Synthesis and anion binding properties of porphyrins and related compounds

Flávio Figueira\(^a\), João M. M. Rodrigues\(^a\), Andreia A. S. Farinha\(^b\), José A. S. Cavaleiro\(^a\), João P. C. Tomé*\(^{a,c,d}\)

\(^a\)Department of Chemistry and QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal
\(^b\)King Abdullah University of Science and Technology (KAUST), Water Desalination and Reuse Center (WDRC)
Biological and Environmental Science & Engineering (BESE), Thuwal 23955-6900, Saudi Arabia
\(^c\)Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal
\(^d\)Department of Organic and Macromolecular Chemistry, Ghent University, Gent, B-9000, Belgium.

Dedicated to Professor Tomás Torres on the occasion of his 65\(^{th}\) birthday

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**ABSTRACT:** Over the last two decades the preparation of pyrrole-based receptors for anion recognition has attracted considerable attention. In this regard macrocyclic porphyrins, phthalocyanines and expanded porphyrins have been used as strong and selective receptors while the combination of those with different techniques and materials can boost their applicability in different applications as chemosensors and extracting systems. Improvements in the field, including the synthesis of these types of compounds, can contribute to the development of efficient, cheap, and easy-to-prepare anion receptors. Extensive efforts have been made to improve the affinity and selectivity of these compounds and the continuous expansion of related research makes this chemistry even more promising. In this review, we summarize the most recent developments in anion binding studies while outlining the strategies that may be used to synthesize and functionalize these type of macrocycles.

**KEYWORDS:** Porphyrins, phthalocyanines, expanded porphyrins, supramolecular chemistry, anion (chemo)sensors, anion binding

*Correspondence to: João P.C. Tomé, email: jnome@ua.pt, tel: +351 234-370-342, fax: +351 234-370-084.
INTRODUCTION

Over the past decades a great attention has been devoted to the synthesis and development of analytical methods for the reliable detection of target species such as anions. The detection, differentiation and visualization of these entities are crucial challenges for the design of selective optical chemosensors.

Anions are abundant in nature, and are associated with numerous roles. Pollutant anions such as phosphate and nitrate from fertilizers are responsible for the eutrophication of rivers and lakes, whilst pertechnetate produced from the reprocessing of nuclear fuel and its subsequent discharge to the seas, is a matter of ecological apprehension [1-4]. They are also associated with several biochemical processes like transport, recognition and transformations at a cellular level. For instance, they are essential in the formation of enzyme–substrate complexes as well as in the interaction between proteins and DNA or RNA. Small disturbances in these processes are commonly associated with a variety of diseases like osteoporosis, Alzheimer's and cystic fibrosis.

The supramolecular chemistry of anions by pyrrole-containing entities has been extended to structures containing a huge set of functionalizations with unusual binding abilities. Gale and coworkers have discussed these structures in several reviews [5-10]. Nevertheless, despite all the efforts directed towards receptors design, strategies for receptors with high affinity and specificity for a specific anion are still rare. This gap is associated to the complexity of the precise requirement of conformational factors and the numerous non-covalent interactions, making it difficult to predict if a certain molecule that can act or not as a receptor for a specific guest [11,12]. For example, molecular engineering of receptors requires a precise control of binding interactions, correct cavity size and solvation parameters [13]. Furthermore, anionic species have a wide range of geometries and therefore a higher degree of design may be required to make receptors specific to their anionic guests [14].

One pathway for successful molecular design is the synthesis of pre-organized receptors that will have an energetic advantage over other flexible structures [15,16]. This makes the design of highly pre-organized and rigid receptors with complementarity with the guest molecule extremely complex. Therefore, the advantages of using semi-rigid systems over rigid systems lay in the ability to adopt favorable conformations to fit the guest molecule. With this in mind it is possible to create receptors for a specific guest molecule with simple modulation of the receptor [13,17,18].

This review article highlights important developments in anion recognition while outlining the strategies that may be used to synthesize and functionalize porphyrin type compounds, such as porphyrins, phthalocyanines and expanded porphyrins, mainly saphyrins and hexaphyrins.

PORPHYRINS

In the last years, porphyrins and related compounds have been a subject of widespread developments in diverse fields such as: catalysis [19,20], photodynamic inactivation of pathogenic microorganism [21,22], photodynamic therapy [23-25], photoinduced energy- and electronic-transfer materials [26,27], nanomaterials [21,28], amongst others [29-31]. However, the development of porphyrins and phthalocyanines as anion binding agents is still in the beginning when compared with their expanded counterparts. Few examples of porphyrins can be found in the literature exhibiting the ability to bind halides and nitrate anions, mostly in their protonated forms [32-34]. More recently, the use of protonated non-chiral porphyrins has found its use in the determination of the ee in chiral acids. This result may be extended to a wider family of chiral guests and was performed with the dicationic form of meso-tetraphenylporphyrin I (Figure 1) [35,36].
Porphyrid dication was found to bind two chiral guests in fast exchange equilibrium and each face of the macrocycle acts independently because of its saddle-shaped structure. The $^1$H NMR peak splitting at extremes of $ee$ (only one face of the molecule is shown for clarity) shows that the chiral guest bound between the opposing pyrrole groups induces non-equivalency in the adjacent pyrrolic $\beta$-$H$, $H_a$, and $H_b$. The corresponding chiral environment induces different shielding in the shifts of $H_a$ and $H_b$ as schematically represented by arrows in figure 1 and a reduction in the $ee$ value causes isochronicity of $H_a$ and $H_b$ as a result of averaging [35].

