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Pyrrolic and polypyrrolic anion binding agents

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Contents

Abstract

This review traces the emergence of pyrrole-based receptors for anion recognition. It outlines how serendipitous findings that the diprotonated form of sapphyrin, a pentapyrrolic expanded porphyrin, formed a centrally-bound complex with fluoride anion made over a decade ago spawned studies of this and other expanded porphyrins as receptors, carriers, and sensors of anions. Further evolutions of the field, including in particular the finding that neutral, non-aromatic oligopyrrole macrocycles, such as the

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calixpyrroles and calixphyrins, can act as cheap, and easy-to-prepare anion receptors will also be highlighted, as will recent work with acyclic systems, including dipyrrolylquinoxalines (DPQs) and simple derivatives of pyrrole itself.

Keywords: Anion binding; Pyrroles; Oligopyrroles; Expanded porphyrins; Supramolecular chemistry

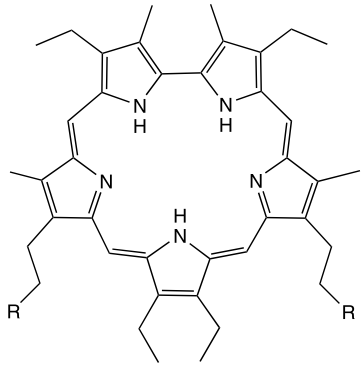
1. Introduction

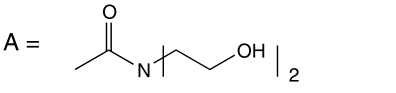
In recent years, pyrrole-containing entities have emerged as among the most versatile and useful of all known anion-binding agents [1]. They have seen application in areas as diverse as anion sensing and transport and have allowed for the stabilization of supramolecular structures with species as simple as fluoride anion and complex as DNA. Part of the attraction of pyrrole as an anion recognition motif is that, in contrast to many other entities employed for this purpose that often self-associate via C=O···HN interactions (e.g. amides and ureas) [2], pyrrole does not contain a built-in hydrogen bond acceptor. Nor, by itself, is it particularly acidic or basic, meaning pyrroles can be used to support NH-anion hydrogen bond interactions under a variety of conditions [1]. Pyrroles are also relatively easy to functionalize and incorporate into cyclic and acyclic structures as venerable as porphyrins (and related naturally occurring tetrapyrroles) and as new and obviously anthropogenic as pyrrole amides, calixpyrroles, dipyrrolylquinoxalines (DPQs), expanded porphyrins, cryptophyrins and most linear oligopyrroles. As a result, pyrrole-based anion receptors display a richness in size, shape, structure and electronic characteristics (i.e. color and conjugation pathways), that is unmatched by other approaches to anion binding. In this review the anion recognition chemistry of pyrrolic and polypyrrolic systems are traced from their initial serendipitous origins in 1990 through to the present day (late 2002). While the presentation is largely historical in nature, an effort has been made to break down the field into generalized receptor classes and to present each in its own separate section or sub-section and as fully as possible. The one exception to this rule comes in the case of calixpyrroles insomuch as this class of pyrrolic receptors has recently been reviewed in detail in this journal [3]. The anion binding chemistry of sapphyrins, although treated here, has also been the subject of a recent account [4]. The interested reader is also referred to recent specialized reviews on expanded porphyrins [5], DPQs [6], and calixphyrins [7].

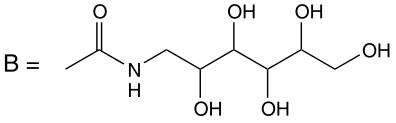
2. Protonated expanded porphyrins

2.1. Sapphyrins

The chemistry of pyrrole-based anion recognition dates to 1990 and, as implied above, had its origins in a serendipitous result. At that time Sessler and co-workers were working to develop a more efficient synthesis of sapphyrin **1**, a member of a class of pentapyrrolic macrocycles initially discovered by Woodward and his group [8]. In the context of these efforts, they succeeded in generating what they thought were







1 R = H
6 R = CH_2OH
7 R = A
8 R = B
9 R = CO_2H

diffraction grade crystals of the bis HPF_6 salt of sapphyrin **1**. In contrast to expectations, however, the resulting X-ray structure, solved by Ibers and McGhee, revealed the presence of electron density in the center of the pentapyrrolic macrocycle that, on the basis of independent synthesis and ^{19}F-NMR spectroscopic analyses, was ascribed to a fluoride counter anion bound within the diprotonated core (Fig. 1) [9]. A PF_6^- counter anion was also found in the lattice but not proximate to the nearly planar sapphyrin skeleton. The fluoride anion itself was found to be within hydrogen bonding distance of all five proton-bearing nitrogen atoms.

The above result immediately gave rise to a number of questions, prime among which was that of generality. Specifically, was the solid-state result found for $[H_2\mathbf{1}^{2+}\cdot F^-]\cdot PF_6^-$ unique or would other anions form complexes with diprotonated sapphyrin? Likewise, could other polypyrrolic receptors be found that would show similar anion recognition properties? If so, what would be the constraints of size, geometry and charge? In the specific case of sapphyrin, could anion complexes of the monoprotonated form ($H\mathbf{1}^+$) be stabilized and would these, like those of $H_2\mathbf{1}^{2+}$ and its analogues persist in solution? If solution state binding behavior were in fact seen, how would the affinities be affected by the chose of solvent, concentration and counter cation and how well would solid state structural information serve to predict the anion recognition events transpiring under the more dynamic conditions, including those associated with solution phase binding, extraction, and transport? Finally, could the latter chemistry, to the extent it was observed, be parlayed into the development of anion-specific sensors, carriers, or extractants? Could interfacial media be produced and could they play a role in anion purification? Would there be opportunities for drug development; could polypyrrolic anion binding systems be produced that would have a role to play in physiology and medicine and, if so, what modifications to the basic core structure would be needed to make them useful in such a context? Needless to say, many of these same questions, now appreciated as being even more open ended than when first conceived, continue to animate the field of pyrrole-based anion binding chemistry.

A first, partial indication that polypyrrole-based anion recognition, or at least that associated with diprotonated sapphyrin, might be general came in 1992 when the X-ray structure of **1**·2HCl was solved [10]. It revealed the presence of two chloride anions roughly 1.8 Å above and below the face of he sapphyrin core, held in place by two or three hydrogen bonds, depending on the side in question (Fig. 2). Later on, the X-ray structure of the mono HCl salt of a sapphyrin was solved [11]. While interesting in its own right because it provided prima facie evidence that the monoprotonated form of sapphyrin could bind anions in the solid state, this structure was also important because it revealed that the chloride anion was not accommodated within the NH-rich, ca. 5.5 Å sapphyrin core (Fig. 3). The fact that the chloride anions in **1**·2HCl were apparently too large to fit within the sapphyrin plane, led to the suggestion that chloride anion would be bound less well than fluoride anion in solution. Consistent with this supposition was the finding that, in dichloromethane solution, the bis-HF complex of **1** displayed an absor-

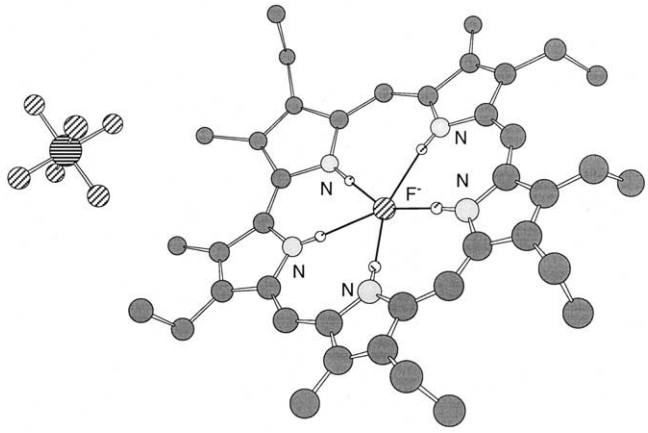


Fig. 1. Single crystal X-ray structure of the mixed HF–HPF_6 salt of sapphyrin **1**. This figure was generated using information down-loaded from the Cambridge Crystallographic Data Center (CCDC) and corresponds to a structure originally reported in reference [9]. Selected hydrogen atoms have been omitted for clarity.

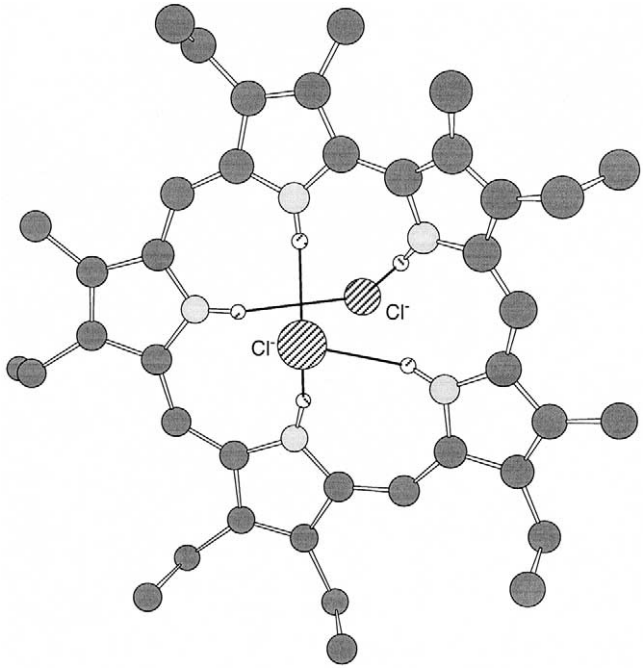


Fig. 2. Single crystal X-ray structure of the bis-HCl salt of sapphyrin **1**. This figure was generated using information down-loaded from the CCDC and corresponds to a structure originally reported in reference [10]. Selected hydrogen atoms have been omitted for clarity.

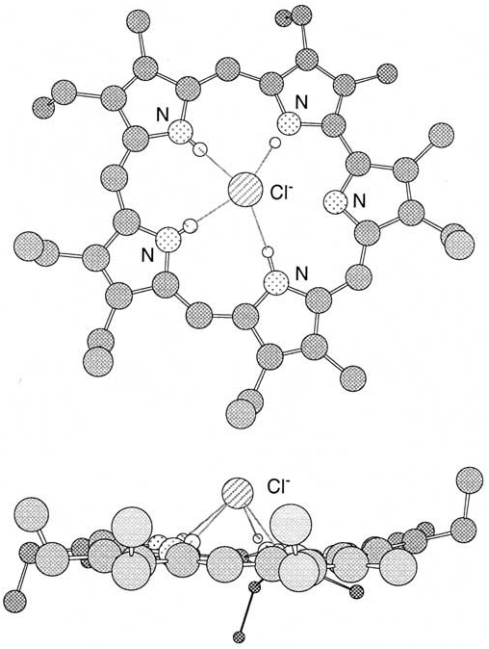


Fig. 3. Top and side views of the single crystal X-ray structure of the mono-HCl salt of sapphyrin **1**. This X-ray structural figure was generated using unpublished data provided by Sessler et al., but corresponds to a structure originally reported in reference [11]. Selected hydrogen atoms have been omitted for clarity.

bance maximum at $\lambda_{max} = 446$ nm in its UV–vis spectrum that was blue-shifted compared with that of not only **1**·2HCl but also **1**·2HBr ($\lambda_{max} = 456$ and 458 nm, respectively) [11].

