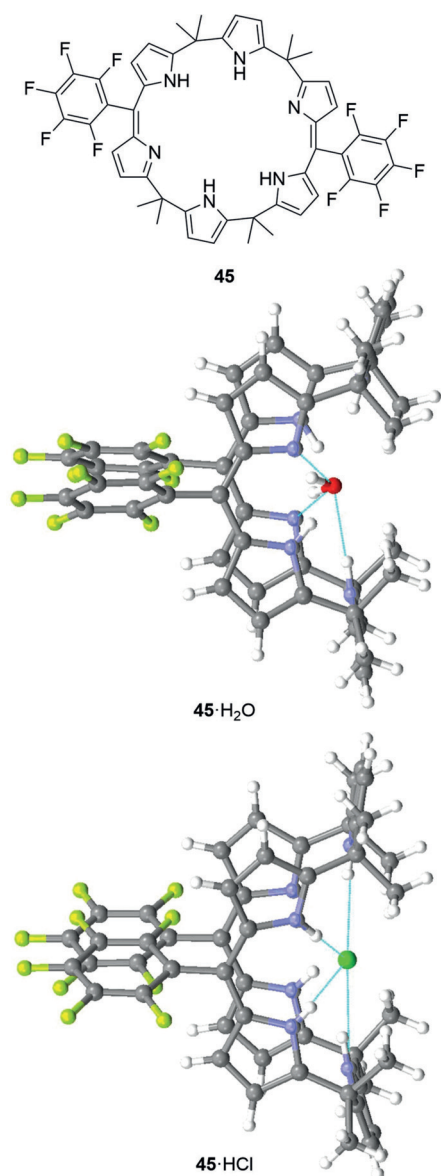
## 3. Accessing N–H Units in Porphyrins

A brief look at nonaromatic porphyrin analogues shows that they are to a large extent involved in many applications that are desirable for porphyrins, too; including organocatalysis and a rich receptor chemistry. However, due to the porphyrin motif’s planarity, rigidity, and the presence of “only” two N–H donors, as opposed to up to four in tetrapyrrolic porphyrinoids, it is traditionally more challenging to apply them in the same manner and to the same extent. But an increased availability—and therefore reactivity—of the core amine and imine moieties can be achieved through rationally altering their orientation within the mean-plane via molecular engineering. While various methods to deform the molecular skeleton in such a way exist (Figure 12),<sup>[1,88]</sup> herein we will focus on a case study of two of the most feasible and widely used strategies, namely core protonation and high



**Figure 9.** A: Views<sup>[58]</sup> of selected calix[4]pyrrole-based supramolecules in the crystal. Dimer **32** (CCDC: MAVZIS) linked by hydrogen bonds with DMF. Trimer **33** (CCDC: MAVZOY) linked by hydrogen bonds with AcOH.<sup>[62b]</sup> Homotropic allosteric calix[4]pyrrole receptor **34** (GUNDUP) with hydrogen-bonded 2,4,6-trinitrophenol.<sup>[72]</sup> B: Acid-catalyzed condensation of pyrrole and pyrrolic synthons **39–41** with ketones followed by partial oxidation as an efficient sequence to synthesize calixpyrins **35–38**. The differentiation of calix[4]pyrins into porphomethenes **35**, 5,10-porphodimethenes **36**, 5,15-porphodimethenes **37**, and phlorins **38**, is also highlighted. C: Structures<sup>[58]</sup> of nonplanar calix[4]pyrins in the crystal: **42** (CCDC: LISSIP), **43** (QENDOC), and **44** (QENDIW).<sup>[81]</sup>





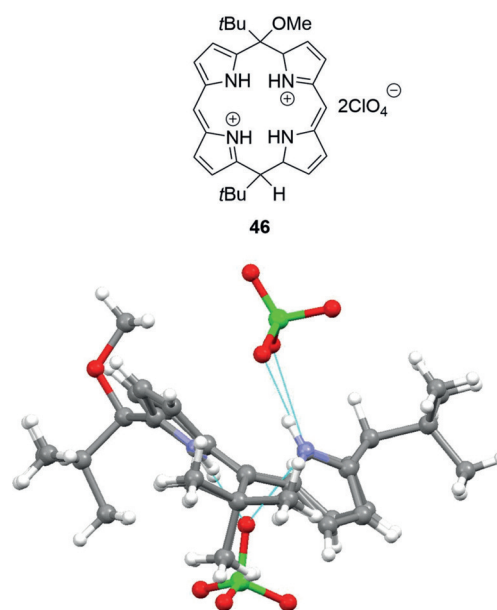
**Figure 10.** Expanded calixphyrin **45** and the structures of two of its hydrogen-bonding complexes in the crystal. **45**·H<sub>2</sub>O (CCDC: XETYUQ) and **45**·HCl (XETZAX).<sup>[58,85]</sup>

peripheral substitution. Additionally, these approaches will be compared to the mode of action of the natural chelataes; enzymes that can induce porphyrin ring distortion.

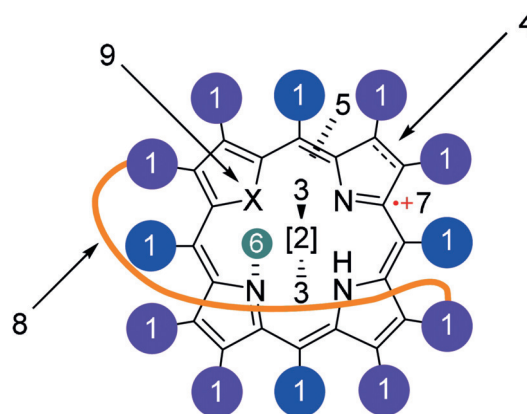
Note, that corroles, expanded-, *N*-confused porphyrins, and various other analogues show an ample (chemo)receptor chemistry, too, paralleling that of “true” porphyrins. However, they have recently been reviewed<sup>[4a]</sup> and will therefore not be discussed subsequently.

### 3.1. Porphyrin (Di)cations

Porphyrin cations are readily produced in the form of core diacids through protonation of the internal imine groups (Figure 13 A). This is accompanied by distortion of the macrocycle, which increases the vector of the N–H orienta-



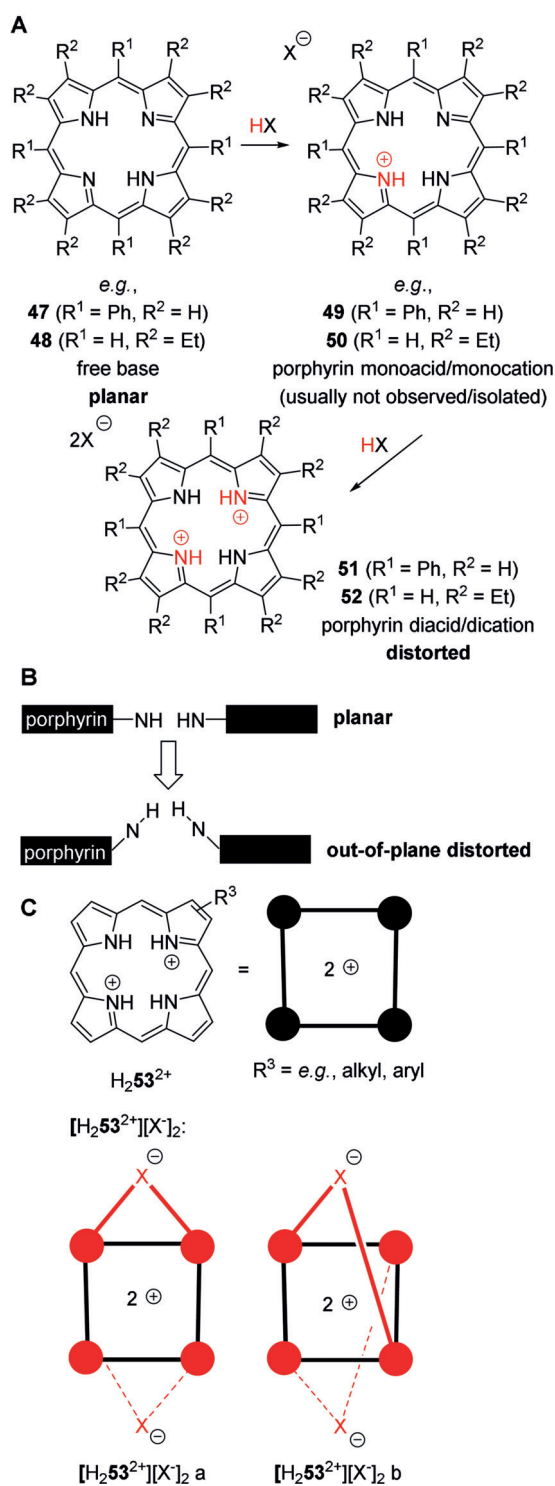
**Figure 11.** View of the molecular structure of calix[4]phyrin salt **46** in the crystal (CCDC: HETDEP).<sup>[58,87]</sup>



**Figure 12.** Possibilities to alter the macrocycle's conformation: 1) introduction of sterically demanding substituents; 2) metallation; 3) axial ligands; 4) degree of reduction; 5) interruption of the conjugated system (see Section 2); 6) *N*-alkylation, -arylation, or protonation; 7) cation radical formation; 8) “strapping” of the macrocycle via covalent linkage of the *meso*- or  $\beta$ -pyrrole positions; 9) heteroatom substitution. Core and skeleton transformations are possible, too.