An assessment of the literature involving porphyrin-based anion receptors show a propensity for the functionalization of porphyrins in their meso positions to provide a source of hydrogen bond donors that allow an extensive modulation of their anionic guest recognition. Urea subunits and amine moieties are particularly popular in this regard [37-40].

A common porphyrinic template used in the synthesis of relevant anion binding receptors is 5,10,15,20-tetrakis($o$-aminophenyl)porphyrin 2 (Scheme 1). This template can be synthesized as several atropisombers and while the most commonly used in functionalization’s aiming anion sensing purposes is the $a,a,a,a$-isomer (2a and 3a), and studies comprehending all the isomers, presented the importance of the structure-affinity relationship in anion recognition (Figure 2) [41-44].
The first set of receptors synthesized, and explored in anion binding analyses were a series of ferrocenyl and cobaltocenium amide atropisomeric porphyrins receptors 4a-4d and 5a-5d. The authors reacted an excess amount of ferrocene and cobaltocenium derivatives ((chlorocarbonyl)ferrocene and (chlorocarbonyl)coobaltocenium, respectively) with the appropriate atropoisomer of 5,10,15,20-tetrakis(2-aminophenyl)porphyrin (2a-2d) in dry dichloromethane in the presence of triethylamine, furnishing the corresponding crude products in good yields ranging from 67 to 72% (Figure 2) [44].
In nature, the selective binding for anions is dependent on the positional alignment of the anion binding sites, and these receptors were designed to have the positional alignment of the hydrogen bond groups and different cavity dimensions, creating unique topological amide hydrogen-bonding environments. Nevertheless, it was found that only in the presence of a Lewis acidic center, Zn(II) incorporated in the porphyrin core was able to work as anion receptors, both spectrally and electrochemically for 5a-5d, 7a and 7d.

Remarkable anion selectivity differences are displayed by the various atropisomers, which highlight the importance of the relative positions of the cobaltocenium/ferrocene amide moieties in the anion recognition process. The ferrocene derivatives, \(a,a,a,\beta\) isomer of 5b exhibited the selectivity sequence \(\text{NO}_3^- > \text{Cl}^- > \text{HSO}_4^-\) whereas the \(a,a,a,a\) isomer of 5a is bromide selective. Moreover, the cobaltocenium \(a,a,a,a\)-atropisomer 5a exhibits the selectivity trend \(\text{Cl}^- > \text{Br}^- > \text{NO}_3^-\) in which all four cobaltocenium moieties cooperatively form a cavity complementary to the spherical halide anion guest. In contrast the \(a,a,\beta,\beta\) atropisomer 5d displayed the selectivity sequence \(\text{NO}_3^- > \text{Br}^- > \text{Cl}^-\) indicating a complementary trigonal host cavity exists for nitrate [44,45].

Likewise, Kim et al., developed a neutral anion receptor containing a unique combination of an immobilized Lewis acidic binding site and carbamate groups enabling additional hydrogen bond moieties [46]. Here the use of 2a in combination with the same synthetic methodology previously described, with a different condensation substituent (ethyl chloroformate), furnished the carbamate-appended porphyrins 10a, which after refluxing with Zn(OAc)$_2$, gave rise to 11a. UV-Vis titration binding studies were in accordance with the previous findings, where the free-base porphyrin 4a was a poor complexing agent for anions. In contrast, the zinc metalloporphyrin receptor 9a strongly bound anionic guests and
selectivity turned out to be dependent upon the anion basicity and geometrical complementarity between 9a and the guest. As described before, the Lewis acidic Zn(II) functioned as an additional anion-binding site orthogonal to the carbamate hydrogens and thus increasing the overall binding strength of 9a in a 1:1 stoichiometry, binding dihydrogenophosphate ($K_a = 2.2 \times 10^4$ dm$^{-3}$ mol$^{-1}$) and fluoride ($K_a = 2.6 \times 10^4$ dm$^{-3}$ mol$^{-1}$) anions selectively and strongly using cooperative force of both the coordination to the Lewis-acidic zinc metal ion and multiple hydrogen bonds.