The differences seen in the absorption spectra of **1**·2HF, **1**·2HCl, and **1**·2HBr were magnified in the case of the respective fluorescence emission spectra. For instance, relative to what was observed for dichloromethane solutions of **1**·2HF, the emission intensities of solutions of both **1**·2HCl and **1**·2HBr, also recorded in dichloromethane solution, were found to be extensively quenched. The greater emission intensity seen in the case of the fluoride complex was ascribed to the fact that in **1**·2HF the central protons are tied up tightly in nitrogen-to-fluoride anion hydrogen bonds, thereby reducing the ability of the NH groups to act as vibrational energy sinks [11]. Two discrete fluorescence lifetimes were also observed for dichloromethane solutions of **1**·2HCl and **1**·2HBr, in contrast to the single lifetime seen for the corresponding fluoride anion complex. From these data, association constants of 1.8×10^7 and 1.5×10^6 M^{-1} were calculated for the binding of the first molar equivalent of Cl^- and Br^-, respectively, to $H_2\mathbf{1}^{2+}$ (cf. Table 1). The associated K_a value for the binding of F^- to $H_2\mathbf{1}^{2+}$ proved too large to measure accurately in dichloromethane, although a lower limit (10^8 M^{-1}) could be established. Association constants for the formation of 1:1 complexes between $H_2\mathbf{1}^{2+}$ and fluoride, chloride, and bromide anions in methanol were determined from fluorescence titration experiments and found to be 2.8×10^5, ca. 10^2, and $< 10^2$ M^{-1}, respectively [11]. This clear selectivity of three orders of magnitude for fluoride anion over chloride or bromide anion was considered consistent with the special, stabilizing in-plane hydrogen motif seen in the solid state structure of $[H_2\mathbf{1}^{2+} \cdot F^-] \cdot PF_6^-$, being largely, or even completely, retained in methanol solution. On a more fundamental level it provided direct experimental support for two important conceptual notions, namely that (1) protonated sapphyrins should indeed be considered as bona fide anion receptors and (2) they could be developed as selective fluoride anion sensors. Experimental evidence in support of this latter proposal has recently been put forward by Tabata and colleagues [12].

Table 1
Association constants (K_a) for the interaction of anions with various sapphyrins

Sapphyrin	Method	(Solvent) anion	K_a (M^{-1})	Reference
(H_2O, pH 6.1)				
7	UV–vis	$C_6H_5PO_3^{2-}$	310	[13]
(CH_3OH)				
1	Fluorescence	F^-	2.8×10^5	[10]
1	Lifetime	Cl^-	1×10^2	[10]
1	And UV–vis	Br^-	$< 1 \times 10^2$	[10]
6	^{31}P-NMR	$C_6H_5PO_3^{2-}$	1.8×10^4	[14]
6		$H_2PO_4^-$	1.3×10^4	[14]
2	UV–vis	2′-GMP$^-$	2.2×10^4	[15]
2		5′-GMP$^-$	8.1×10^3	[15]
2		5′-AMP$^-$	1.7×10^3	[15]
2		5′-CMP$^-$	8.8×10^2	[15]
16	^{2}H-NMR	Terephthalate	4.6×10^3	[16]
16	UV–vis	Oxalate	2.6×10^2	[16]
(5% CH_3OH in CH_2Cl_2)				
17	(UV–vis)	*N*-CBZ–L-ASP	1.6×10^4	[16]
17		*N*-CBZ–D-ASP	9.7×10^3	[16]
17		*N*-CBZ–L-GLU	3.8×10^3	[16]
17		*N*-CBZ–D-GLU	1.6×10^4	[16]
(CH_2Cl_2)				
1	Fluorescence	F^-	$> 10^8$	[10]
1	Lifetime	Cl^-	1.8×10^7	[10]
1		Br^-	1.5×10^6	[10]
1	^{1}H-NMR	*p*-Toluate	9.5×10^3	[17]

Once the basic halide anion binding behavior of sapphyrin **1** was established, efforts in the Austin laboratories turned to exploring its potential utility as an anion carrier. Driven originally by a desire to map out further the basic anion binding behavior of sapphyrins, it was also recognized early on that appropriate polypyrrolic carriers might be useful in terms of permitting the into-cell delivery of anionic, nucleotide-type antiviral agents or the management of cystic fibrosis via the control of chloride anion fluxes. Such potential applications, which are directly relevant to the question of whether synthetic pyrrole-based anion receptors have a role to play in medicine, have been

discussed in several separate reviews ([5a,11,18–20]). Not yet discussed in previous reviews, or indeed to the best of our knowledge anywhere in the open literature, is the possibility that protonated sapphyrin could act as an immunosuppressive or antineoplastic agent as the result of facilitating the concurrent into-cell transport of both protons and chloride anions. That such suggestions are new is not surprising when considered in an historical context: they are inspired by the recent proposals, made well after the initial reports that sapphyrin could act as an anion receptor and carrier, that prodigiosin, a naturally occurring pyrrolylbipyrrole (cf. Section 6.1 below), could owe its promise as a potential antineoplastic and immunosuppressive drug to its ability to effect such co-transport.

The first tests of sapphyrin as a potential anion carrier were made using a standard Pressman-type U-tube model membrane consisting of an aqueous phase, Aq. I, separated by an organic layer from a second, aqueous receiving phase, Aq. II (Fig. 4). With dichloromethane as the organic phase, the presence of sapphyrin **1** in the hydrophobic layer was found to enhance the transport of the fluoride anion from Aq. I to Aq. II over a wide range of initial (Aq. I) pH. For instance, with Aq. I held at neutral pH, where it was first inferred [21] and then established (vide infra) that sapphyrin is monoprotonated [14] the rate of transport observed with sapphyrin **1** was nearly two orders of magnitude greater than the background rate. By contrast, the presence of octaethylporphyrin in the organic phase improved the fluoride anion transport rate by only a factor of 3 [21]. These results, supported by similar studies involving chloride anion (a species that was actually found to be transported more effectively [21]) were rationalized in terms of a key difference between porphyrin and sapphyrin: whereas sapphyrin was expected to be protonated under the conditions of the experiment (and hence able to act as an efficient anion+proton co-carrier), porphyrin, being smaller and less basic, was expected to remain uncharged.

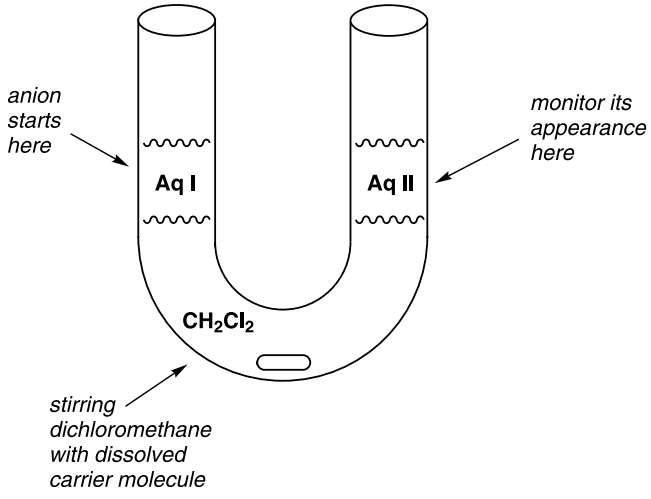
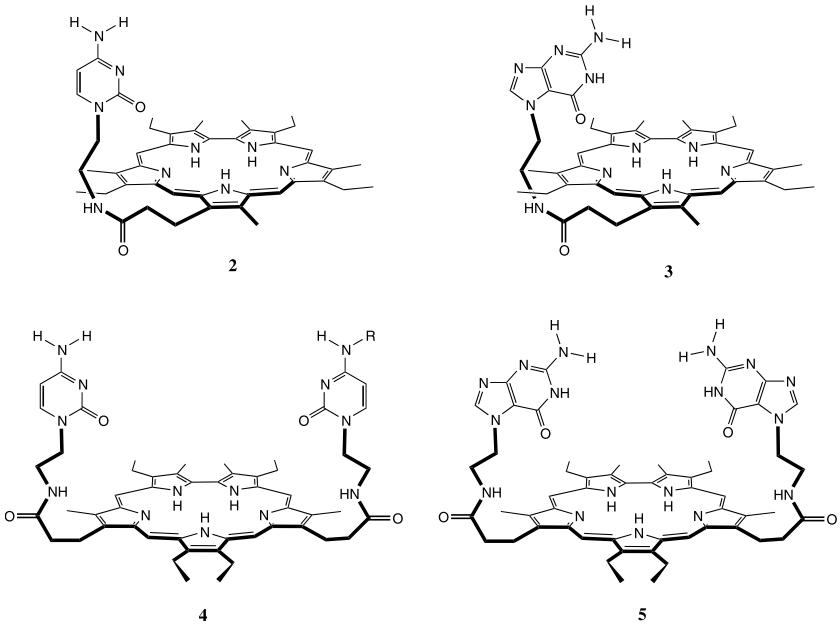


Fig. 4. Schematic representation of the Pressman-type model membrane used to measure rates of transport with sapphyrin and other synthetic anion carriers.

At the time of these initial studies, carried out before the mechanistic proposals involving prodigiosin were put forward, the potential biological benefits of being able to effect the concurrent into-cell transport of chloride anions and protons was not appreciated. On the other hand, it was recognized that carriers that would allow for the through-membrane transport of nucleotides could be useful in the area of antiviral drug delivery. This is because many antiviral agents are water soluble nucleotide derivatives whose bioavailability is limited by their inability to pass through cell walls. Thus, further efforts to explore whether sapphyrins could be used as anion carriers involved testing whether they could be used to effect the selective transport of phosphate-type species. As above, this work relied on the use of a Pressman, U-tube model membrane.

In a first set of studies, it was found that the use of **1** as a carrier enhanced the transport of nucleotides (e.g. GMP and AMP) under conditions where octaethylporphyrin would not [22]. In a follow up study, it was found that the addition of triisopropylsilyl protected cytidine (C-Tips), added as a complementary co-transporting agent, enhanced the sapphyrin-mediated transport of GMP [23]. This then led to the suggestion that transport efficiency and selectivity might both be improved by appending a nucleobase recognition unit onto the sapphyrin skeleton. To test this latter hypothesis, the cytosine and guanosine functionalized sapphyrins **2**–**5** were prepared; in accord with expectations, these systems enhanced, by roughly a factor of 10, the transport rate of nucleotides capable of forming complementary Watson–Crick base pairs as compared with various 'mis-matched' control nucleotides [15,18]. Presumably, the two putative recognition motifs, namely sapphyrin–phosphate binding and complementary Watson–Crick base pairing, function in concert to effect both selective and effective transport. While the exact nature of the base-pairing interactions, as they relate to the proposed nucleotide–sapphyrin nucleobase supramolecular complex remain to be elucidated, they do appear to be sensitive to small structural changes as evidenced by the fact that different isomers of the same nucleotide monophosphate are transported at different rates (e.g. 2′- over 3′- or 5′-CMP in the case of **5**), as well as bound with different homogenous solution phase affinity constants (cf. also the K_a data for **2** in Table 1), even though the complementary nature of the underlying Watson–Crick recognition process is formally unchanged [15].