tion outwards (Figure 13 B). At the same time, such conformational manipulation dramatically boosts the amine groups' capacity to contact appropriate small molecules and ions. Accordingly, porphyrin cations can be considered as large anion sensors due to their capability to form hydrogen bonds with counterions (Figure 13 C).<sup>[3]</sup>

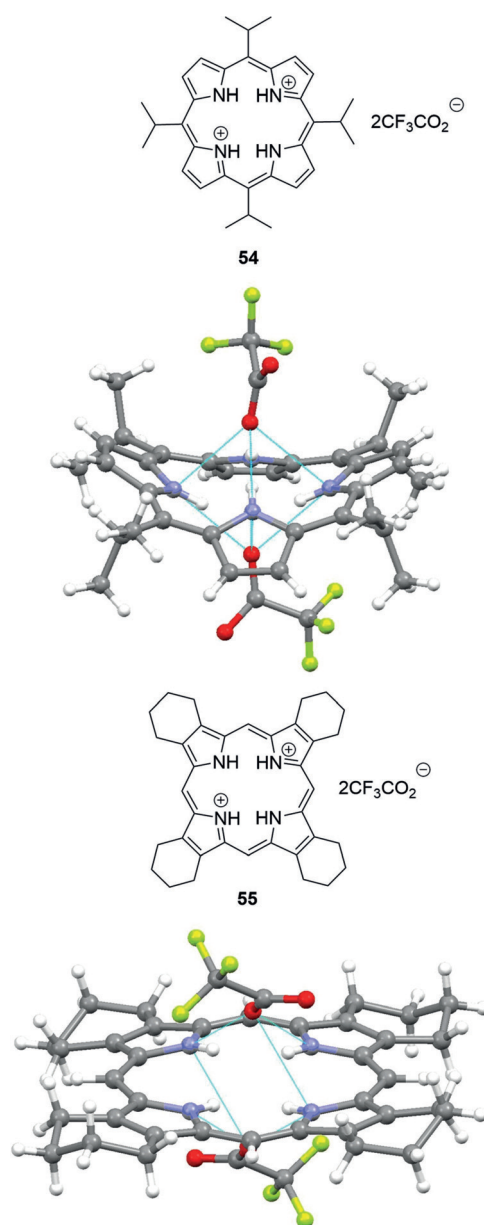
Indeed, crystal structures of porphyrin diacid salts indicate severely nonplanar geometries of the macrocycles as a result of both steric interactions of the crowded core and electrostatic repulsion of the partially positive pyrrole nitrogen atoms.<sup>[89]</sup> In most cases, protonation results in the formation of saddle-distorted (*sad*-type) porphyrins with 1,3-alternating pyrrole tilts (“up and down”,  $\uparrow\downarrow\uparrow\downarrow$ , e.g., in **54**).<sup>[90]</sup> However, individual cases of 1,2-alternating forms



**Figure 13.** A: Protonation of free base-porphyrins, for example, 5,10,15,20-tetraphenylporphyrin ( $\text{H}_2\text{TPP}$ , **47**) or 2,3,7,8,12,13,17,18-octaethylporphyrin ( $\text{H}_2\text{OEP}$ , **48**) by acids  $\text{HX}$  results in the formation of porphyrin dications and their salts, for example,  $[\text{H}_4\text{TPP}^{2+}][\text{X}^-]_2$  (**51**) or  $[\text{H}_4\text{OEP}^{2+}][\text{X}^-]_2$  (**52**). This proceeds via a monocation, for example, **49** or **50**, which cannot usually be isolated.  $\text{X}^-$  = acid anion. B: Illustration of pyrrole out-of-plane distortion in porphyrins/porphyrin core acids. C: Porphyrin acid salts, for example,  $[\text{H}_2\mathbf{53}^{2+}][\text{X}^-]_2$  are H-bonding complexes where various conformations, such as  $[\text{H}_2\mathbf{53}^{2+}][\text{X}^-]_2$  a and b are conceivable.

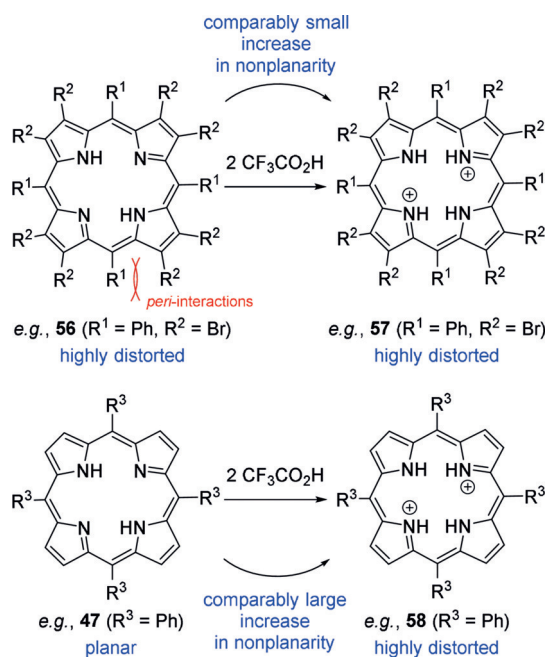
( $\uparrow\downarrow\downarrow$ ) have also been observed, for example, in 2,3,7,8,12,13,17,18-octaalkylporphyrin diacid salts such as **55** (Figure 14).<sup>[90a,91]</sup>

The question of how much the porphyrin macrocycle can be distorted by this means or whether there is a “breaking point” has been thoroughly discussed and an understanding of this approach is vital for the design of sensors based on weak interactions with the core. Accordingly, it was elaborated that peripheral (see Section 3.3) and core steric strain<sup>[88]</sup> (i.e. protonation and *N*-substitution)<sup>[91,92]</sup> are some of the most important “adjusting screws” to exert conformational control.<sup>[1]</sup> One case study indicated that the ditrifluoroacetate salt of **56**, **57**, is one of the most nonplanar porphyrins described so far.<sup>[91]</sup> A comparison with the analogous salt of **47**, **58** that is



**Figure 14.** Top: View of the molecular structure of porphyrin salt **54** in the crystal (CCDC: KIBMEN).<sup>[58,90b]</sup> Bottom: View of the molecular structure of **55** in the crystal (YEVKAL).<sup>[58,91]</sup>

less distorted, clearly points at the additional distorting effects of peripheral substituents. These are involved in repulsive *peri*-interactions, which cause a highly substituted porphyrin like **56** to be “pre-distorted” even without protonation. Thus, by comparing dodecasubstituted free-base porphyrins (e.g., **56**) with their dicationic (e.g., **57**), an increase in nonplanarity of only 13–25%, depending on the individual substituents, was noted. At the same time, this effect is significantly stronger in sterically unhindered systems (e.g., **47**) where protonation can result in distortion of up to 300% (**47**→**58**), suggesting that there is a maximum level of nonplanarity for porphyrins (Figure 15).

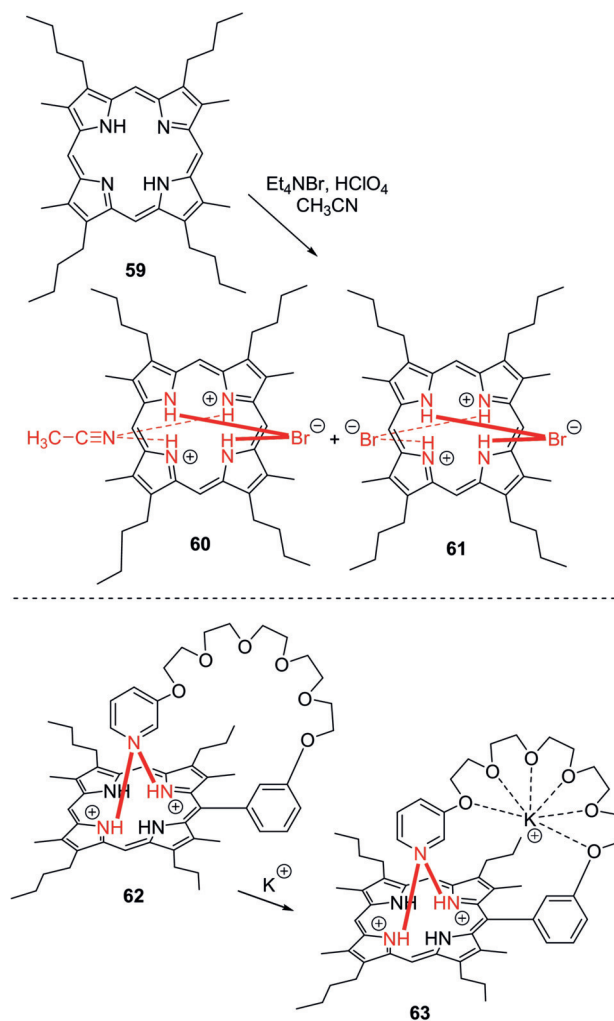


**Figure 15.** A dodecasubstituted porphyrin like **56** is “pre-distorted” due to repulsive *peri*-interactions of the *meso*- and  $\beta$ -substituents. As such, core protonation results in a comparably small increase in nonplanarity in **57**. At the same time, sterically unhindered **47** undergoes a significantly large increase in distortion upon formation of **58**.