Using also a condensation reaction to incorporate imidazolium and triazole pending moieties in the “picket fence” structure discussed before, Beer and coworkers developed the synthesis of compounds 10a and 11a, reacting porphyrin 2a with an excess chloroacetyl chloride in dry dichloromethane in the presence of triethylamine [47-50]. These compounds proved to be valuable intermediates in the synthesis of receptors 12a and 13a bearing imidazolium and triazole groups, respectively. Interestingly, both receptors have exhibited a strong affinity for SO$_4^{2−}$ anions ($K_a > 10^6$ dm$^{-3}$ mol$^{-1}$ for both receptors) while exhibiting some affinity for halogen anions as well, though at a lower affinity. In addition, the charged nature of receptor 12a allowed it to form complexes with sulfate in H$_2$O:DMSO (5:95) solvent mixtures in a cooperative 1:1 stoichiometry.

In 2001, Wang et al. have developed a porphyrin framework reacting derivative 2c with protected amino acids as pending groups. Complexation experiments were performed in dichloromethane solution, using UV-Vis spectroscopy, circular dichroism spectra and molecular modeling in order to study the enantioselectivity of 15c towards L and D amino acid esters. The experimental results reveal that the host 15c prefers to bind the D-enantiomer guests. The strongest enantioselective binding of D,L-amino acid esters is provided by the esterified phenylalanine as guest, which is as high as $K_D/K_L = 21.54$ at 25 °C. The enantioselectivity $K_D/K_L$ is temperature dependent and molecular modeling to examine the enantioselectivity differences of host 15c, between the chiral guests of the same family are mainly from steric repulsion [51].

An important factor to take into consideration when synthesizing porphyrinic receptors is the accumulation of H-bond donor sites in close vicinity to each other [52]. This allows a maximum number of hydrogen bonding contacts for the anionic guests. Introducing urea subunits around porphyrins in a similar fashion as the amide motifs produces again a “Picket fence”, where the planar porphyrins and the urea arms delineate a spherical cavity, resulting in improved binding affinities. Initially, these modifications were performed reacting porphyrins 2a with 4 equiv. of the 4-fluorophenyl isocyanate in chloroform at room temperature. The final product 16a and 17a were achieved in yields ranging from 70 to 85% (Scheme 2) [53,54].
Herein, the Zn(II) complex 17a while exhibiting the same general selectivity trend of Cl\(^-\) > Br\(^-\) > H\(_2\)PO\(_4\)\(^-\), NO\(_3\)^- exhibited a Cl\(^-\):NO\(_3\)^- and Cl\(^-\):H\(_2\)PO\(_4\)\(^-\) lower selectivity when compared to the corresponding free-base urea porphyrins 16a. The binding constants for chloride, bromide, and H\(_2\)PO\(_4\)\(^-\) were up to 10 times less than with their respective free-base porphyrin receptor. This decrease in selectivity and binding strength for the zinc(II) complex may be attributed to an increased rigidity of the metallocorphyrin. The exceptionally strong affinity for Cl\(^-\) (K\(_a\) > 10\(^5\) dm\(^3\) mol\(^{-1}\)) in DMSO-d\(_6\) and in DMSO/H\(_2\)O, was seen at a much greater extent (1000:1) when compared with the trigonal NO\(_3\)^- (280:1). This selectivity and strength of binding for anions, compared with the positively charged functionalized cobaltocenium porphyrins 7a and 7d and metallated neutral zinc ferrocene atropisomeric porphyrin receptors 5a-5d (Scheme 1), was increased by two orders of magnitude, and the selectivity pattern for halogen anions was maintained (Cl\(^-\) > Br\(^-\) >> H\(_2\)PO\(_4\)\(^-\) > HSO\(_4\)\(^-\) > NO\(_3\)^-). Furthermore, it was observed that the solvent inclusion in the “picket-fence” porphyrin 16a cavity enhanced anion binding and concluded that solvent interaction can exert a positive influence on overall binding energy [38,55].

Other examples using urea pending groups were achieved transforming 2a into its isocyanate derivative after reaction with triphosgene in dry dichloromethane with addition of piperazine or precursors 24 and 25, yielding compounds 18a, 20a and 22a, respectively (Scheme 2) [56]. Complexation reactions of these receptors with Zn(OAc)\(_2\) provided compounds 19a, 21a and 23a respectively [38,56].