In contrast to the base-pairing interactions, whose importance was inferred in the transport described above, there is considerable independent experimental support for the proposed sapphyrin–phosphate anion binding events. For instance, a number of phosphate-type salts of diprotonated sapphyrin have yielded to X-ray diffraction analysis with 1:1, 2:1, and mixed complexes all being seen in the solid state. The single crystal X-ray structure of the 1:1 inner sphere cationic complex formed between hydrogen phosphate and the diprotonated form of functionalized sapphyrin **6** is shown in Fig. 5 and typifies one type of sapphyrin–phosphate interaction, wherein the phosphate anion is coordinated to the protonated sapphyrin core via five near-identical "helicopter-like" hydrogen bonds. A second kind of interaction is illustrated by the structure of the 2:1 complex formed between $H_2 \cdot \mathbf{1}^{2+}$ and monobasic phenylphosphate shown in Fig. 6. Here, as in the mixed chloride cyclic-AMP complex of $H_2 \cdot \mathbf{6}^{2+}$ shown in Fig. 7, the two anions are bound on opposite faces of the sapphyrin macrocycle with the phosphate oxyanions being tethered via two or three hydrogen bonds in analogy to what is seen in the structure of **1**·2HCl (Fig. 2) [14].

In addition to solid-state data, there is considerable experimental support for the notion that the protonated forms of various sapphyrins (e.g. **2**, **6** and **7**) bind phosphate-type anions in solution, including in rather polar media. For instance, upfield shifts in the ^{31}P-NMR signals of phosphoric acid and phenylphosphonic

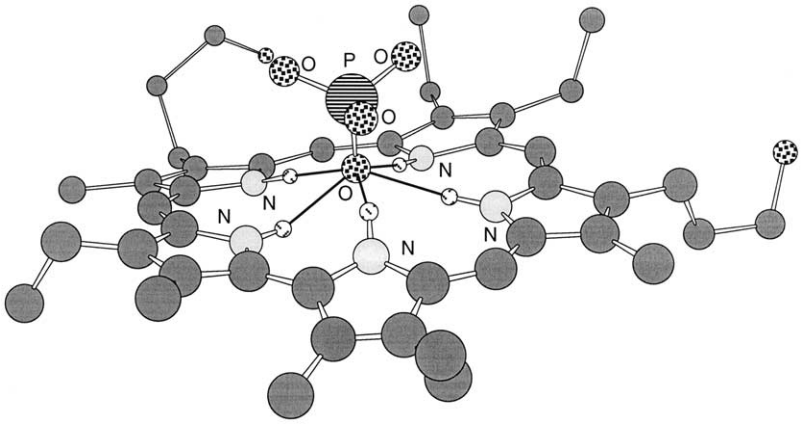


Fig. 5. View of the 1:1 cationic inner-sphere complex formed between sapphyrin **6** and monobasic phosphoric acid. This X-ray structural figure was generated using information downloaded from the CCDC and corresponds to a structure originally reported in reference [14]. Selected hydrogen atoms have been omitted for clarity.

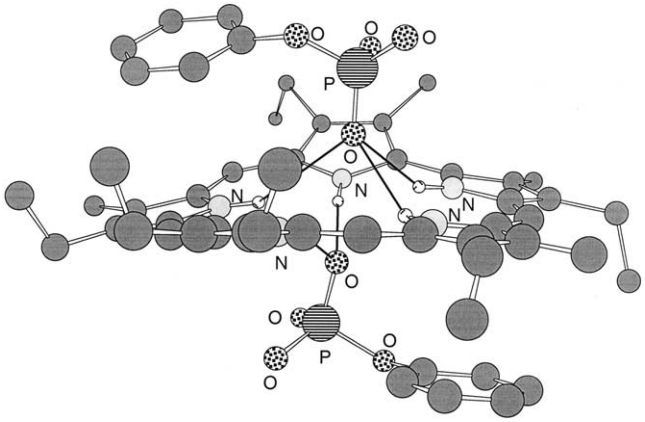


Fig. 6. View of the 1:2 complex formed between diprotonated sapphyrin **1** and monobasic phenylphosphate. This X-ray structural figure was generated using information downloaded from the CCDC and corresponds to a structure originally reported in reference [14]. Selected hydrogen atoms have been omitted for clarity.

acid are observed following the addition of sapphyrin **6** in methanol [14]. Sapphyrin-derived ring current effects were also observed when the ^{1}H-NMR spectrum of phenylphosphonic acid was recorded in water (pH 6.1) in the presence of sapphyrin **7** [14]. The observation of these and other spectroscopic changes allowed the binding of various phosphate species to be quantified; as summarized by the data in Table 1, high binding affinities were generally observed, albeit generally not as high as those seen for fluoride anion under comparable conditions.

As part of the general study of sapphyrin–phosphate anion interactions, specific efforts were made to work in aqueous media. As a prelude to these studies various water solubilized sapphyrins, including **7** and **8**, were prepared. The availability of these systems allowed the pK_a values of sapphyrin to be quantified (those for the diprotonated form of **7** were found to be 4.8 and 8.8, respectively [14]) thus confirming the predicative hypothesis that sapphyrins did indeed remain monoprotonated at neutral pH. On the other hand, even solubilized systems **7** and **8** were found to be highly aggregated at pH 7.

The addition of surfactants, such as SDS, was found to effect the break up of sapphyrin aggregates formed in aqueous media [13]. Using this and other experimental methods, including monitoring pH effects, carrying out dilution studies and making comparisons to systems studied in less polar media, three distinct states came to be identified spectroscopically, namely (i) the monomer, characterized by a strong, sharp Soret-like absorbance around 450 nm, (ii) the dimer, displaying a relatively broad absorbance with a lower extinction coefficient around 420 nm, and (iii) higher-order aggregates, which give rise to a collective absorbance at ca. 410 nm [4,13].

With these states identified, it became possible to carry out semi-quantitative studies of phosphate anion binding in neutral aqueous media. Specifically, it was found that the addition of inorganic phosphate and organic phosphates to solutions of the water soluble sapphyrin **8** induced a large increase in the fluorescence emission intensity, that was rationalized in terms of the liberation of a small amount of the highly fluorescent monomer as the result of sapphyrin–phosphate binding interactions. On the other hand, significant fluorescence enhancements are not observed when water-soluble sapphyrins such as **8** are treated with chloride anion. This has led to the suggestion that water-soluble sapphyrins might find practical utility as aggregation–deaggregation-based sensors for phosphate anions in biological milieus [4].

The success encountered in terms of binding simple phosphate-type anions led Sessler and Iverson and coworkers to explore the interactions between sapphyrin and DNA. Here, an initial indication that sapphyrins and DNA interact strongly came from the finding that adding sapphyrin **9** to an aqueous solution of double-

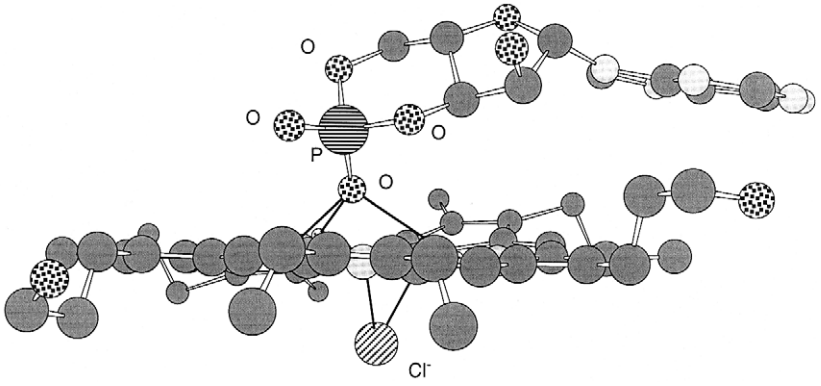


Fig. 7. Single crystal X-ray structure of the mixed salt formed between sapphyrin **6**, HCl, and the acid form of *c*-AMP. This figure was generated using information down-loaded from the CCDC and corresponds to a structure originally reported in reference [13]. Selected hydrogen atoms have been omitted for clarity.

stranded DNA led to the rapid formation of a green (and hence sapphyrin-containing) fiborous precipitate [24]. Formation of this precipitate was ascribed to charge neutralization arising from the interaction between the anionic DNA phosphodiester sites and the protonated sapphyrins. Based on the solid-state data presented above, it was proposed that this interaction involved specific "phosphate chelation", wherein individual phosphate oxyanions along the DNA backbone were bound by sapphyrins via multiple NH-phosphate oxyanion hydrogen bonds [13,24].

More direct evidence for the proposed close association between DNA and sapphyrin came from a range of independent experiments. For instance, it was found that mixing sapphyrin **7** with a dilute solution-phase mixture of double-stranded DNA (but not singled-stranded DNA) gave rise to a strong, induced CD signal for the Soret-like transition of the normally achiral sapphyrin. Likewise, under conditions where the known intercalator ethidium bromide was seen to effect the topoisomerase I mediated unwinding of supercoiled plasmid DNA, the addition of this sapphyrin did not [24]. While not a specific proof of phosphate chelation, this latter finding helps rule out groove binding and intercalation, plausible alternative binding modes commonly seen with porphyrins. On the other hand similar UV–vis spectral shifts were seen when water-soluble sapphyrins were added to either single-stranded or double stranded DNA, supporting the contention that groove binding is not a dominant mode of sapphyrin–DNA interaction.