Webb and Bampos investigated the dynamics and the complexation behavior of porphyrin diacids in solution and offered insight into the mechanisms of both porphyrin protonation and acid-accelerated metallation.<sup>[93]</sup> They also showed the effects of varying both the acid and the porphyrin on proton transfer and anion recognition and put an emphasis on the role of macrocyclic conformational control in intramolecular proton transfer. In addition, the effects of saddling, *meso*-phenyl twisting, and different hydrogen-bonded counterions on the optical properties of  $[\text{H}_4\text{TPP}^{2+}][\text{X}^-]_2$  (where  $\text{X}^- = \text{F}^-$ ,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ) were elaborated theoretically via density functional theory (DFT) and time-dependent density functional theory (TDDFT) by Rosa and co-workers.<sup>[94]</sup>

Next to this fundamental research, a broad landscape of applications emphasizing the H-bonding and anion-binding properties of porphyrin dicationic hosts exists: The diprotonated form of octaalkylporphyrin **59** acted as a bromide-selective sensor in the system **59**- $\text{Et}_4\text{NBr}$ - $\text{HClO}_4$ - $\text{CH}_3\text{CN}$

(Figure 16).<sup>[95]</sup> Under these conditions, the stable H-bonding complexes **60** and **61** formed preferably, which was considered as a step towards halogen-selective molecular anion receptors of good detectability. A later study investigated the



**Figure 16.** Top: Selective formation of hydrogen-bonding complexes **60** and **61** in situ from the system **59**- $\text{Et}_4\text{NBr}$ - $\text{HClO}_4$ - $\text{CH}_3\text{CN}$ .<sup>[95]</sup> Bottom: Dicationic hydrogen bonding complex **62** for complexation of potassium, yielding **63**.<sup>[96]</sup>

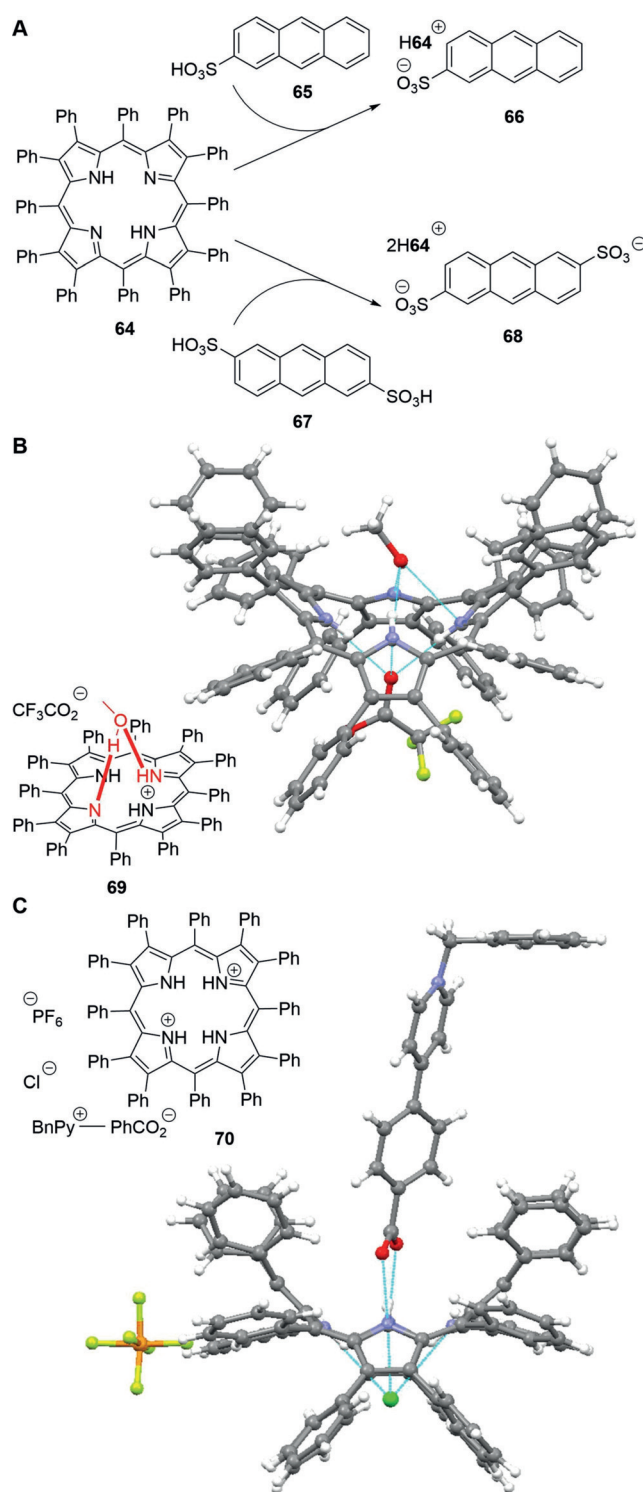
binding of various halides and alkali metal cations by diprotonated porphyrin hosts **59** and **62**, respectively (Figure 16).<sup>[96]</sup> Upon titration of a **59**- $\text{HClO}_4$ - $\text{CH}_3\text{CN}$  system with various halide salts, stable 1:1 and 2:1 hydrogen-bonding complexes with the halogens formed. While the complexation constants decreased in the order  $\text{Cl}^- > \text{Br}^- > \text{I}^-$ , strong fluorescence quenching occurred in the presence of iodide. On the other hand, alkali metal ions could be trapped with monoarylporphyrin dication **62** containing a complexing polyether fragment that was both peripherally attached and hydrogen-bonded to the core through a pyridyl moiety. Note, that a high binding selectivity of **62** for  $\text{K}^+$  over  $\text{Li}^+$  and  $\text{Na}^+$  was observed.

Other efforts focused on nonplanar porphyrin diacids in supramolecular assemblies.<sup>[97]</sup> In one report, Honda and co-

workers constructed a series of hydrogen-bonded supramolecular complexes of saddle-distorted diprotonated **64** and electron donors with carboxylic acids.<sup>[98]</sup> These were then investigated in terms of photo-induced electron transfer dynamics. In such studies, the role of the H-bound counterions is often crucial. For example, 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin dihydrochloride showed chloride-specific aggregation in aqueous solution.<sup>[99]</sup> The presence of  $\text{Cl}^-$  induced H-aggregation followed by conversion into J-aggregates with increasing chloride concentration. Nakanishi et al. investigated the photoconductivity of nanochannels composed of *sad*-type porphyrin dication and electron donors.<sup>[100]</sup> Specifically, the dihydrochloride salt of **64**,  $[\text{H}_4\text{DPP}^{2+}][\text{Cl}^-]_2$ , gave supramolecular architectures by self-assembly based on intermolecular  $\pi-\pi$  interactions that could host tetrathiafulvalene and *p*-aminophenol. Additionally, porphyrin diacid-polyelectrolyte supramolecules formed via electrostatic self-assembly in aqueous solution were used as effective photocatalytic systems for iodide oxidation.<sup>[101]</sup> Herein, the cationic porphyrin architectures showed a significantly higher catalytic activity than aggregates under neutral conditions. Porphyrin dications have also generated some interest, for example, in nonlinear optics (NLO), where laser-induced protonation of free-base porphyrin in chloroform gave a positive nonlinear absorption (NLA) due to conformational distortion.<sup>[102]</sup>

Often, the more elusive porphyrin monocations are also saddle-distorted, although tendentially less than the corresponding diacids<sup>[103]</sup> and stand as a “missing species” in porphyrin chemistry since they are generally difficult to produce, characterize, and isolate. Porphyrin monoacids are usually less stable than their diprotonated counterparts; it is likely that a large saddle-distortion destabilizes the monoacids because their out-of-plane distortion significantly reduces the steric crowding of the remaining unprotonated nitrogen atom. This leads to the uptake of a second proton being more energetically favorable than the first.<sup>[89]</sup> As a result, most observations of these species are limited to theoretical methods and spectroscopic sightings, often in equilibria with the respective dication.<sup>[104]</sup> Nevertheless, the crystal structure of the H-bonded complex  $[\text{H}_3\text{TPP}^+][\text{I}_3^-]$  has been solved<sup>[105]</sup> and in another study, Kojima and Fukuzumi obtained the stable monocation complexes **66** and **68** of saddle-distorted **64** by reaction with anthracene sulfonic acids **65** and **67**.<sup>[106]</sup> This was possible presumably due to the only weakly hydrogen-binding character of the conjugate anthracene bases (Figure 17 A).

$\text{H}_2\text{DPP}$  (**64**) also formed a stable monoacid complex **69** in the presence of methanol and trifluoroacetic acid in dichloromethane.<sup>[107]</sup> The crucial role of methanol is highlighted as stabilizing the monoacid through hydrogen bonding with an out-of-plane N–H group and an imine moiety at the same time, preventing the second acid–base reaction of the macrocycle (Figure 17 B). Furthermore, Almarsson and co-workers were the first to observe a monoprotonated *meso*-tetraphenylporphyrin, which was capped on one face so that the access of a trifluoroacetate anion to the second protonation site was restricted.<sup>[109]</sup> In another notable study, the group of Kojima formed supramolecular hetero-triads of diprotonated **64**, for



**Figure 17.** A: Stable  $\text{H}_3\text{DPP}^+$  H-bonding complexes **66** and **68** made from **64** in the presence of anthracene sulfonic acids **65** and **67**, respectively.<sup>[106]</sup> B: Structure of **69** in the crystal (CCDC: RATXOC) where the monoacid  $\text{H}_3\text{DPP}^+$  is stabilized by hydrogen bonding with methanol.<sup>[58,107]</sup> C: Supramolecular hetero-triad **70** and its structure in the crystal (RARQEJ).<sup>[58,108]</sup>

example, **70**.<sup>[108]</sup> In this context, formation of  $[\text{H}_3\text{DPP}^+][\text{X}^-]$  species was correlated with destabilization of  $[\text{H}_4\text{DPP}^{2+}][\text{X}^-]_2$  due to decreasing  $\text{p}K_a$  values of the protonating acids used.