The novel doubly strapped zinc porphyrin 19a showed high affinity and selectivity for H\(_2\)PO\(_4\)\(^-\) (8.43x10\(^5\) M\(^{-1}\)), F\(^-\) (3.98x10\(^5\) M\(^{-1}\)) and AcO\(^-\) (1.53x10\(^4\) dm\(^3\) mol\(^{-1}\)) over other anions by combining Lewis acid binding site Zn(II) with NHs of the urea groups [57]. On the contrary, receptors 20a and 22a exhibited binding selectivity in the order of AcO\(^-\) > H\(_2\)PO\(_4\)\(^-\) in DMSO-d\(_6\), showing that the number of anion binding sites as well as the orthogonal binding site might be relevant when comparing affinities between AcO\(^-\) (K\(_a\) = not determined for 20a and 4.4x10\(^4\) M\(^{-1}\) for 22a) and H\(_2\)PO\(_4\)\(^-\) (K\(_a\) = 4.5x10\(^4\) M\(^{-1}\), for 20a and 2.0x10\(^4\) M\(^{-1}\) for 22a). While 20a and 21a show a high binding affinity for AcO\(^-\) anions, 22a has a colorimetric selectivity for F\(^-\) since it interacts more effectively with azophenol groups. This tendency is associated with the basicity order of anions, F\(^-\), H\(_2\)PO\(_4\)\(^-\) and AcO\(^-\), leading to noticeable color changes compared to other anions (Figure 3).
Most of the investigation described, shows the use of porphyrins 2a and 3a for the synthesis of anionic hosts, introducing pending groups to increase the anion binding sites in a spatial arrangement where the picked fence structure interacts with the anions. These structures were designed containing a planar porphyrin acting as a reporter group and sterically bulky axle-stoppering group. Nevertheless, several other porphyrinic frames have been used as uniquely as reporter group, making use of their unique optical and redox properties to signal changes in the electrochemical, absorbance or emission properties of the guest-complexation process.

While pursuing new receptors for chloride recognition, Beer and coworkers explored methodologies for the synthesis of interlocked [2]rotaxane host systems. The incorporation of porphyrins as reporter groups into [2]rotaxane architectures has demonstrated that this general approach can be extended to the design and synthesis of interesting receptors for chloride anions (Figure 4) [58]. Compounds 26 and 27 were synthesized using a chloride anion-templated clipping protocol, which involves the ring-closing-metathesis-mediated cyclisation of an acyclic bis-vinyl-functionalized isophthalamide derivative around a stoppered porphyrin.
Despite the promising halide anion recognition properties of compounds 26 and 27, they revealed to be inefficient as optical sensors since no variations could be detected over UV-visible and fluorescence experiments. Nevertheless, $^1$H-NMR studies showed that the constricted cavity of 27 strongly binds Cl$^-$ ($K_a = 4.1 \times 10^4 \text{M}^{-1}$) over the larger Br$^-$ and NO$_3^-$ ($K_a = 2.0 \times 10^3$ and $K_a = 60 \text{M}^{-1}$, respectively) in DMSO-$d_6$ with a stoichiometry of 1:1. Changing the solvent for a more competitive media (CDCl$_3$:CD$_3$OD in a 1:1 mixture ratio) showed an increase in the affinity constant of Br$^-$ ($K_a = 5.2 \times 10^4 \text{M}^{-1}$) for a similar order of magnitude of the Cl$^-$ constant ($K_a = 6.0 \times 10^4 \text{dm}^3\text{mol}^{-1}$) for a similar order of magnitude of the Cl$^-$ constant ($K_a = 5.2 \times 10^4 \text{M}^{-1}$), nonetheless the halide selectivity was maintained, presenting a low affinity for AcO$^-$ and H$_2$PO$_4^-$ anions ($K_a = 4.4 \times 10^3$ and $K_a = 1.3 \times 10^4 \text{M}^{-1}$, respectively). In addition, 26 and 27 were capable of detecting Cl$^-$ anions via cathodic shifts in the porphyrin redox couples [58].

TPPF$_{20}$, a simple and reliable platform, has been used by Rodrigues et. al for functionalization with several diamino motifs on the meso positions. The polyamine receptors were obtained from TPPF$_{20}$ via nucleophilic aromatic substitution under microwave irradiation with ethylenediamine, N-tosylethlenediamine and N-isopropylethlenediamine in high yields [39]. Initial findings revealed that hosts 28, 29 and 30 (Scheme 3) displayed selectivity for the H$_2$PO$_4^-$ anion in chloroform. The highest affinity constant was obtained for 30 in both forms, neutral and protonated, in a 1:2 Por:anion stoichiometry ($K_a = 1.62 \times 10^9$ and 5.46x$10^9 \text{M}^{-2}$, respectively). In addition, 28-30 were incorporated into a piezoelectric sensor maintaining his selectivity for HPO$_4^{2-}$ in aqueous media.
The “Picket fence” behavior described before is replaced in this work by a combination of two porphyrins binding the anion in a sandwich-like form (Figure 5), where the porphyrin acts as a revealer group. This spatial arrangement provided receptors 28-30 with a higher selectivity for \( \text{H}_2\text{PO}_4^- \) anion, while maintaining a minor response for \( \text{F}^- \) anions. The crystal structure highlighted in figure 4, displays the method of sequestration of a fluoride anion by a diprotonated imine derivative of 28, which resulted from the reaction of its amine groups with acetone.