Further proof for the interaction between sapphyrin and DNA came from cleavage studies. For instance, the addition of ferrous ammonium sulfate and the reducing agent dithiothreitol (DTT) to the sapphyrin EDTA derivative **10** (prepared from **11**) under aerobic conditions was seen to effect cleavage of the supercoiled plasmid pBR322 very efficiently (i.e. at concentrations roughly 20-fold lower than those required for cleavage using Fe·EDTA alone). In different set of experiments, it was found that irradiation of sapphyrin, a known singlet oxygen producing photosensitizer [25], induced

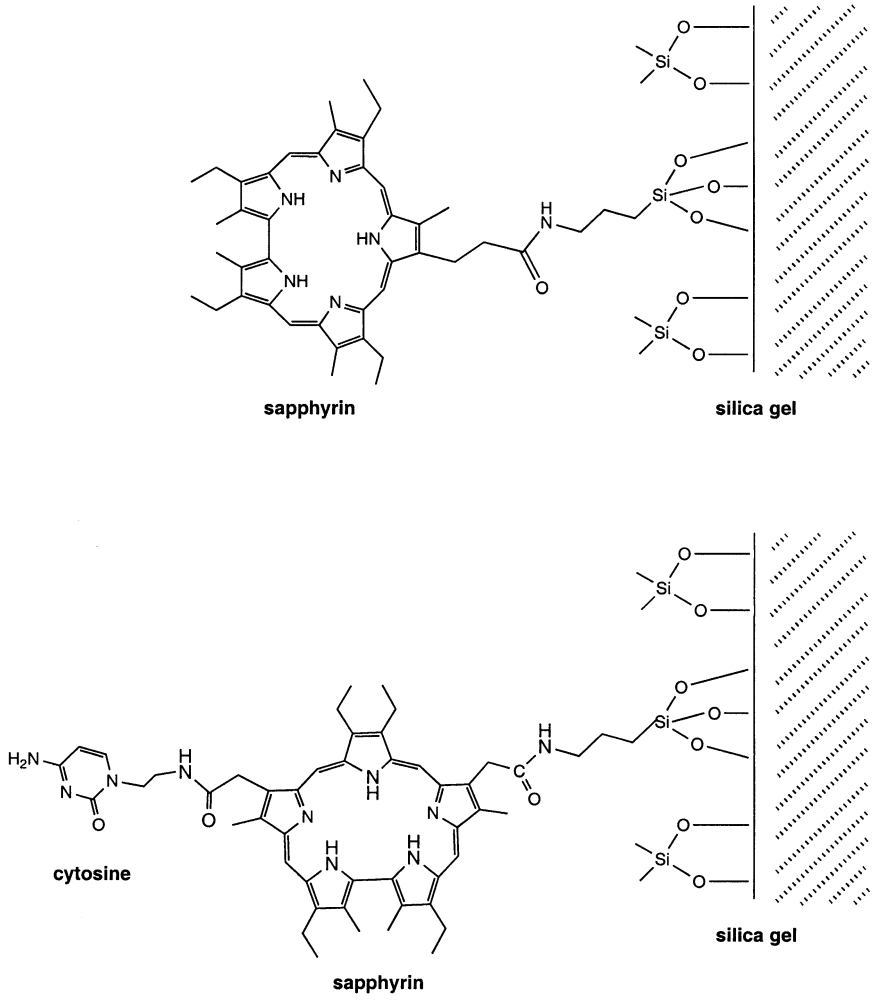


Fig. 8. Schematic representation of functionalized silica gels based on sapphyrin.

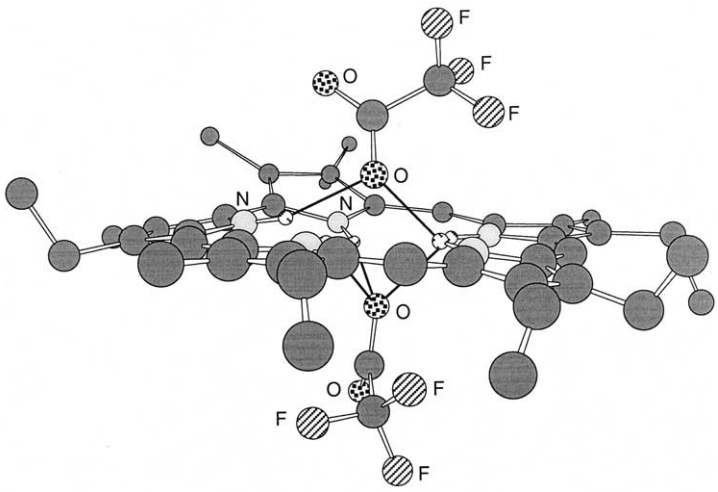
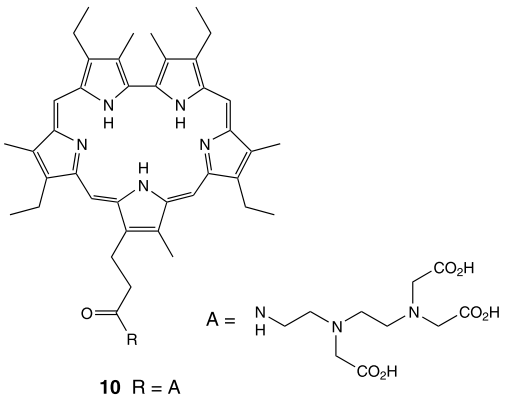
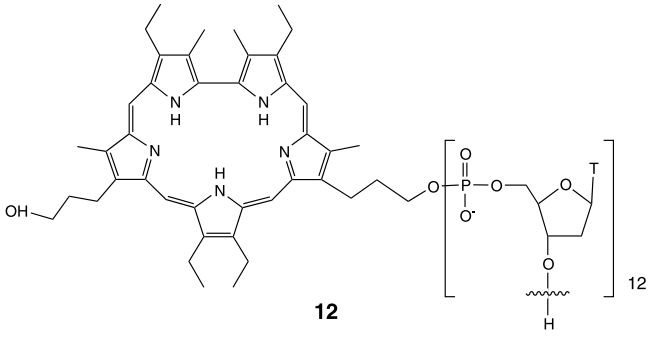


Fig. 9. Single crystal X-ray structure of the bis-TFA salt of sapphyrin **1**. This figure was generated using information down-loaded from the CCDC and corresponds to a structure originally reported in reference [31]. Selected hydrogen atoms have been omitted for clarity.

the photocleavage of DNA [26]. It was also observed that by appending an oligonucleotide conjugate to sapphyrin (to produce, e.g. **12**), the site selective photocleavage of complementary strands could be achieved [27]. These latter findings were considered important in that they point the way toward the day when sapphyrins or other pyrrole-based anion binding agents could be used to effect the specific targeting of selected RNA or DNA sequences in the context of, e.g. so-called antisense or antigene therapy applications.



10 R = A
11 R = OH



12

The interactions between nucleotides, oligonucleotides, and other anions have also been probed via the construction of modified silica gel chromatography supports generated from the carboxylic acid sapphyrin **11**. The resulting supports, shown schematically in Fig. 8, were found to allow for the HPLC-based separation of both mixtures of oligonucleotides and mixtures of mono, di and trinucleotides under isochratic, aqueous conditions [28]. These same supports were also used to study the rate at which AMP could be eluted by various putative competing anions. The rates observed (arsenate > phosphate > chloride > sulfate > nitrate = bromide > iodide > acetate) were found to be consistent with the relative protonated sapphyrin-anion binding affinities recorded in solution (Table 1) [29].

As part of this work, a more sophisticated cytosine-functionalized sapphyrin was bound to silica gel. The use of this latter support allowed GMP, GDP and GTP to be separated from one another and from a mixture of XMP, XDP and XTP (where X = A, C, U and G) [30]. This latter level of selectivity was considered important because it provided independent support for the proposed two-site recognition of anions invoked to rationalize the selective transport of nucleotides by sapphyrins **2**–**5** as discussed above.

One interesting feature of the solid support studies was the implication that carboxylate anions would be only weakly bound to sapphyrin. On the other hand, structural studies revealed that such species would bind to sapphyrin in the solid state. For instance, the single crystal X-ray diffraction structure of the bis-TFA salt of sapphyrin **1** was solved and revealed a direct interaction between the diprotonated sapphyrin core and the carboxylate anions (Fig. 9) [31]. Likewise, the structure of **11**, obtained from crystals generated in the presence of TFA, revealed the presence of a 1:1 dimer in the solid

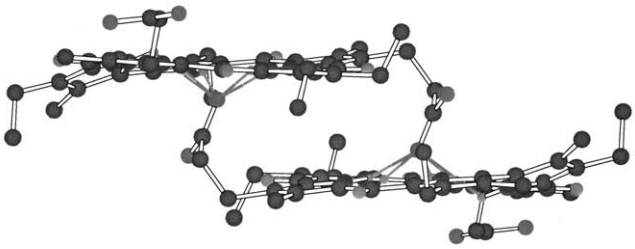


Fig. 10. View of the self-assembled dimer formed from sapphyrin **11** in the presence of trifluoroacetic acid. This X-ray structural figure was generated information down-loaded from the CCDC and corresponds to a structure originally reported in reference [32]. Key: carbon, gray; oxygen, red; nitrogen, blue; hydrogen, cyan. Selected hydrogen atoms have been omitted for clarity.

state wherein the anionic carboxylate "tails" of each sapphyrin subunit within the supramolecular pair was found to be bound to the diprotonated core of the other sapphyrin present in the ensemble (Fig. 10). In this latter instance, qualitative and semi-quantitative measurements (e.g. mass spectrometry, vapor pressure osmometry) were used to confirm that the dimer was retained, at least partially, in solution but that it could be broken up by the addition of fluoride anion as implied by the schematic shown in Fig. 11 [32].

More direct evidence for carboxylate anion binding by sapphyrin came from studies of the energy transfer ensemble **13**. Here, self-assembly is based on the binding of a carboxylate-appended, free-base porphyrin photodonor by a monoprotonated sapphyrin acceptor [33]. Upon irradiation at 573 nm, singlet-singlet energy transfer from the porphyrin to the sapphyrin subunits takes place rapidly ($k = 4.3 \times 10^{10}$ s^{-1}) with energy transfer dynamics consistent with a Föster-type mechanism. Supporting NMR spectroscopic binding studies revealed that ensemble is formed with an affinity constant of ca. 2×10^3 M^{-1} in CD_2Cl_2, whereas *p*-toluate anion is bound by the monoprotonated form of sapphyrin **1** with an affinity constant of ca. 9.5×10^3 M^{-1} in CD_2Cl_2. Parallel X-ray diffraction analyses confirmed that the benzoate anion is bound by monoprotonated sapphyrin in the solid state (Fig. 12) [16].

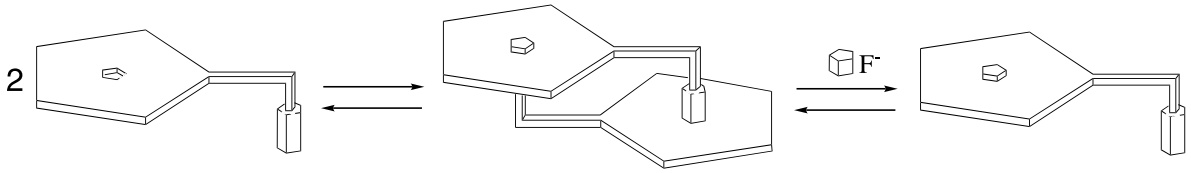


Fig. 11. Schematic representation showing both the dimerization of sapphyrin, **11**, that occurs spontaneously in solution, and the inhibition of this dimerization process that can be effected by adding fluoride anion.