This occurred as stronger acids provided weaker corresponding bases that were weaker H-bond acceptors (Figure 17C).

Still, while anion binding, material science, and other applications of such salts are of contemporary interest, we are ultimately interested in the use of neutral free-base porphyrins as receptors and organocatalysts. As illustrated in Figure 13B, this requires nonplanar macrocycle conformations with accessible N–H and imine donors/receptors. As such, methods to achieve significant distortion while retaining the tetrapyrrole's characteristics will be discussed in the following.

### 3.2. Nature's Way—Chelataases

Here—as so often—nature provides inspiration when taking a closer look at how conformational control in tetrapyrroles is achieved by chelataases. As was surmised for a long time, these natural enzymes incorporate a range of metals (such as iron, magnesium, nickel, and cobalt) into porphyrins by a distortion-mediated mechanism. This commences by deforming the macrocycle, thus rendering the core more accessible, followed by metal insertion and relaxation of the system.<sup>[110]</sup> The product, a metalloporphyrin, is then released from the protein to fulfill its biological function (Figure 18).

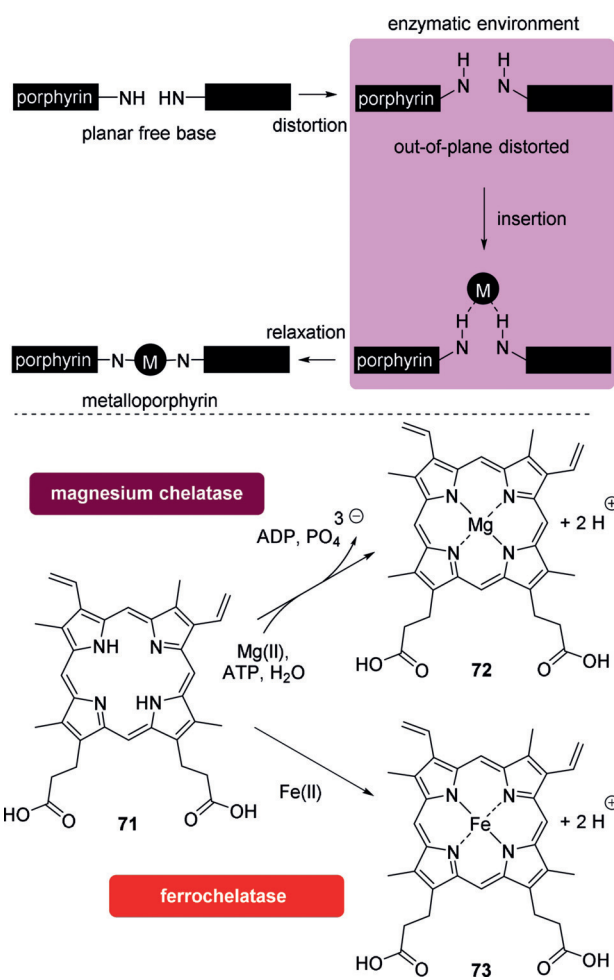
This mechanism was initially proposed on the basis of kinetic studies, chemical modifications, and the enzyme's strong inhibition by *N*-alkylporphyrins<sup>[111]</sup> and supported by the finding that antibodies elicited to a distorted *N*-methylporphyrin (= analogue of ferrochelatase–substrate transition state) could catalyze metal-ion chelation.<sup>[112]</sup> Further indications were obtained through spectroscopic analyses,<sup>[103,113]</sup> and crystal structural studies yielded final proof.<sup>[110]</sup>

In the case of ferrochelatase, the terminal enzyme in heme biosynthesis that inserts Fe<sup>II</sup> into the macrocycle **71**, the energetics of the accompanying ring-distortion process have been calculated.<sup>[114]</sup> Therein, it was argued that once the metal is inserted, the porphyrin becomes stiffer and flatter, resulting in a lower binding affinity to a site designated to bind its nonplanar form. This would ultimately result in release of the metalloporphyrin **73** from the enzyme. It was also suggested that the protein may increase the basicity of the pyrrole nitrogen atoms by macrocyclic deformation. Furthermore, the structure of the PPIX (**71**) substrate bound to ferrochelatase was estimated: all pyrrole rings were tilted out of the mean-plane, most towards the putative binding site of the metal ion.

This brief overview illustrates how nature uses an efficiently “designed” method to achieve what is tedious, maybe even unimitable, in a synthetic setting. Accordingly, researchers have yet to find a synthetic methodology that mimics all the conveniences of these natural enzymes in less time than nature used through evolution.

### 3.3. Highly Substituted, Nonplanar Porphyrins

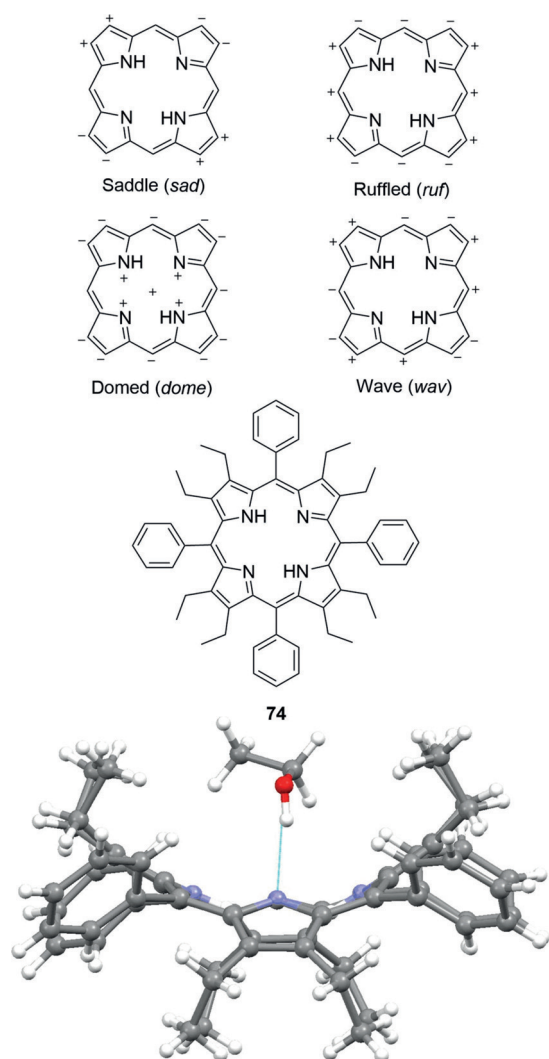
Uncharged nonplanar porphyrins (i.e. opposed to core dications in Section 3.1) are essential for biological functions



**Figure 18.** Top: Schematic illustration of metal insertion into porphyrins by chelataases. Bottom: Net reactions of the biocatalyzed Mg<sup>II</sup> and Fe<sup>II</sup> complexation by PPIX (**71**) to produce (protoporphyrinato IX)magnesium (**72**) and (protoporphyrinato IX)iron(II) (heme b, **73**), respectively. ADP = adenosine diphosphate; ATP = adenosine triphosphate.

and frequently found in, for example, photobiological systems<sup>[115,116]</sup> and other proteins.<sup>[21a]</sup> However, the first experimental proof of such nonplanar conformations was provided in the early 1960s, namely with the tetragonal forms of H<sub>2</sub>TPP (**47**) and Cu<sup>II</sup>TPP.<sup>[117]</sup> The historical development and classic cases of tetrapyrrole nonplanarity have been discussed elsewhere<sup>[88]</sup> and nowadays, the family of dodecasubstituted porphyrins stands as a typical workhorse for studies in this area as they are often accessible by rational syntheses towards conformationally designed targets.<sup>[55,118]</sup> Therefore, it is important that we give a brief introduction to the basic characteristics (e.g., conformation–properties relationships) of such compounds here before deducing their potential as nonplanar receptors.

The various nonplanar distortion modes for highly substituted porphyrins were defined and categorized by Medforth et al. (Figure 19, top).<sup>[12,119]</sup> However, in H<sub>2</sub>OETPP (**74**) and its derivatives, a well-understood and frequently used class of saddle-distorted free-base porphyrins that are structural hybrids of H<sub>2</sub>TPP (**47**) and H<sub>2</sub>OEP (**48**), the central N–H donors are severely forced out-of-plane.



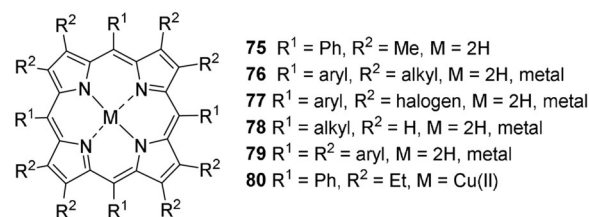
**Figure 19.** Top: Representation of the four most common distortion modes for porphyrins. Only the most significant displacements are shown. Bottom: H<sub>2</sub>OETPP (**74**):EtOH and its structure in the crystal (CCDC: SATQOU).<sup>[58, 120b, 121]</sup>

More precisely, a main structural consequence of the repulsive *peri*-interactions between neighboring *meso*- and  $\beta$ -substituents is an alternating “up and down” tilt of the individual pyrrole rings in **74**, which are rotated ca. 30° out of the mean-plane.<sup>[120]</sup> At the same time, *meso*-aryl groups in nonplanar porphyrins show increasing in-plane rotation. Altogether, the *sad*-type conformation of OETPPs and other 2,3,7,8,12,13,17,18-octaalkyl-5,10,15,20-tetraarylporphyrins causes the amine functions to be oriented significantly towards the sphere of the tetrapyrrole rather than in-plane and increases the chances to interact with surrounding H-bond acceptors. On the other hand, a similar effect may be expected for the imine groups in the form of both increased basicity and H-bond acceptor potential (Figure 19, bottom).