Figure 5: Schematic representation of the bis-HF complex of a imine derivative of 28 [39].

In a more complex manner, porphyrins have also been modified in the \( \beta \)-positions to produce relevant receptors (Scheme 4). The synthesis of porphyrin 32, containing two sulfonamide units, was accomplished by the condensation of the ortho-diamine functionalized disulfonamide with tetraphenylporphyrin-2,3-dione 31 in toluene at 90 °C [59]. In the same report, the authors claimed the synthesis of 31 in a simple two-step process [60,61].

The association constants of the complex upon addition of anions in their tetrabutylammonium salts displayed a mixed behavior consistent with a 1:1 binding model for some anions (Cl\(^-\), HSO\(_4\)^-, Br\(^-\), and I\(^-\)), while for others (F\(^-\), H\(_2\)PO\(_4\)\(^-\) and CH\(_3\)CO\(_2\)\(^-\)) the 1:2 binding model offered a small improvement in the analysis, which suggested a second anion weakly binded to 32. The selectivity trend observed in this case essentially parallels the basicity of the anions [59].
Scheme 4

The configuration determination of bioactive molecules is a significantly important topic in chemistry because many of these bioactive molecules are only effective when they have a specific stereo configuration. In this regard porphyrin tweezer 33 has been developed as probes for absolute stereochemical determination based on exciton-coupled circular dichroism, which is a circular dichroism signal induced by a chiral twist of the two porphyrin units due to the binding of chiral guest to tweezer 33 (Figure 6) [62,63].

Figure 6: Compound 33 and proposed mechanism of circular dichroism enhancement of 33 by guest bindings [62,63].
When the chiral carboxylates were added to 33, only weak CD signals were obtained. Without the guest binding, 33 can form both cis- and trans-conformation and after the chiral carboxylate inclusion, 33 adopts cis-conformation. In this process, the direction of chiral twist would be dependent on the chirality of amino acid derivatives. However, during this process 33 exhibits only weak CD signals due to the formation of co-facial structure between porphyrin units. The strong signals amplification was only observed when the authors added DAD to the complex formed between the porphyrin tweezer and the chiral carboxylate. Thereafter, the chiral distortion sensed by the urea groups was effectively transferred to the two porphyrin units [63].

The formation of complexes between the anions and the complexes requires a rather high degree of pre-organization of the receptor. It is required to be rigid, concave and possibly with a cavity size and shape compatible with those of an anion, and it should contain multiple points of interaction, strategically placed inside its cavity [64]. More recently a considerable effort in the anion receptor chemistry field has been devoted to the construction of so-called container systems that contain well-defined voids suitable for inclosing substrates or in this specific case, anions [64]. Investigation in this area with porphyrins shows a variety of molecules containing triazole, calix[4]pyrroles and amide derivatives as binding motifs (Figure 7).

![Porphyrin cages 34-39.](image)

Figure 7: Porphyrin cages 34-39.

The host–guest chemistry of the porphyrin cage 34 in d6-acetone and CH2Cl2 was monitored by the addition of azide tetrabutylammonium salts [65]. During the process, two different types of complex formation were observed for receptor 34. The addition of TBAN3 until 0.4 equiv. to a solution of 34 changes the signals of the 1H NMR spectrum of 34 upfield, in accordance with the formation of the complex porphyrin:anion, where the anion interacts inside the cage (Figure 6 Binding mode I). Further addition of the anion salts up to 30 equiv. changes this upfield tendency in the 1H NMR, being this change coherent with the coordination of N3- on the periphery of the cage, resulting in a larger distance between the two porphyrin planes when compared with the previous complex (Figure 8, Binding Mode III). More recently the same authors reported a similar version of this di-porphyrinic cage receptor, changing the length of the triazole linkers to adjust the porphyrin–porphyrin distance for fullerene inclusion [66].
Beer and coworkers also developed porphyrin-cages containing triazole and triazolium groups for anion sensing applications [67]. The anion recognition and sensing properties of cage porphyrins 35 and 36 were investigated by UV-visible spectroscopic titrations and both host systems exhibit strong anion binding affinities forming 1:1 stoichiometric complexes with a range of halides and oxoanions in acetone and acetone–water mixtures. The positively-charged triazolium porphyrin cage 36 displayed a marked preference for sulfate in 15% water–acetone.

In addition, chemosensor 35 has also discriminated chromogenically, chloride anions showing a distinct green color in comparison pinkish in colorations displayed for the remaining studied anions (Figure 9).

The strapped calix[4]pyrrole-metallloporphyrin conjugate was described by Panda et al., where the synthesis and characterization of two isomers 37 and 37 was achieved [68, 69]. The anion binding studies revealed that only isomer 37 showed strong binding with fluoride anion in organic solvent, and neither of the isomers showed any appreciable binding with the larger halogen counterparts (Cl−, Br− and I−). The experimental results from 1H-NMR titration and Job plots indicated that the fluoride anion interacts inside the cavity of 37.