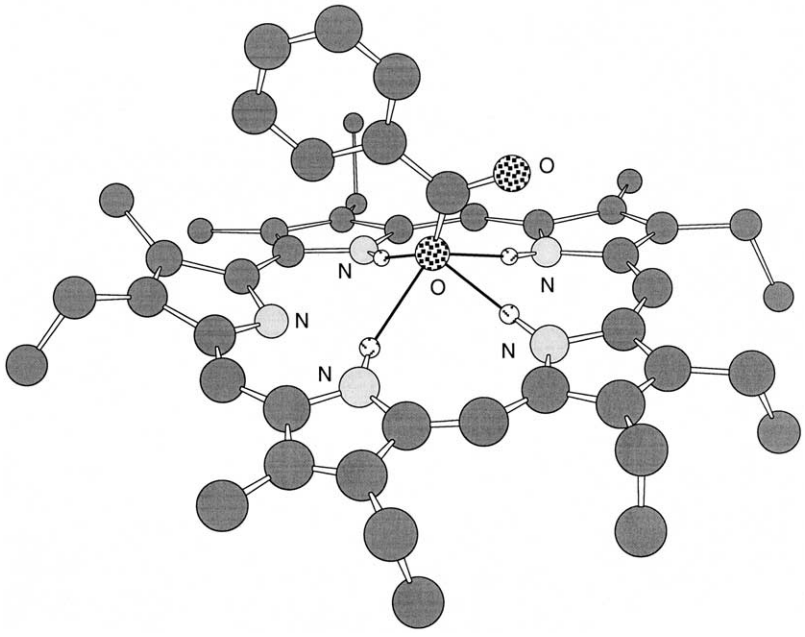
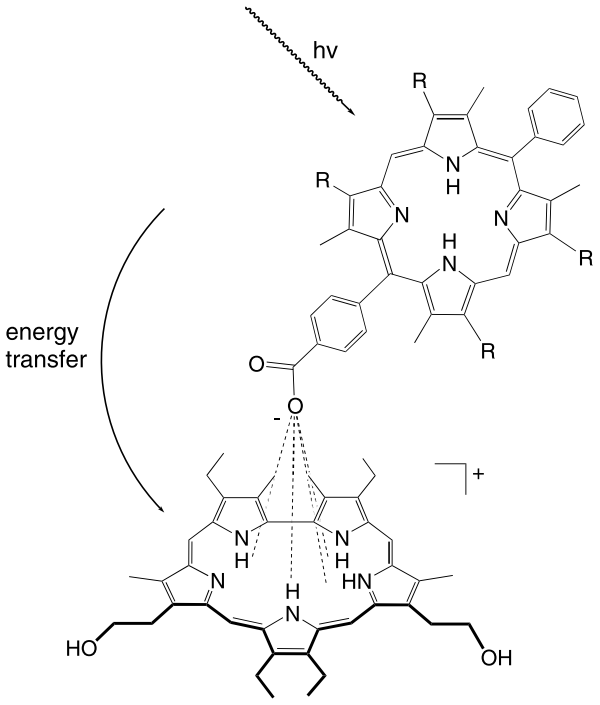


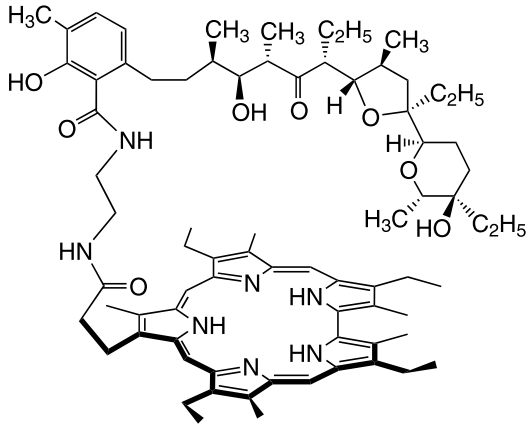
Fig. 12. Top and side views of the single crystal X-ray structure of a 1:1 inner-sphere, neutral complex of benzoate anion with monoprotonated sapphyrin **1**. Select hydrogen atoms have been omitted for clarity. Thermal ellipsoids are scaled to the 30% probability level. This figure was generated using data down-loaded from the CCDC and corresponds to a structure originally reported in reference [16].



13 R = $CH_2CH_2CH_2CH_3$

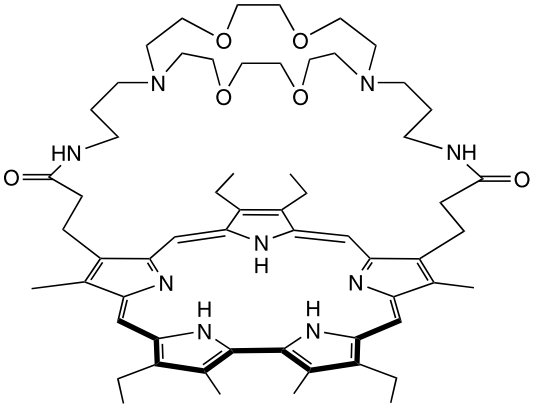
In an effort to develop carboxylate anion receptors with higher affinities, greater selectivities, or which might function as carriers under rather polar interfacial conditions, a variety of elaborated sapphyrin systems were prepared [34]. Once such system was the sapphyrin lasalocid conjugate **14**. This system, which contains subunits capable of recognizing both carboxylate anions (the sapphyrin) and ammonium cations (the lasalocid), was designed to allow for the recognition and through-membrane transport of amino acids. In accord with expectations, it was found that at neutral pH compound **14** did indeed effect the efficient transport of phenylalanine and tryptophan through the dichloromethane phase of a standard Pressman-type H_2O–CH_2Cl_2–H_2O model membrane [34a]. Further, in direct competition experiments, L-phenylalanine was found to be transported four-times faster than L-tryptophan and a 1000-times faster than L-tyrosine. On the other hand, little or no transport was observed when a porphyrin–lasalocid "control conjugate" directly analogous to **14** was used or when a mixture of sapphyrin and lasalocid was added to the organic phase.

More direct support for the contention that conjugate **14** can act as an amino acid binding agent came from quantitative visible spectroscopic titrations carried out in dichloromethane. It was found that both phenylalanine and tryptophan are bound in a 1:1 fashion in this solvent and with relatively high affinity ($K_a = 4.86 \times 10^5$ M^{-1} (L-Phe), 5.35×10^5 M^{-1} (D-Phe), 0.83×10^5 M^{-1} (L-Trp) and 0.94×10^5 M^{-1} (D-Trp), respectively).



14

Another approach to generating a sapphyrin-based system that could bind anions and cations concurrently (i.e. a so-called ditopic receptor) involved the "crowned" sapphyrin **15** [34b]. While some evidence was put forward in favor of this system being capable of binding



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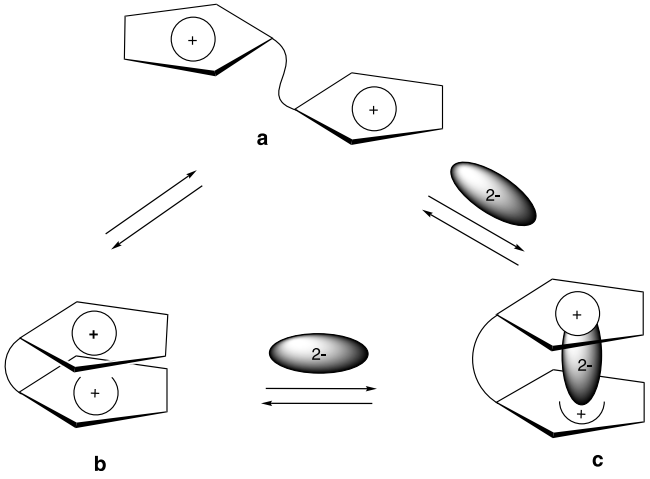
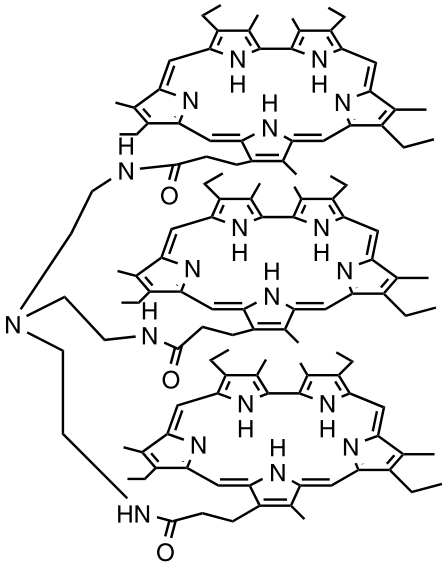


Fig. 13. Schematic representation of solution state conformations of sapphyrin dimer **16**: (a) open, (b) π-stacked, and (c) dicarboxylate "sandwich" complex.

NH_4^+ and F^- simultaneously, the exact nature of the interactions were never detailed.

In an effort generate receptors for dianions, including specifically, dicarboxylates, several sapphyrin dimers (e.g. **16** and **17**) were prepared [16,35]. In contrast to the monomers from whence they derived, these covalent dimers were characterized by the presence of two Soret-like maxima in both methanol (λ_{max} = ca. 422 and 441 nm) and dichloromethane (λ_{max} = ca. 426 and 450 nm). The presence of these two bands was ascribed to the



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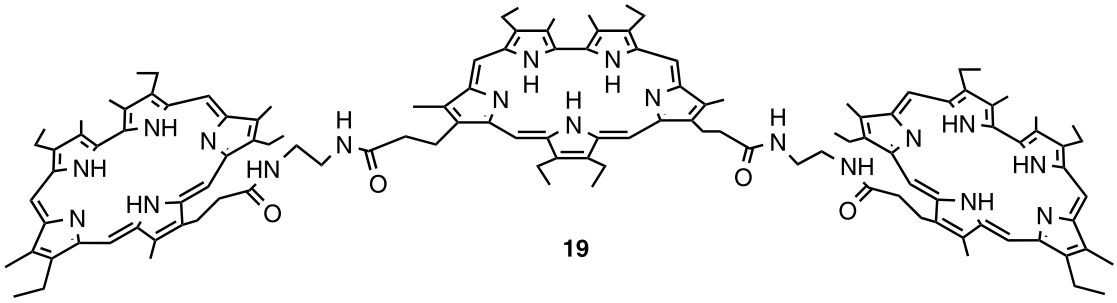

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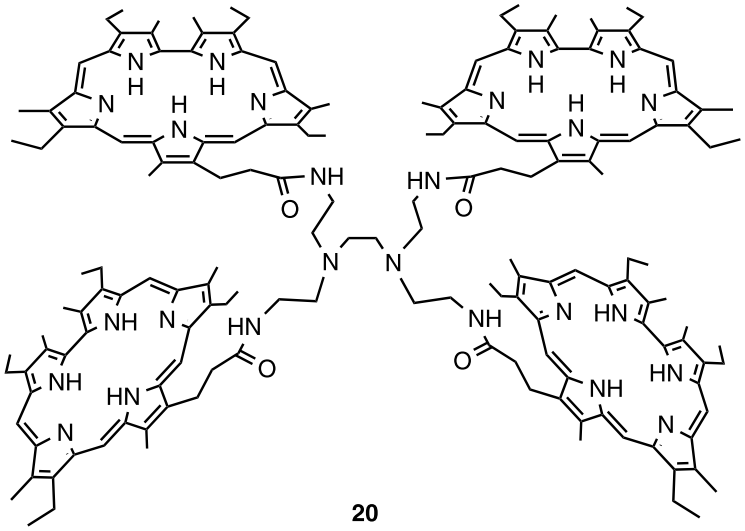

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existence of two conformational states, as shown schematically in Fig. 13, namely (a) "open" and (b) "π-stacked" forms [16,35].

The intensity of the higher energy absorbance, ascribed to the open conformation not involved in π-stacking, was found to increase at the expense of the lower energy (π-stacked) band when dicarboxylate anions were added. This observation and follow up ^{1}H-NMR spectroscopic analyses were considered consistent with a model where the bound state is best represented schematically as structure c in Fig. 13, i.e. a situation wherein the dicarboxylate dianion is 'sandwiched' between the two subunits of the sapphyrin dimer.