Nonplanarity results in a range of measurable physicochemical effects besides changes in the electronic absorption spectra (i.e. a bathochromic shift).<sup>[122]</sup> Their increased basicity was noted during the initial synthesis of 2,3,7,8,12,13,17,18-octamethyl-5,10,15,20-tetraphenylporphyrin (H<sub>2</sub>OMTPP, **75**)

by Dolphin.<sup>[123]</sup> The product was protonated even by water and also showed broad absorption bands, which were attributed to steric interactions between the *meso*-aryl and  $\beta$ -methyl functions. And metallation experiences a significant rate enhancement in nonplanar tetrapyrroles—an effect that is likely to benefit the distortion-mediated metal insertion by chelataes.<sup>[124]</sup> These and more effects of macrocyclic deformation have been summarized by Shelnutz et al. with an emphasis on new functional properties and their significance in biological systems.<sup>[21a]</sup> Another early observation was that nonplanar porphyrins have altered oxidation and reduction potentials compared to flat analogues and that this effect can be as powerful to the extent that electronic substituent effects are surpassed.<sup>[37,40,125]</sup>

Various other studies have evaluated the nature and effects of nonplanarity in tetrapyrroles, including investigations into (dynamic) photophysical and excited state properties,<sup>[120b,126]</sup> the oxidation to  $\pi$ -cation radicals,<sup>[127]</sup> spectroelectrochemistry,<sup>[128]</sup> and conformational flexibility<sup>[129]</sup> of “stereotypical” representatives, such as 2,3,7,8,12,13,17,18-octaalkyl-5,10,15,20-tetraarylporphyrins **76**, 2,3,7,8,12,13,17,18-octahaloeno-5,10,15,20-tetraarylporphyrins **77**, ruffled 5,10,15,20-tetraalkylporphyrins **78**, 2,3,5,7,8,10,12,13,15,17,18,20-dodecaarylporphyrins **79**, and their metal complexes (Figure 20).

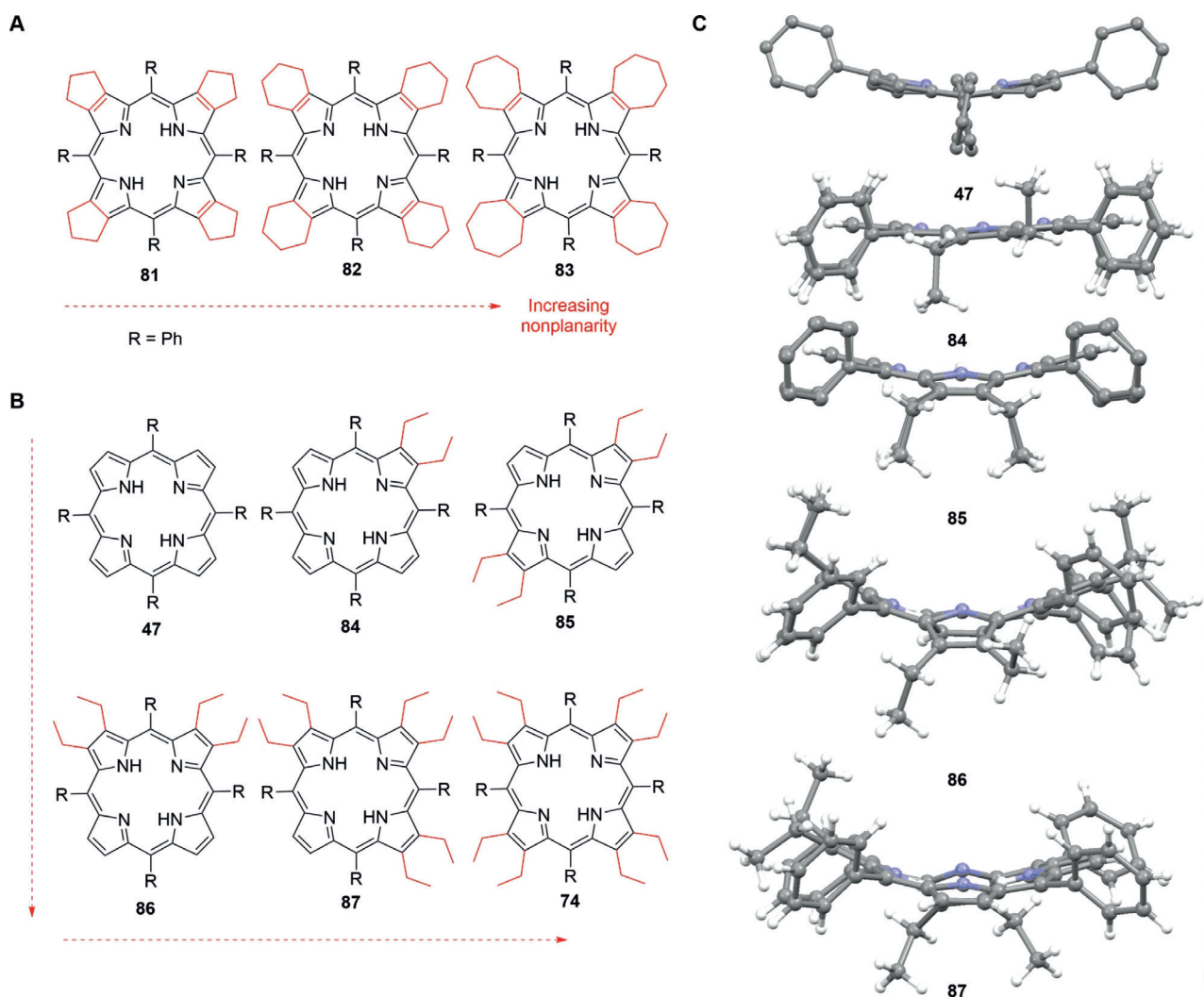


**Figure 20.** Selected porphyrins and their metal complexes discussed in various studies on distorted systems.

Notably, almost all photophysical parameters are directly affected by macrocycle distortion: nonplanar porphyrins have significantly lower fluorescence yields, large Stokes shifts, and shorter lifetimes of the lowest excited state due to faster intersystem crossing and internal conversion.<sup>[1,130]</sup> This qualifies highly substituted, distorted porphyrins as a good starting point to engineer artificial photosynthetic chromophores.

An illustrative example of how substituent bulk and their interactions may be utilized for conformational control on the macrocycles is the series of cycloalkenyl-substituted porphyrins **81–83** “enclosing” the  $\beta$ -positions that was prepared by Medforth et al.<sup>[118b]</sup> These became increasingly nonplanar with larger peripheral cycloalkenyl rings by forcing the methylene groups into closer contact with the *meso*-phenyl substituents (Figure 21 A). In line with that are X-ray studies of conformationally designed nonplanar Ni<sup>II</sup> porphyrins by Barkigia et al.<sup>[131]</sup> and a comparative study on the synthesis and stereochemical properties of **47**, **74**, and tetraphenylporphyrins with graded degrees of  $\beta$ -ethyl substitution **84–87** (“H<sub>2</sub>Et<sub>4</sub>TPPs”) plus their metal complexes.<sup>[132]</sup>

Macrocycle distortions lead to the formation of cavities on both sides of the tetrapyrroles where small molecules can



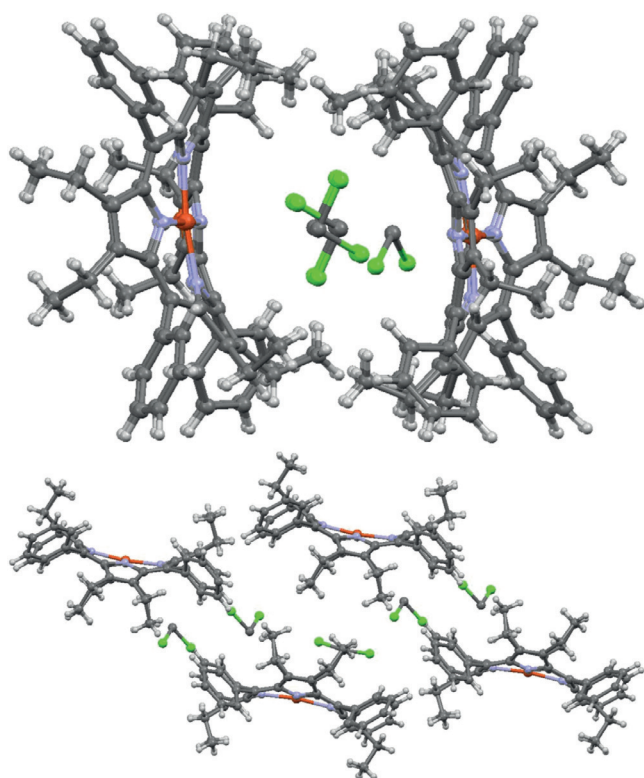
**Figure 21.** A: Gradually distorted cycloalkenyl-substituted porphyrins **81–83**.<sup>[118b]</sup> B: Distorted “H<sub>2</sub>Et<sub>x</sub>TPPs” **84–87** as well as **47** and **74** with graded degrees of β-ethyl substitution and incrementally increasing nonplanarity.<sup>[132]</sup> C: Structures<sup>[58]</sup> of **47** (CCDC: TPHPOR10)<sup>[117a]</sup> and **84–87** (TATPOT01, TATPUZ01, TATQAG01, TATQEK01) in the crystal.<sup>[132]</sup> For comparison see Figure 19 for a crystal structure of **74**.