Likewise, Swager and coworkers recently described by a “doubly strapped” porphyrin comprising four bis-thiophene fragments in the belts, 39 was found to bind two fluoride anions in dichloromethane in a cooperative binding mode involving the pyrrole NH protons in a sandwich-like pattern [70]. The narrow cleft between the straps and the porphyrin plane was found to accommodate fluoride while the larger anions, such as Cl−, Br−, I−, AcO−, CN− and H2PO4− failed to stimulate a change in the UV-Vis spectrum.

PHTHALOCYANINES

Phthalocyanines (Pc) have been recently studied as anion (chemo)sensors, nonetheless few reports of Pcs as anion sensors have been described until recent years [71]. Recently research conducted by our group, endeavored the synthesis of Pcs 40-43 bearing eight and four tosylamino groups in its periphery [72, 73]. These Pcs were prepared via cyclotetramerization of the corresponding phthalonitriles mixed with magnesium in a mixture of pentanol:octanol (1:1) at 160 °C [72, 73]. Both magnesium Pcs were then treated in acidic conditions (trifluoroacetic acid) giving the correspondent free base Pcs 40 and 41 (Scheme 5).
Remarkably Pcs 40-43 showed chromogenic properties upon addition of anions, nonetheless they presented stronger affinity constants towards different anions. Addition of different anions to solutions of 40 resulted in sharp color modifications for each specific anion and the stronger affinity constant was presented for $F^-$ (figure 10).

As expected the binding motifs placed at the periphery of the 40 gave the expected response towards the addition of anions, nevertheless, the selectivity factor was low [72]. A similar behavior was observed for phthalocyanines 41-43, where the stronger binding constant is obtained for acetate anions, nonetheless no significant selectivity differences were found in the constants. On the contrary, the colorimetric capabilities of compound 43 in mixtures containing competitive media was able to selectively change its color only upon addition of cyanide anions (Figure 11) [73]. The host:guest complexes formed during the sensing events can be reverted by acid treatment with a solution of trifluoroacetic acid without loss of the sensing ability of the chemosensors allowing their reuse.
The interaction of anions with expanded porphyrins has been exhaustively reviewed in the literature [74-76]. This field gained attention in the early 1990’s with the first reports of diprotonated sapphyrins to bind halides, as well as transport phosphates and aromatic α-amino acids [77-79]. Saphyrin is an expanded porphyrin capable of hosting small anionic guests in its cavity, when in their protonated form, a feature also observed in the cyclo[8]pyrrole family. Due to its versatility cyclo[8]pyroles 47-49 have found use in miscellaneous fields concerning the wide capability to bind anions.

Initially, the preparation of these kind of receptors was achieved using a highly efficient one-step synthesis based on the use of FeCl₃ as oxidant, sulfuric acid and the readily available α,α-unsubstituted bipyrroles 44-46. The formation of the sulfate anion-complexed form of diprotonated cyclo[8]pyroles 47-49 is obtained in yields up to 70% depending on the substitution pattern on the α,α-unsubstituted bipyrrole (Scheme 6). Latter, it was possible to obtain smaller counterparts namely cyclo[6] and cyclo[7]pyrrole, when hydrochloric acid was used instead of sulfuric acid, these species were isolated as the respective bisHCl salts [80].
Since these compounds were able to bind sulphate in the solid state it was proposed that these could also function as receptors that can act as sulfate anion extractants. In this regard, a study conducted by Sessler and Moyer showed that 49 could mediate sulfate exchange under interfacial conditions in the presence of a phase transfer catalyst (Figure 12) [81]. The shorter chain counterpart 47 failed to show the same behavior since it presented solubility difficulties [82].

![Figure 12: Schematic showing anion exchange and subsequent phase transfer of sulfate as induced by 49 [82].](image)

The findings that 49 was able to extract sulfate selectively in the presence of high levels of nitrate showed that 49 had the ability to overcome the inherent propensity for nitrate over sulfate. This was the first example where this level of selectivity has been observed in a sulfate vs nitrate extraction experiment [82]. In 2003, Sessler and coworkers also synthesized a wide variety of water soluble sapphyrins that were able to act as fluorescent sensors for phosphate. Sapphyrins, are still a subject of ongoing research and have been thoroughly studied in terms of synthetic methodologies and anion binding capabilities [83-87]. The water soluble structures here discussed are depicted in figure 13 [86,88-90].