Sapphyrin dimer **16** was also found to be considerably more effective than monomer **1** in enhancing the rate of transport of dicarboxylate anions through a Pressman-type U-tube membrane model. In addition, sapphyrin dimers linked by chiral linkers (e.g. **17**) were found to exhibit enantioselective recognition of N-protected amino acids, as reflected in the association constants listed in Table 1 [16].

Inspired by these findings, several novel oligosapphyrins, **18**–**20**, were prepared and studied as potential carriers for phosphorylated nucleotides [36]. It was found that the trimers **18** and **19** (linear and branched) and the tetramer **20**, showed two distinct Soret bands in the UV spectrum. This finding was considered to reflect the fact that these species are aggregated in solution. Addition of phosphate anion was found to induce an increase in the intensity of the higher wavelength portion of the split Soret-like band at the expense of the one at lower wavelength, a finding that was rationalized in terms of first encapsulation of the anionic species followed by de-aggregation of the oligomer.

The next step involved testing compounds **18**, **19** and **20** as carriers for the transport of nucleotides across bulk liquid membranes. Here, by using the standard U-tube set up used for the study of other sapphyrins, it was shown that compounds **18** and **19** were indeed efficient carriers for nucleotide diphosphates. However, they failed to effect the transport of nucleotide triphosphates. By contrast, compound **20** proved to be an effective carrier for all these latter, highly charged species, as well as the other phosphorylated species under consideration [36].

2.2. Heterosapphyrins

Heterosapphyrins are analogues of sapphyrins wherein one or more of the NH-containing pyrrolic subunits is replaced by a furan, thiophene, selenophene, etc. They have a time-honored place in the chemistry of expanded porphyrins and have been the subject of several reviews [5,37]. From the perspective of anion binding, heterosapphyrins are of interest because each "replacement" of an NH moiety by an O, S or Se atom leads to a net loss in hydrogen bond donor capability and should lead to a relatively less effective anion receptor. In a first attempt to test this hypothesis by experiment, Sessler and coworkers prepared several heterosapphyrins, including the selenasapphyrin **21** [38], the monoxasapphyrin **22** [31], and the dioxasapphyrin **23** [31], which in their protonated forms were found to stabilize anion complexes in the solid state (cf. Figs. 14–17). Unfortunately, while efforts were made to study the anion recognition properties of these systems in standard organic solvents, in no cases were any spectroscopic changes observed that could be ascribed to anion binding, a finding that most likely reflects a very low affinity [31].

Subsequent to Sessler's initial reports of anion complexes being stabilized by heterosapphyrins in the solid state, Chandrashekar and coworkers prepared a number

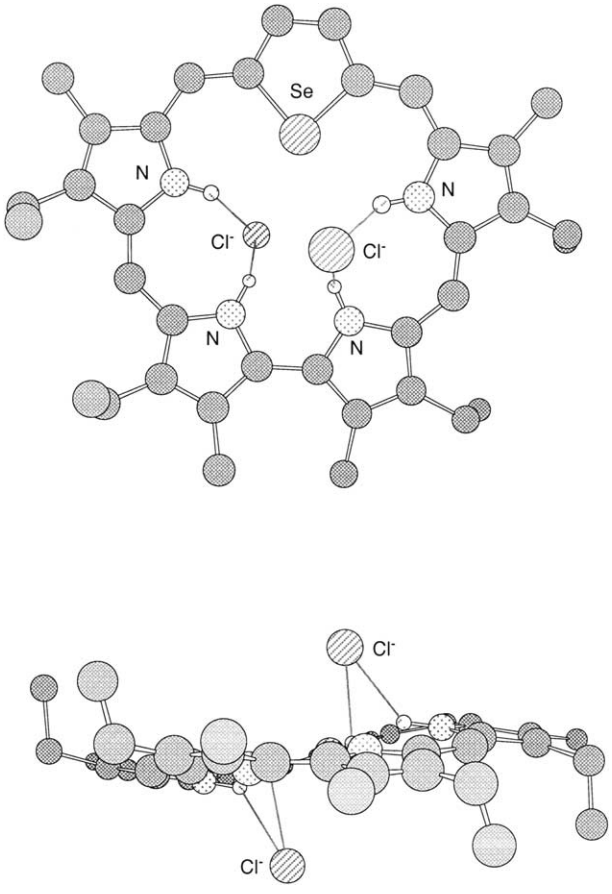
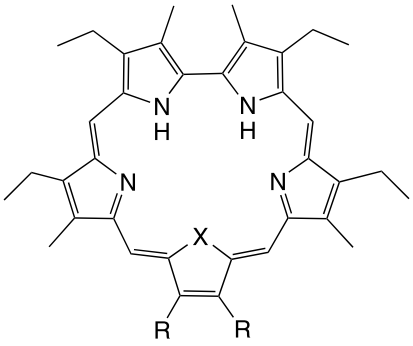
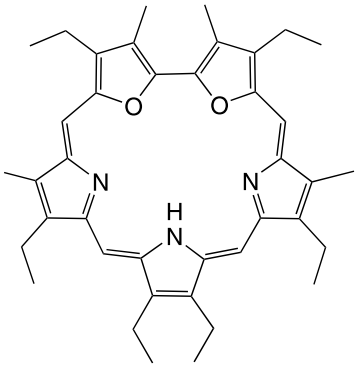


Fig. 14. Top and side views of the single crystal X-ray structure of the 2:1 chloride anion complex stabilized in the solid state by the diprotonated form of the selenasapphyrin **21**. Select hydrogen atoms have been omitted for clarity. This figure was generated from data down-loaded from the CCDC and corresponds to a structure first appearing in reference [38]. Selected hydrogen atoms have been omitted for clarity.



21. X = Se; R = H
22. X = O; R = CH_3



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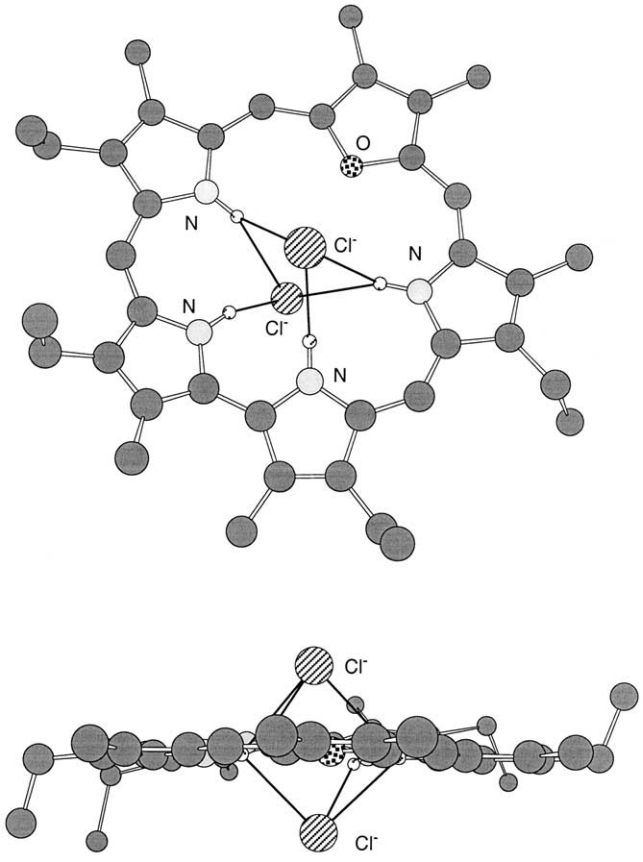


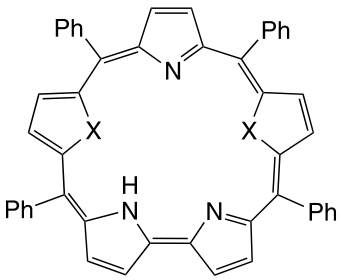
Fig. 15. Top and side views of the single crystal X-ray structure of the 2:1 chloride anion complex stabilized in the solid state by the diprotonated form of the monoxasapphyrin **22**. Selected hydrogen atoms have been omitted for clarity. This figure was generated from data down-loaded from the CCDC and corresponds to a structure first appearing in reference [31].

of *meso*-substituted hetrosapphyrin derivatives, including **24**–**29** [5d,39,40]. Many of these systems were characterized by X-ray diffraction analysis, but generally in the form of the free-base. However, in the case of the diprotonated, bisthiophene system, **24**, X-ray diffraction analysis confirmed that one of the trifluoracetate counter anions was bound in the solid state (cf. Fig. 18), with qualitative ^{1}H-NMR spectroscopic studies being used to support the contention that an analogous anion complex is retained in methanol solution [40]. More quantitative solution-phase studies [39], carried out in methanol using *meso*-phenyl sapphyrin derivatives containing heteroatoms in other positions (i.e. **26**–**29**), confirmed the proposed anion binding but revealed K_a values (1180, 890, 830 and 730 M^{-1} for the binding of fluoride anion to **26**, **27**, **28** and **29**, respectively) that were substantial reduced as compared with what was seen with the all-aza beta-alkyl substituted parent system, **1** under comparable conditions ($K_a = 2.8 \times 10^5$ M^{-1}; cf. Table 1). To the extent this reduction reflects the loss of NH donor sites, as opposed to inherent electronic or structural changes associated with the use of *meso*-aryl, as opposed to beta-alkyl, substituents, it would underscore the important role hydrogen bonds, rather than just pure charge effects, play in defining the anion binding properties of protonated sapphyrins.

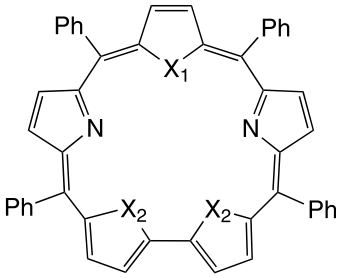
3. Larger carbon-bridged expanded porphyrins

3.1. Rubyrins and smaragdyrins

Shortly after Sessler and coworkers discovered that sapphyrin acted as an anion binding agent, they



24. X = S
25. X = Se



26. X_1 = O, X_2 = S
27. $X_1 = X_2$ = S
28. X_1 = Se, X_2 = S
29. X_1 = O, X_2 = Se

reported the synthesis of a larger homologue, rubyrin **30**. This system, the first hexapyrrolic macrocycle to be characterized by X-ray diffraction analysis, was found to bind to chloride anions in the solid state in its diprotonated form (Fig. 19) [41]. As proved true in the case of sapphyrin, the two chloride anions were found to be held above and below the plane of the relatively planar macrocycle by specific hydrogen bonding interactions. While not studied in detail, support for the notion that rubyrin **30** could act as an anion binding agent in solution came from transport studies; under conditions identical to those used to test sapphyrin (e.g. U-tube set-up; source phase pH 6.0; [C-Tips] = 10 mM; [rubyrin or sapphyrin] = 0.1 mM in carrier phase), it was found to enhance the transport of GMP roughly 30-times more effectively than this smaller system [42].

Much more recently, heteroatom analogues of rubyrin, such as **31**–**34** have become available as the result of efforts by Chandrashekar and coworkers [43a]. While no structural information currently appears available that confirms anion recognition in the solid state, these systems were found to bind fluoride anion weakly in methanol solution ($K_a < 100\ M^{-1}$ in all cases). The low affinity constants seen for fluoride anion binding, as much as an order of magnitude lower than seen in the corresponding *meso*-substituted heterosapphyrins, were ascribed to a size mis-match between this particular anionic substrate and relatively large protonated receptor core.