bind. As a result, solvents can often be found incorporated within the crystal lattice of nonplanar porphyrins. For example, saddle-shaped tetrapyrroles often produce tunnel-like structures in the solid state, which are commonly filled with solvate molecules, as in the case of Cu<sup>II</sup>OETPP (**80**)-2DCM (Figure 22; DCM = dichloromethane).<sup>[133]</sup>

Although conformationally close to OETPPs, the structural chemistry of *sad*-type DPPs, including weak interactions with guests, appears to be more variable. This is best illustrated by **64** itself, which can undergo macrocycle inversion in solution, as shown by variable temperature (VT) NMR spectroscopy.<sup>[55]</sup> The broad conformational landscape of DPPs is also represented by its various crystal structures: First reported was that of the free-base **64** in an orthorhombic modification,<sup>[119]</sup> then another orthorhombic form (albeit in a different space group) with a more symmetric saddle-distortion than previously seen and three water molecules incorporated within the unit cell.<sup>[134,135]</sup>

Similarly to **64**, ethanol has also been found within the crystal structure of **74** where it was coordinating to the central nitrogen atoms (Figure 19).<sup>[121]</sup> It should also be noted that multiple conformations in a single dodecaarylporphyrin have been observed, including *sad*, *ruf*, *wav* modes, and mixtures thereof, which is once again ample evidence for their remarkable flexibility, if not adaptability and points at utilization as selective H-bonding sensors.<sup>[119]</sup>

It should be highlighted that due to the wealth of literature on distorted porphyrins, any synoptic view can only be a screenshot of this fast-developing and diverse landscape, with their applications spanning from medicinal, optical, and technical uses to crystal engineering, methods development,<sup>[136]</sup> catalysis,<sup>[137]</sup> and sensing.<sup>[138]</sup> As we have shown, only the introduction of saddling results in significant N–H exposure and as such, this approach is the basis of a number of new and up-and-coming methods for the binding and activation of small molecules.



**Figure 22.** Cu<sup>I</sup>OETPP (**80**)·2DCM and excerpts of its crystal structure lattice diagram at different visual angles (CCDC: WADROL).<sup>[58,133]</sup>

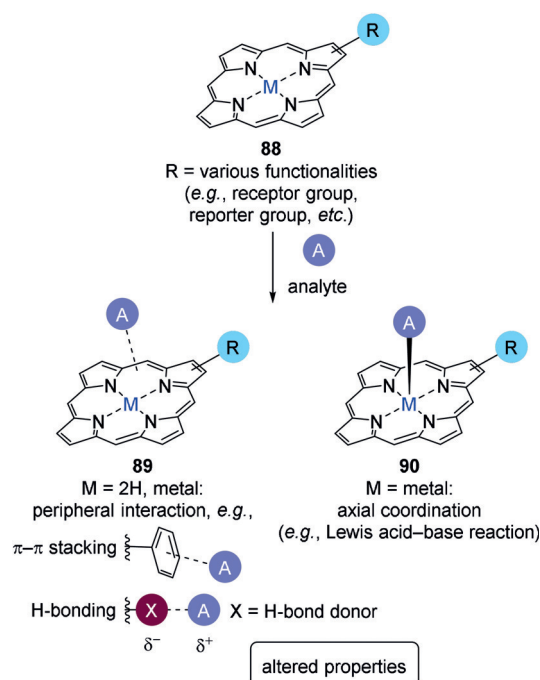
## 4. Applications

Surprisingly, distortion as a method to achieve nonplanar tetrapyrrole conformations for use as sensors and organocatalysts has remained mostly unexplored. This leaves the high potential of the inner nitrogen atoms—the primary structural motif of all free-base porphyrins—to bind and recognize analytes and to activate small molecules unexploited. Therefore, our goal is to explore and discuss the opportunities that conformational design provides as a novel tool to access porphyrin sensors and organocatalysts with an exposed core.

### 4.1. Porphyrins as Sensors: Anion Binding, Explosive Detection, “Chemical Nose”

When porphyrins applied as sensors, the properties of the porphyrin macrocycle change upon interaction (e.g., metal coordination, H-bonding,  $\pi$ - $\pi$  interactions, irreversible chemical reactions) with a substrate, resulting in a detectable response such as a color change, fluorescence quenching/“turn off” or “turn on”, or an electric signal, which mirrors the presence of the analyte (Figure 23).

The development of such molecular probes benefits from the distinct relationship between the porphyrins’ physicochemical features and structure, which provides diverse opportunities to design sensors with tailored characteristics. Such methods involve covalent synthetic modification (i.e. the introduction of additional functions, including receptor and

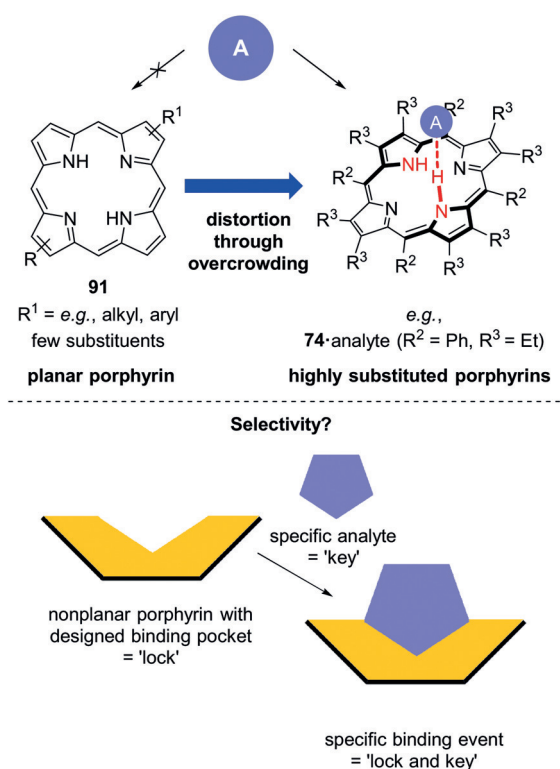


**Figure 23.** Porphyrins **88** for use as sensors and schematic representation of peripheral (in **89**) and axial binding (in **90**).

reporter groups), metal insertion, or altering the molecular skeleton itself, to name but a few. As outlined above, macrocycle conformation and size can be tuned to a great extent by the number and nature of peripheral substituents,<sup>[1,3]</sup> thus modulating ion selectivity and sensitivity. What qualifies porphyrin–substrate complexes in particular for straightforward optical and fluorescence-based detection are their excellent photophysical properties, for instance intense absorption in the Soret and Q bands and red to near-infrared emission. On a different note, they often mimic biological functions, such as reversible binding of gaseous compounds or catalytic activation as methods of action.<sup>[139]</sup>

In practical terms, since there are often scenarios where multiple analytes compete, it is crucial to engineer receptor platforms of high selectivity that specifically emphasize desired interactions while neglecting interferers. This is where the broad and tunable landscape of macrocyclic conformations may take a critical position: as we have elaborated above, porphyrins that have similar substitution patterns can have significantly different conformations. As such, next to say, modulation of the peripherally attached groups and electronic effects, three-dimensional distortion could benefit the specificity of a recognition process. That is because in a sense, nonplanarity may be seen as an additional “adjusting screw” to produce a situation comparable to the lock-and-key model on a molecular level: synthesizing a family of deformed porphyrins based on differing stereochemical parameters (e.g., specific volume and diameter of the binding pocket, chirality) would result in a diverse toolbox of conformationally designed porphyrins to serve as a close fit to specific substrates while disregarding others (Figure 24). This could also be achieved in liaison with surface science, as it has been evidenced that porphyrins undergo structural





**Figure 24.** Top: Concept of distortion-dependent porphyrin sensors. The core of planar porphyrins **91** is unable to complex an analyte, while highly substituted, distorted analogues (e.g., **74**) are able to do so. Bottom: One conceptual example of new sensors based on engineered nonplanar porphyrins.

transformations when anchored to a surface.<sup>[140]</sup> One approach by the group of Aida that relied on such molecular geometry-based considerations for sensing fabricated a  $D_2$ -symmetric, dodecasubstituted, *sad*-type porphyrin where the absolute configuration of chiral acids could be recognized and “memorized” through formation of asymmetric core hydrogen-bonding complexes and circular dichroism (CD) as an analytical tool.<sup>[141]</sup> The “chirality memory” could also be “released” and “retrieved” in response to stimuli such as heat and light.