![Figure 13: Water-soluble sapphyrins 50-52 used as fluorescent sensors for phosphate anions.](image)

The phosphate-sensing ability displayed by receptors 50-52 was based on a fluorescence quenching effect caused by the inherent ‘aggregation’ of sapphyrins. Upon phosphate binding, sapphyrin disaggregates resulting in a higher
concentration of the monomeric form, which is significantly fluorescent. The effective association constant were calculated using a stoichiometric 1:1 curve fitting method and ranged from 6 to 19 M⁻¹ for receptors. Apparently, these values seem to be low when compared to other systems, however considering the competitive media and the dramatic changes in emission intensity associated with phosphate binding, small changes in concentration could be detected. For instance, at the concentration of 0–7 mM, the emission intensity of sapphyrin 50 was seen to increase by a factor of three [90].

Among other potential pollutants, the tetrahedral oxoanions, pertechnetate and perrenate, are also especially important. Pertechnetate, TcO₄⁻, the most stable form of the radioactive element technetium, is among the most hazardous of all radiation-derived contaminants, due to its long half-life [91-93]. Here, Sessler and coworkers considered the possibility of sapphyrin 50 to serve as as receptors for pertechnetate [94]. To test these hypothesis, binding studies were carried out in a mixture of 2.5% methanol–water at an initial pH of 7.0. Under these conditions, 50 exists predominantly in its mono-protonated form and was found to interact with TcO₄⁻. In analogy with the previous work where the addition of phosphate anions to aqueous solutions of sapphyrin 50 induced a disaggregation phenomenon, thus increasing the fluorescence of the sapphyrin, the same occurred when addition of aqueous pH 7 solutions of pertechnetate anions were added to a diluted aqueous 2.5% MeOH solution of 50. The fitting of the spectroscopic titration data to a 1:1 binding profile revealed that the effective $K_a$ describing the interaction of pertechnetate anion with 50 was 3900 M⁻¹. More recently, cyclo[8]pyrrole 49 was found to display perrenate and pertechnetate anion properties. The binding constant for the formation of a 1:1 complex could be calculated with good reliability and the resulting $K_a$ value was 530,000 M⁻¹, deduced from the spectral changes at 1165 nm in CHCl₃. Moreover, it has been shown that can act as a phase-transfer catalyst facilitating the extraction of pertechnetate from an aqueous to an organic phase in the presence of sulfate [95].

Sapphyrins have also been extensively studied in enantioselective recognition of carboxylic anions. This first generation of sapphyrin dimers 53-56 was designed to function as “pacman” receptors. These receptors (Fig. 14) were accomplished by the induced coupling of the mono acid sapphyrin precursors with 1,3-diaminopropane, (S)-2,2’-diamino-1,1’-binaphthale and (1,5,2S)-1,2-diaminocyclohexane moieties, respectively [96].
The mono linked covalent dimer 53 displayed unique attributes in the visible absorbance spectra, where precisely two Soret-like maxima in both methanol (422 and 441 nm) and dichloromethane (426 and 450 nm) were found. The cause of these two bands was consistent with the existence of two different conformational states, the “open” and “sandwich-like” forms. These characteristics allowed this sapphyrin dimer to coordinate bigger anions such as dicarboxylate anions causing the Soret band with the higher wavelength maximum to increase in intensity at the expense of the lower wavelength one. This kind of behavior was consistent with a binding model where the dicarboxylate substrate is coordinated inside the sapphyrin with a “sandwich-like” form. Ligands 54 and 55 preferred N-Cbz-Glu against N-Cbz-Asp, with very weak enantioselection.

Encouraged by these results the same authors showed a double linked dimer with (1S,2S)-1,2-diaminocyclohexane moieties 56 where the fact of being a more pre-organized cyclic system, emphasized the importance of a good size and shape match between the receptor and the substrate. As expected the visible absorbance spectrum of this cyclic dimer 56 differs from its previous analogs 53-55. The spectra showed only one maximum Soret band that confirmed that regardless of the solvent the structure of this dimer remains in “sandwich like” form. Important to refer is that this cyclic dimer exhibited recognition of N-protected amino acids, as evidenced by the differences in the association constants between enantiomers: N-Cbz-L-Asp =16,700 M\(^{-1}\); N-Cbz-D-Asp =9,700 M\(^{-1}\); N-Cbz-L-Glu = 3,800 M\(^{-1}\); and N-Cbz-D-Glu =16,200 M\(^{-1}\) [96].