Chandrashekar and his group have also recently reported the synthesis of several *meso*-functionalized, heteroatom-containing smaragdyrins, including the monoxa system **35** [43b]. Solid state analysis of this system in the form of its mono-HCl salt, revealed that the chloride counter anion was tightly bound to the central protonated core via hydrogen bonding interactions, as shown in Fig. 20. Supporting solution-phase UV–vis binding studies, carried out in methanol,

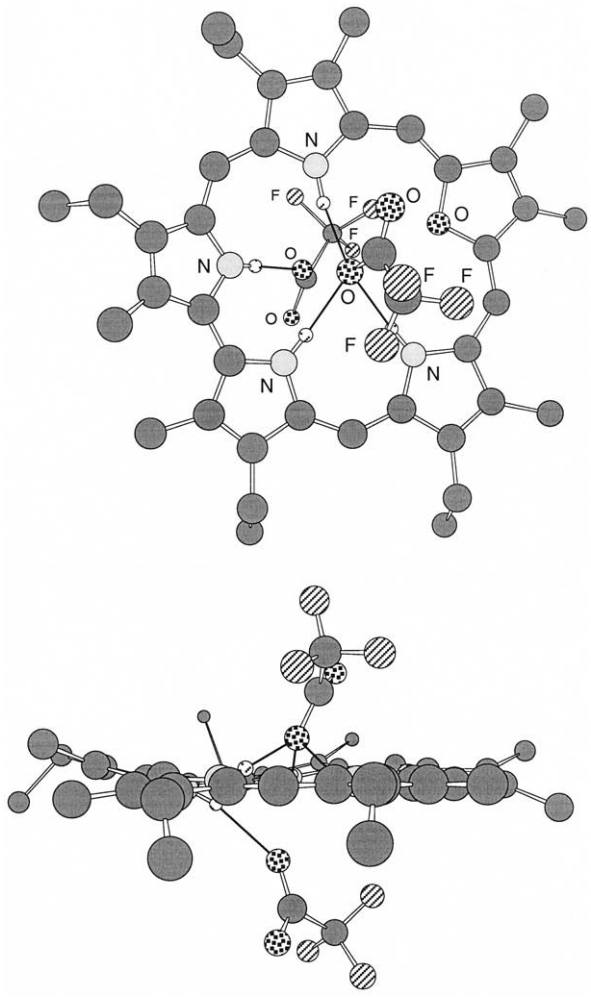
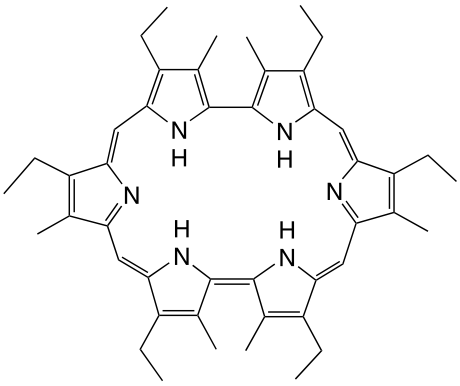
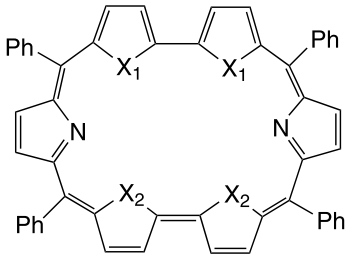


Fig. 16. Top and side views of the single crystal X-ray structure of the 2:1 trifluoroacetate anion complex stabilized in the solid state by the diprotonated form of the monoxasapphyrin **22**. Selected hydrogen atoms have been omitted for clarity. This figure was generated from data down-loaded from the CCDC and corresponds to a structure first appearing in reference [31].



30



31. $X_1 = O, X_2 = S$
32. $X_1 = X_2 = S$
33. $X_1 = Se, X_2 = O$
34. $X_1 = X_2 = Se$

revealed that F^- and Cl^- are bound with K_a values of ca. 7.6×10^4 and 2.1×10^4 M^{-1}, respectively. It is noteworthy that these values are roughly a factor of 3 lower and two orders magnitude greater than the corresponding values recorded for sapphyrin **1** (cf. Table 1). Thus, a very different selectivity is seen for these two well-studied systems (**1** vs. **35**).

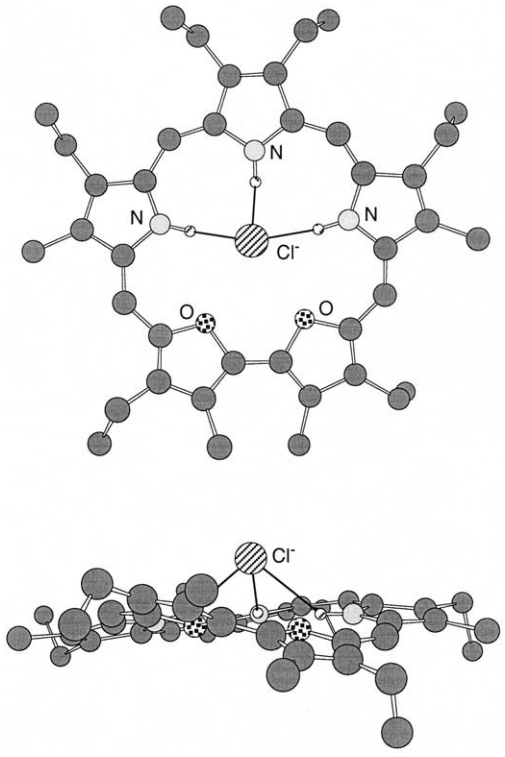


Fig. 17. Top and side views of the single crystal X-ray structure of the 1:1 chloride anion complex stabilized in the solid state by the diprotonated form of the dioxasapphyrin **23**. Selected hydrogen atoms have been omitted for clarity. Also omitted is the other chloride counter anion as it is not proximate to the macrocyclic core. This figure was generated from data down-loaded from the CCDC and corresponds to a structure first appearing in reference [31].

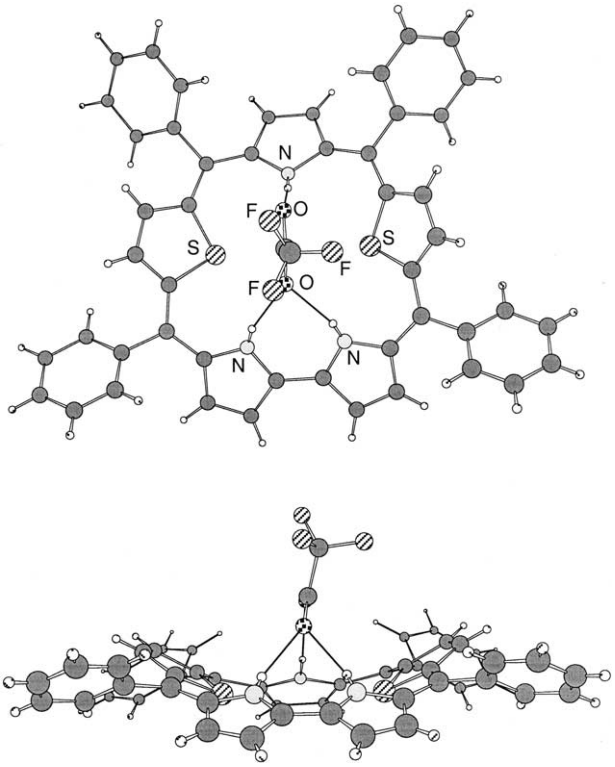


Fig. 18. Top and side views of the single crystal X-ray structure of the trifluoroacetate anion complex stabilized in the solid state by the protonated form of the dithiasapphyrin **24**. The phenyl substituents have been omitted for clarity in the side view as have the four additional trifluoroacetic acid molecules (per dithiasapphyrin) found co-crystallized in the lattice. This figure was generated from data down-loaded from the CCDC and corresponds to a structure first appearing in reference [40].

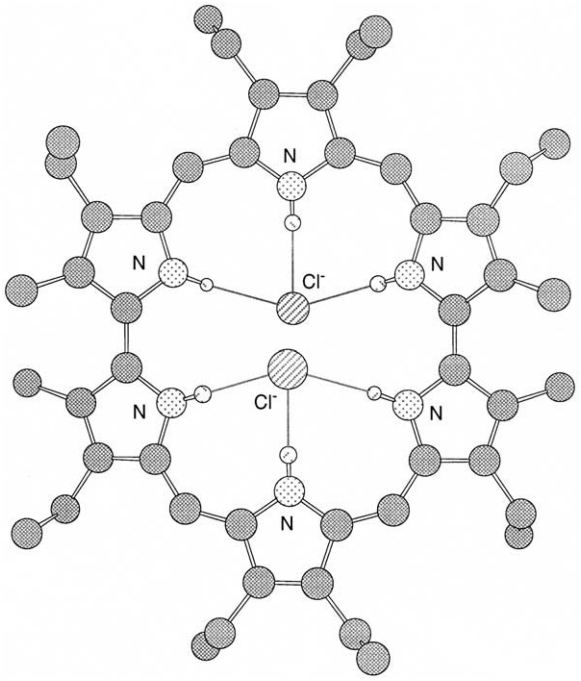
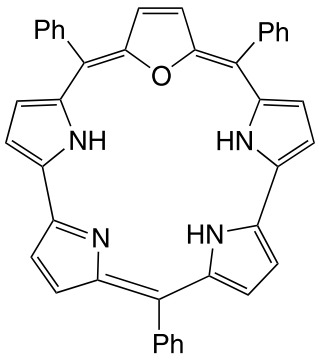


Fig. 19. Single crystal X-ray structure of the bis-HCl salt of rubyrin **30**. This figure was generated using information down-loaded from the CCDC and corresponds to a structure originally reported in reference [41]. Selected hydrogen atoms have been omitted for clarity.