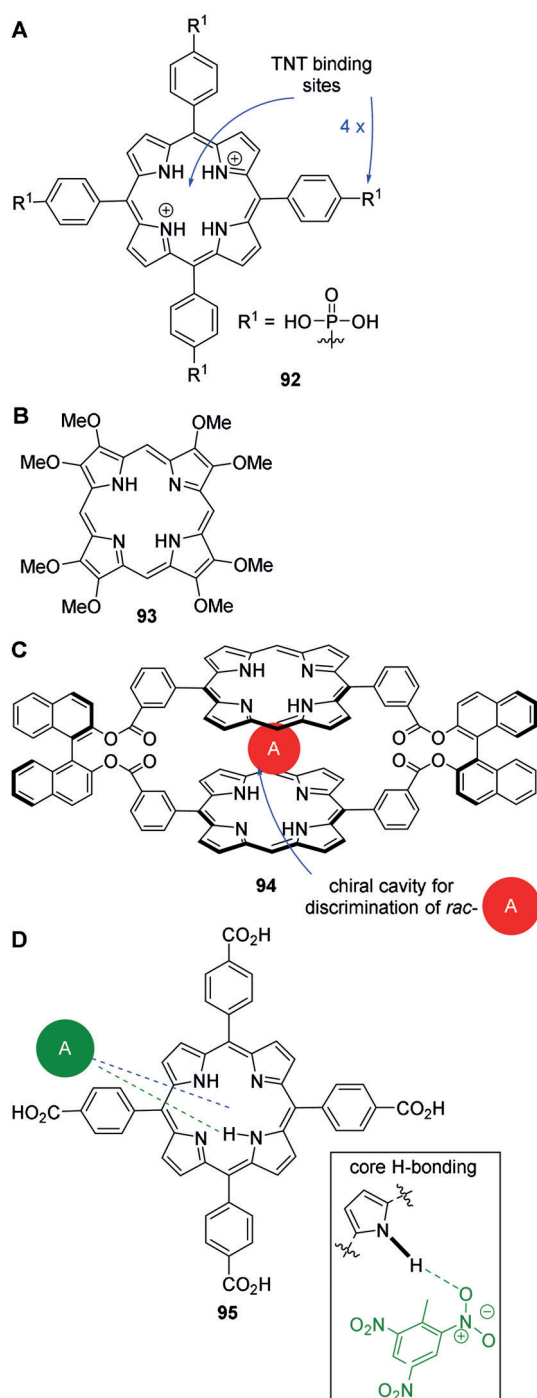
While this approach would mainly depend on N–H...X hydrogen bonding as the type of interaction between substrate and sensor and has yet to be translated into a first case study, metalloporphyrins can facilitate multiple interactions and allow for tailoring their physicochemical properties through alteration of the macrocycle, the complexed metal, and the functional groups. Similarly, free-base porphyrins equipped with particular functional moieties acting as peripheral reporter groups or binding sites are important classes of receptors already at hand. As such, typical (metallo)porphyrin- and porphyrinoid-based chemical sensors can spot gaseous substrates, such as NO<sub>2</sub>, CO<sub>2</sub>, and volatile organic compounds (VOCs), as well as analytes in liquid phase; for instance, many common anions, NO in cells, H<sub>2</sub>O<sub>2</sub>, dopamine and other neurotransmitters, explosives, pollutants, pharmaceutical analytes, ammonia and amines, metal ions, protons, ascorbic acid, glucose, ion pairs, and reactive oxygen

species (ROS).<sup>[4a,b,6d,139,142]</sup> Moreover, porphyrins are of interest for military and security-related applications and can counteract explosives (as in the case of **92–95**) and hazardous biological, chemical, and radiological/nuclear materials (Figure 25).<sup>[138,143–146]</sup> However, currently this rarely involves the core of free-base porphyrins, leaving plenty of room for new developments and to exploit the high potential of the N–H...X binding motif for probing.

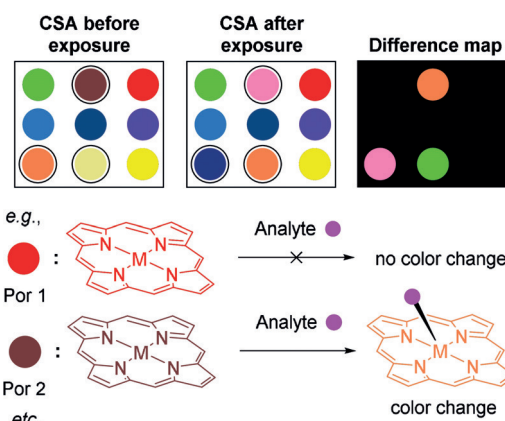
Selective chemical sensors that sense gaseous and liquid analytes based on molecular interactions can be compared to the receptors of the olfactory and gustatory systems. This insight inspired research into artificial sensory organs,<sup>[147]</sup> with the result that today, a range of “chemical noses” and “tongues” are at hand,<sup>[139,148]</sup> often based on porphyrins. The current trends in such tetrapyrrole-based applications have been reviewed by Paolesse et al. who engaged in studies on “chemical noses”,<sup>[139]</sup> spanning from basic research<sup>[149]</sup> to applications as far as breath testing and food analysis.<sup>[150]</sup>

At the same time, others have merged the same molecular interactions with intelligent, novel analytical methods, resulting, for example, in “optoelectronic noses” based on chemoresponsive dyes or fluorophores. Introduced by Suslick and co-workers, “optoelectronic noses” can utilize (metallo)porphyrins as platforms for odor visualization<sup>[151]</sup> and since then, their scope has broadened continually<sup>[142a]</sup> to recognize explosives,<sup>[152]</sup> pathogens,<sup>[153]</sup> toxic industrial chemicals,<sup>[154]</sup> and even to monitor foods freshness.<sup>[155]</sup> For this purpose, simplest, a colorimetric sensor assay (CSA) is digitally imaged before and during contact with a substrate to produce a difference map via digital subtraction, that is, pixel by pixel of the image of the array before and after contact with regards to red, green, and blue (RGB) values (Figure 26).<sup>[156]</sup> An overview on Suslick’s and other groups’ work in this area, including phthalocyanine/porphyrin metal complexes<sup>[157]</sup> and doped materials<sup>[157a]</sup> for “smell seeing” applications<sup>[151b]</sup> was given in 2013.<sup>[142a]</sup>

While these reports often depend on metallation of the core, this has the drawbacks of 1) decreased conformational flexibility of the macrocycle (core) and 2) essentially rendering the central nitrogen atoms inert towards the formation of intermolecular hydrogen bonds. However, we propose that the availability of the central amine and imine motifs is critical for novel applications of free-base nonplanar porphyrins as shape-selective hydrogen-bonding sensors. In planar porphyrins, the N–H units are “buried” by the macrocyclic system but distortion, for example, through core protonation or the introduction of a high number of peripheral substituents, is an opportunity to prompt them for such bonds. In line with this is a study on aryl phosphonate- and phosphonic acid-functionalized porphyrins for molecular recognition of  $\geq 5$  ppb TNT where macrocyclic distortion upon protonation increased selectivity towards the explosive at nanomolar levels.<sup>[143]</sup> Additionally, quantitative complexation of TNT (0.46 ppm) by a complex of carboxylporphyrin **95** and a metal–organic framework (MOF) occurred in aqueous media and involved hydrogen binding with the porphyrin’s central N–H groups.<sup>[146]</sup> Our proposed concept of distortion-dependent sensing is also supported by early studies on porphyrin core acids used for anion sensing, for



**Figure 25.** Selected porphyrin-based sensors for nitroaromatic compounds. **A:** Porphyrin diacid **92** for efficient recognition of  $\geq 5$  ppb 2,4,6-trinitrotoluene (TNT) through emission “turn off” following intermolecular hydrogen bonding and  $\pi-\pi$  stacking.<sup>[143]</sup> **B:** Macrocyclic **93** for detection of, for example, TNT, 2,3-dimethyl-2,3-dinitrobutane (DMNB), 1,3,5,7-tetranitro-1,3,5,7-tetrazocane (HMX), and 1,3,5-trinitro-1,3,5-triazinane (RDX).<sup>[144]</sup> **C:** Chiral dimer **94** for naked-eye recognition of 1,3,5-trinitrobenzene and chiral discrimination of racemic mixtures of nitroaromatics by guest intercalation into a structural cavity via cooperative  $\pi-\pi$  stacking.<sup>[145]</sup> **D:** Complex of **95** and TNT (green dashed line = N—H...X-type hydrogen bond, blue-dashed line =  $\pi-\pi$  stacking).<sup>[146]</sup>



**Figure 26.** Illustration of a CSA where each spot represents a different chemoresponsive dye (e.g., (metallo)porphyrins) before and after analyte exposure. Following testing, a difference map was generated. Some ligands showed a color change upon contact with the substrate.<sup>[156]</sup>

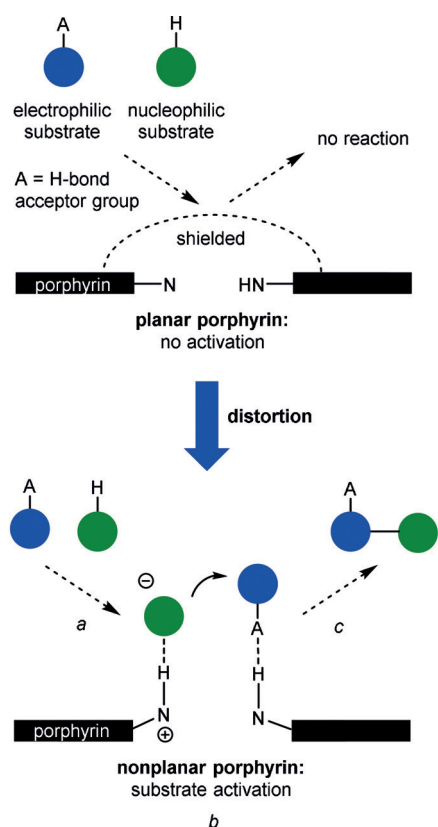
example, where protonated **59** was used<sup>[96,149e]</sup> and the binding of neutral substrates, for example, by **80**,<sup>[133]</sup>  $\text{H}_2\text{OETPP}$  (**74**),<sup>[121]</sup> and  $\text{H}_2\text{DPP}$  (**64**)<sup>[88]</sup> (see Section 3.3).