Recent findings that hexaphyrins can in fact interact with anions were made by Tomé and coworkers [97,98]. A macrocycle initially discovered by Cavaleiro and coworkers and latter widely explored synthetically as well studied for its aromaticity properties by Osuka, regular hexaphyrins have two different oxidation states. The higher oxidation state, having 26 π-electron at its shortest conjugation pathway presents itself as aromatic and nearly planar structure. However, its lower oxidation state congener presents no planarity and has no aromaticity. Inspired by a previous work where several diamino moieties were introduced in TPPF\(_{20}\), Tomé and coworkers sought to mimic the same chemistry with hexakis(pentafluorophenyl [28].hexaphyrins where the diamino pending motifs in 59 and 60 were introduced following a modified procedure from the one used for TPPF\(_{20}\) [39,97].
The association constants of compounds 59 and 60 were found to fit 1:2 binding interaction between the para substituted [28]hexaphyrins and different anions (F-, AcO- and H2PO4-) in DMSO and as compared to its non substituted congener (58), N-tosylethylenediamine [28]hexaphyrin was found to display enhanced binding affinities for several representative anions in pure DMSO. Similar analyses of the N-isopropylethylenediamine [28]hexaphyrin revealed an increase in the relative affinity for acetate \( (K_a = 2.41 \times 10^8 \text{M}^{-1} \text{in DMSO}) \) over phosphate \( (K_a = 5.24 \times 10^5 \text{M}^{-1} \text{in DMSO}) \) with the decreased electronegativity effect close to the outer NH moieties, as noticeable in the increase of the binding ratio \( K_a(\text{AcO}^-)/K_a(\text{H}_2\text{PO}_4^-) = 459.92 \). Interestingly to note is that receptors 59 and 60 displayed enhanced association constants in competitive solvents. For instance, for acetate anions, compound 60 showed a calculated association in DMSO \( (2.41 \times 10^8 \text{M}^{-1}) \) higher in almost 3 orders of magnitude compared with the association constant obtained for CHCl3 \( (1.63 \times 10^5 \text{M}^{-1}) \). Detection studies in the solid state, involving a piezoelectric crystal deposition of the para substituted [28]hexaphyrins, endorsed the detection and calculation of the association constants for the studied anions in aqueous media [97].

In recent years, the molecular recognition of anions and energy transfer dynamics of non-covalent photoactive complexes has been developed by Sessler and coworkers [99-101]. These reports demonstrate anion binding systems with sapphyrin 57 and cyclo[8]pyrrole 48, can be used to successfully create an electronic transfer systems. This approach exhibits a tremendous versatility considering the range of anions that can be used to establish the non-covalent interaction in addition with carboxylates (Figure 15).

**Figure 15:** Sapphyrin 61 and complexes 62-64 used in electron/energy transfer mediated by anion binding between a carboxylate and an expanded porphyrin.

The dyad sapphyrin:porphyrin is formed with a \( K_a \) of \( 10^3 \text{M}^{-1} \) in a 1:1 stoichiometry and upon irradiation at 417 nm, singlet-singlet energy transfer from the porphyrin to the sapphyrin subunit takes place readily with energy transfer dynamics that are consistent with a Forster-type mechanism [99]. The same kind of analysis using cyclo[8]pyrrole 48, complexes with carboxylated porphyrin and pyrene showed that 48 exhibits a unique androgynous electron transfer behavior. Depending on the complex and in question 48 was able to act as either an electron acceptor or an electron donor in the non-covalent electron transfer model system 63 and 64, respectively [100].

**CONCLUSION**

Pyrrole has the advantage of being readily functionalized and incorporated into an almost infinite number of elaborate receptor systems. While the structural diversity can be remarkable, porphyrins, phthalocyanines and expanded porphyrins
have been explored in anion binding chemistry, which is highlighted in this mini-review. This chemistry was emphasized initially by finding that sapphyrins could bind anions. Later on, porphyrins and more recently phthalocyanines have been also showing promising results in this field, namely when functionalized with binding motifs at their periphery.

Some developments namely, the ones achieved with water soluble sapphyrins showed to be promising upon the recognition of anions in aqueous solvent media, noting that the sensing of anions in cells and across membranes is still very much in its infancy. Nevertheless, it is anticipated that some of these macrocycles namely the ones of the expanded series might find their ways to extraction and environmental remediation devices. Hence, anion supramolecular chemistry will continue to be an innovative, and productive field of scientific research for many years to come and in the future it is expected that receptors like the ones discussed in this review can be found in various sensing ensembles, with chromophores attached to sensor devices provide new knowledge and drive new products to market to serve people in real situations. It is safe to predict that macrocyclic pyrrole-based systems will continue to play an important part in the development of anion recognition and anion sensing.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
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<tr>
<td>Equiv.</td>
<td>Equivalents</td>
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<tr>
<td>Ka</td>
<td>Affinity constant</td>
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<tr>
<td>NMP</td>
<td>N-Methylpyrrolidone</td>
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<tr>
<td>Pc</td>
<td>Phthalocyanine</td>
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<tr>
<td>Por</td>
<td>Porphyrin</td>
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<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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<tr>
<td>TPPF&lt;sub&gt;20&lt;/sub&gt;</td>
<td>meso-tetrakis(pentafluorophenyl)porphyrin</td>
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<tr>
<td>UV-vis</td>
<td>Ultraviolet-visible</td>
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<tr>
<td>&lt;sup&gt;1&lt;/sup&gt;H-NMR</td>
<td>Proton nuclear magnetic resonance</td>
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