#### 4.2. Catalysis

We and others have recently reviewed how (metallo)porphyrins are particularly suited for sensing applications<sup>[4a,b,138,139,142]</sup> and their catalytic activity has been proven in numerous contributions, including our own.<sup>[137]</sup> However, applying free-base counterparts in a similar way remains a tedious task, particularly when the bifunctional properties of the core itself (i.e. basic imine functions for deprotonation, which, in turn, once protonated, become H-bond donors, and acidic pyrroles for hydrogen-bond donation) are to be exploited for probing and catalysis. As mentioned several times, this is because the inner nitrogen atoms are “hidden” for steric reasons and cannot usually be contacted by suitable reaction components (Figure 27).

And while free-base porphyrins, thanks to their various (optical) properties that change upon alteration of the microenvironment of the tetrapyrroles, were indeed used as probes for, for example, sensing of VOCs,<sup>[158]</sup> water and ethanol,<sup>[159]</sup> gases,<sup>[160]</sup> and furthermore, as was recently summarized,<sup>[142d]</sup> ions and ion pairs, ROS, chiral discrimination, and as thermosensitive probes, specific tailoring of the free-base macrocycle skeleton as a form of molecular engineering towards catalysis, improved substrate binding/recognition, and probing appears underrepresented, leaving, in turn, plenty of room for innovation.

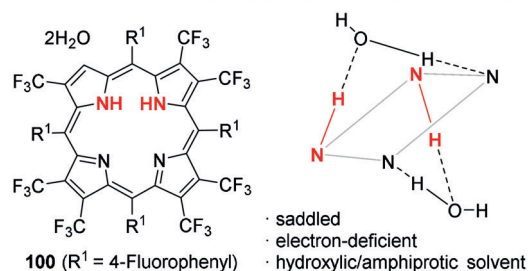
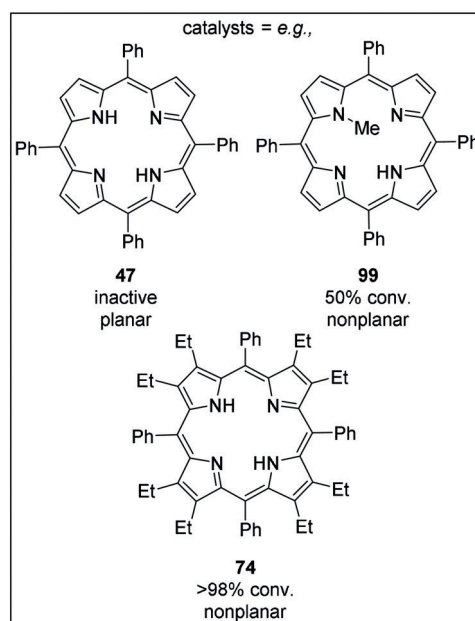
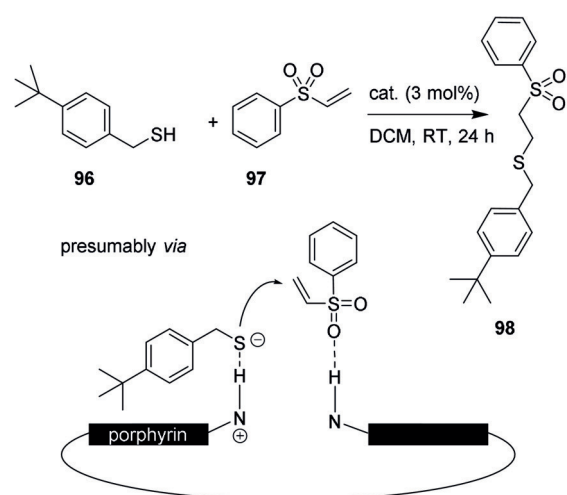
Comparable to sensing, during catalysis the substrates bind to the active center and with this being the case, molecular engineering of the porphyrin macrocycle can principally be used to increase selectivity and sensitivity. Having conducted studies on conformational design of distorted porphyrins,<sup>[1,3a,119,132,161]</sup> and taking into account the accessibility of their nitrogen atoms for hydrogen bonding,<sup>[18d,88]</sup> we elaborated a model of bifunctional substrate



**Figure 27.** Concept of distortion-dependent bifunctional porphyrin organocatalysts. Due to the “shielded” core, planar porphyrins cannot activate the electrophilic reaction component through hydrogen bonding or the nucleophilic reagent through deprotonation followed by hydrogen bonding. However, distortion is a method to render the porphyrin catalytically active (a: binding of substrates; b: activation of both substrates and reaction; c: release of the product).

activation as a potential avenue towards porphyrin-based organocatalysis.<sup>[3b]</sup> Therein, *sad*-type macrocycles were necessary to deliver catalytically active free-base porphyrins. Following this proposal, conformational control was exerted to produce tetrapyrroles with enhanced basicity and a core that was available for hydrogen bonding (distortion-dependent hydrogen bonding).<sup>[137]</sup> Moreover, while previously, all natural and synthetic catalytically active porphyrins were dependent on metallation, this allowed us to apply highly substituted (e.g., **74**) and *N*-methylated compounds (e.g., **99**) as bifunctional organocatalysts. Altogether, this opened a new functional role and points at future perspectives for sensor design based on conformational control.

Specifically, H<sub>2</sub>OETPP (**74**) gave the best results and catalyzed a sulfa-Michael addition of *tert*-butyl benzylmercaptan (**96**) to phenyl vinyl sulfone (**97**) to afford adduct **98** quantitatively; a reaction susceptible to bifunctional catalysis (Figure 28, top). This was also compared to the performance of various common bases, including 4-dimethylaminopyridine (DMAP), triethylamine (TEA), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). While the use of weak amine bases failed to promote the reaction, the conversion using **74** was comparable to that of TEA. However, we are confident that in the future, conformationally designed porphyrins will



**Figure 28.** Top: Porphyrin-catalyzed sulfa-Michael reaction of **96** and **97**.<sup>[137]</sup> Bottom: Structure of *cis*-NH-porphyrin **100**·2H<sub>2</sub>O.<sup>[162]</sup>

surpass the performance of standard bases due to their greater tunability and superior potential for functionalization.

To illustrate this prospect, one may also take a look at the recently isolated *cis*-NH-porphyrins.<sup>[18d, 162]</sup> Ghosh and co-workers laid the foundation for new applications of nonplanar porphyrins when they achieved stabilization of *cis*-NH-tautomers (Figure 28, bottom). Depending on solvent, substituents, and conformational effects, the core itself was altered substantially without losing its bifunctionality and the

stable *cis*-tautomers could show unique binding, sensing, and catalytic properties.

## 5. Summary and Outlook

This Review shows that porphyrins and their nonaromatic analogues offer rich opportunities for the development of ligands with multiple functions. Due to the diverse properties that are tunable over a wide range of parameters, porphyrinoids are legitimately one of the most important classes of macrocyclic ligands altogether. Thanks to their ability to engage in various covalent and non-covalent binding modes, including metal and axial coordination, as well as peripheral covalent and hydrogen bonds, very similar tetrapyrrolic systems may fulfill versatile natural and artificial functions. They have a pronounced biological role and omnipresence in nature and many examples show that porphyrin ligands were successfully utilized for the development of, for example, new (electroactive) materials, supramolecular systems, biomimics, and beyond, ranging from surface technology to DSSCs to medicinal research, to name but a few examples.

While planar (metallo)porphyrins are indeed used as sensors, catalysts, etc.—applications that are highly sought after by scientists—only few cases exist where specific modulation of the macrocyclic skeleton itself was used to tune the binding properties of the ligands.

Prior to discussing “true” porphyrins, we reached out to nonaromatic porphyrinoids—calixpyrroles and calixphyrins—and highlighted their conformational flexibility and unique stereochemical features, which granted them a pole position as N–H···X-type H-bonding-based ligands, sensors, assays, and catalysts. Next, approaching “true” porphyrins, we presented two methods to access their otherwise “hidden” bifunctional core and to utilize them in N–H···X bonds, specifically protonation and peripheral substitution with sterically demanding substituents to create (core) acids and highly substituted macrocycles, respectively. These alterations can lead to saddle-type out-of-plane distortion and outwards orientation of the central amine and imine groups, which allows them to be contacted by surrounding small molecules. As such, diacids have been widely used in supramolecular chemistry and in some cases as anion sensors. On the other hand, highly substituted porphyrins are neutral free bases that take deformed shapes as a result of repulsive *peri*-interactions. This results in the formation of binding pockets that allow them to incorporate and bind guest molecules.

Ultimately, a novel approach yielded the first example of bifunctional porphyrin organocatalysts of tunable basicity,<sup>[137]</sup> which, in turn, is but a screenshot of the many opportunities that conformational design and molecular engineering of free-base tetrapyrroles towards, for example, distortion-dependent sensors and catalysts offer. In this context, we introduced a concept of tailoring free-base tetrapyrroles of specific three-dimensional conformations as a promising avenue towards shape-selective ligands with increased conformational flexibility of the macrocycle (core) and central nitrogen atoms. Therein, free bases readily engage in the formation of intermolecular hydrogen bonds, a feature that

would otherwise be near to inaccessible. Based on this principle, we propose that the N–H···X binding motif in tetrapyrrole ligands can be exploited to a previously unknown extent by means of conformational control to produce improved receptors, sensors, catalysts, or even drugs, advanced (supramolecular) materials, etc. Hopefully, this will open new functional roles and lead to a rethinking, if not renaissance, of the use of natural and synthetic porphyrins, particularly their metal-free derivatives, with a plenitude of new and up-and-coming applications on offer.

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## Conflict of interest

The authors declare no conflict of interest.

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