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3.2. Other carbon-bridged expanded porphyrin systems

It is important to appreciate that sapphyrin, smaragdyrin and rubyrin by no means represent the only known expanded porphyrins. In fact, over the last decade, the chemistry of expanded porphyrins has evolved to the point where it is now recognized as an important independent sub-disciplines within the gen-

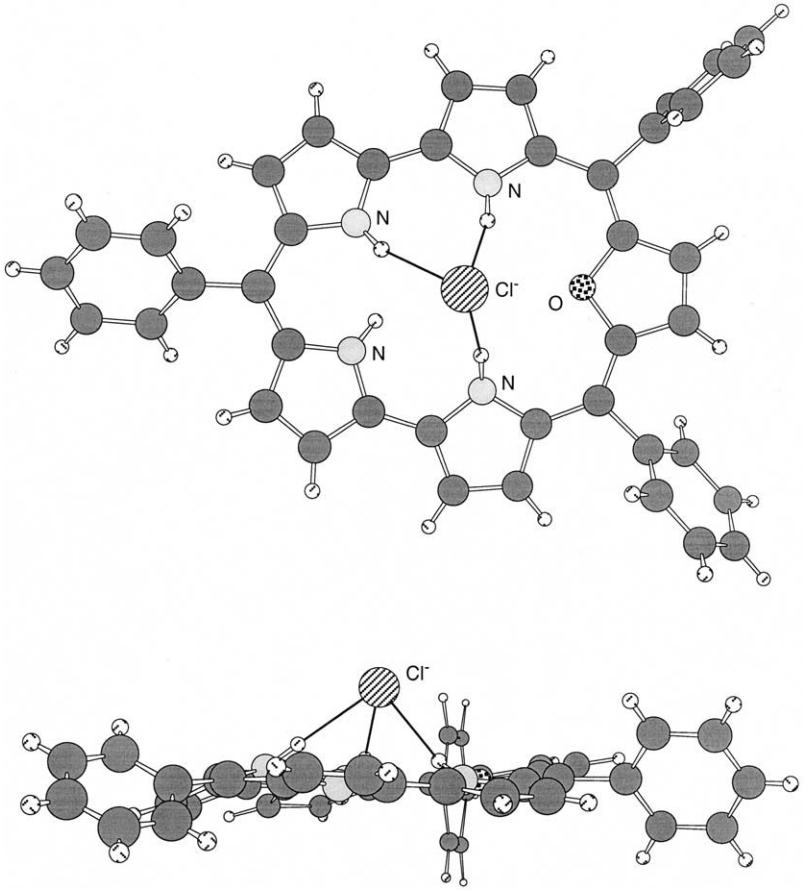


Fig. 20. Top and side views of the single crystal X-ray structure of the chloride anion complex stabilized in the solid state by the protonated form of the monoxasmaragdyrin **35**. The phenyl substituents have been omitted for clarity in the side view. This figure was generated from data down-loaded from the CCDC and corresponds to a structure first appearing in reference [43].

eralized field of porphyrin-related research. Dozens of systems are now known and new ones are emerging with increasing frequency. One of the factors leading to this blossoming of synthetic effort is the promise expanded porphyrins offer as potential anion receptors. To date, this promise remains mostly unrealized as evidenced by the fact that no expanded porphyrin other than sapphyrin and rubyrin has been subject to detailed, proof-of-anion-binding analysis in solution. On the other hand, a large number of X-ray diffraction studies have confirmed the presence of protonated expanded porphyrin–counter anion interactions in the solid state. These findings, illustrated by the specific examples shown in Figs. 21–24 and fully reviewed in detail elsewhere [5c], have served to highlight that planar systems both smaller than sapphyrin (e.g. orangarin **36**) and considerably larger than it (e.g. cyclo[8]pyrrole, **37**) can stabilize core-chelated anion complexes in the solid state, as well as the possibly counter-intuitive finding that expanded porphyrins, such as rosarin **38** and turcasarin **39**, can exist in conformations that are far from planar.

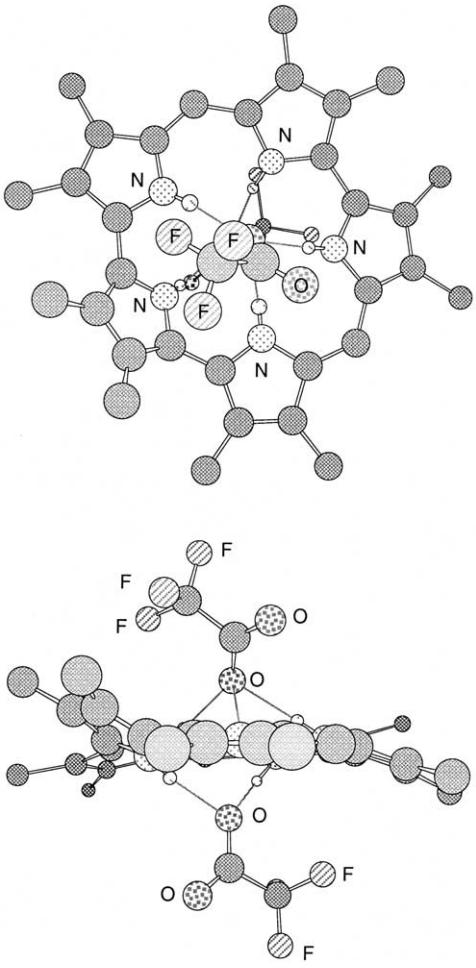


Fig. 21. Top and side views of the single crystal X-ray structure of the bis-TFA salt of orangarin **36**. This figure was originally reported in A. Guba, Diplomarbeit, University of Jena. Selected hydrogen atoms have been omitted for clarity.

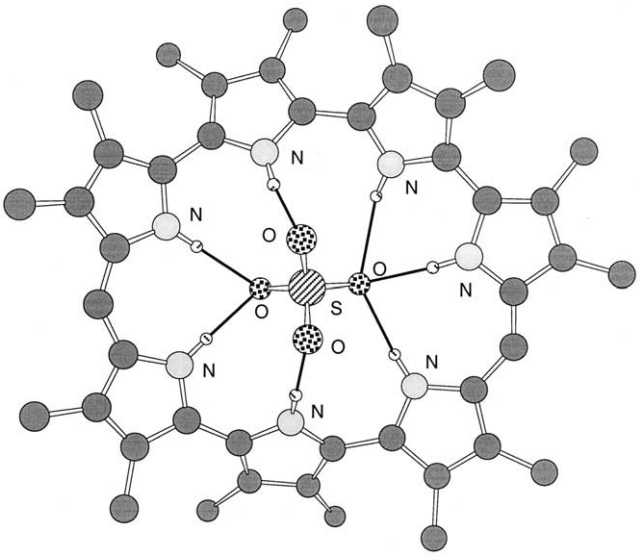


Fig. 22. Single crystal X-ray diffraction structure of the sulfate complex of cyclo[8]pyrrole **37**. This figure was generated using information down-loaded from the CCDC and corresponds to a structure originally reported in reference [44]. Selected hydrogen atoms have been omitted for clarity.

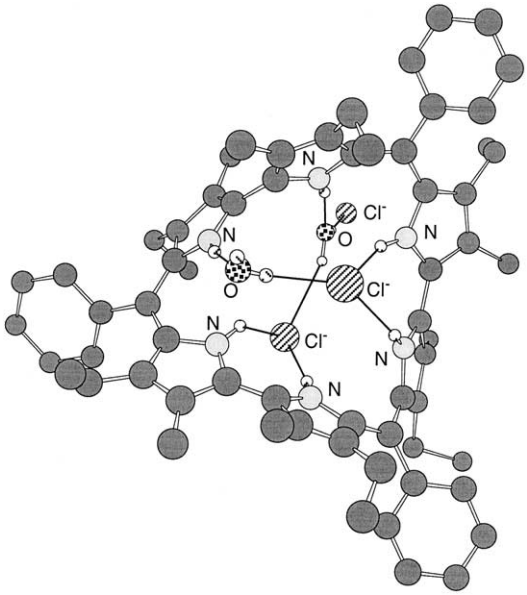
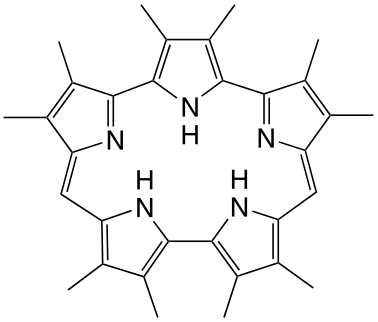


Fig. 23. Single crystal X-ray structure of the tris–HCl salt of rosarin **38**. Only the two chloride anions residing within the macrocyclic "core" are shown, along with the co-bound water molecules involved in hydrogen bonding bridges between NH and Cl^-. This figure was generated using information down-loaded from the CCDC and corresponds to a structure originally reported in reference [45]. Selected hydrogen atoms have been omitted for clarity.



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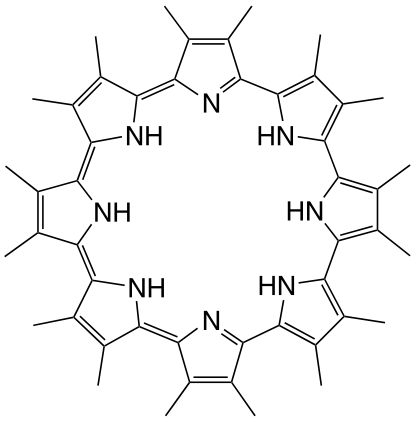

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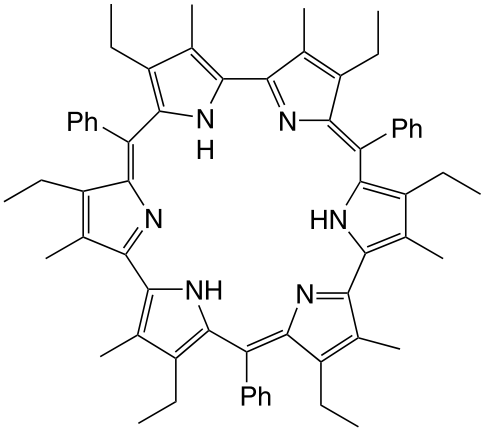

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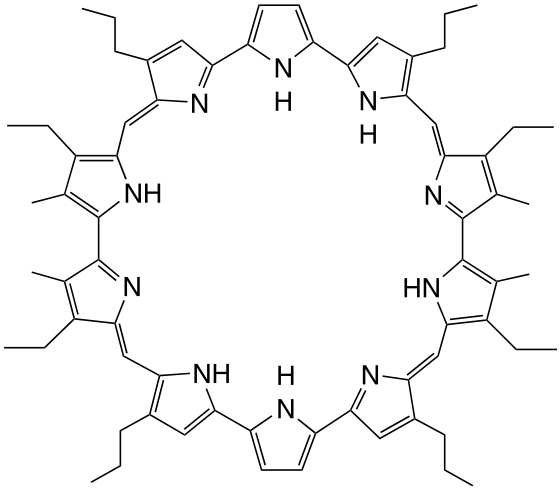

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4. Porphyrin, *N*-confused porphyrin, and modified corrole anion receptors

In recent years, considerable effort has been devoted to developing porphyrins as anion receptors and sensors. Here, most success has been encountered with systems that rely on the use of metalated porphyrins as either the recognition or sensing element. In fact, it is only recently that anion receptors containing metal-free porphyrin centers have been described [47–49]. For the most part, however, as befits the fact that porphyrins are poor anion receptors (see discussion of sapphyrin vs. porphyrin mediated transport in Section 2.1 above; see also ref. [50]), these systems do not rely on direct pyrrole NH-anion interactions to effect anion recognition. Instead, they have employed a variety of known anion binding motifs appended to the porphyrin core to effect anion binding. The porphyrin thus serves as a "passive", albeit highly colored, scaffold and not as an active anion chelating group.

One interesting exception to this general rule comes from the group of Swager [49]. In 2001, these researchers reported the synthesis of a "doubly strapped" porphyrin (**40**) that is thought to coordinate two fluoride anions in dichloromethane solution via a cooperative binding process that involves both the "straps" and the pyrrole NH protons. As yet, there is no definitive confirmation of this assignment from, e.g. solid-state structural analyses. On the other hand, it is noteworthy that a high selectivity for fluoride anion was found, at least as inferred from the observation that the addition of larger anions, such as chloride, bromide, iodide, acetate, cyanide and dihydrogen phosphate, fails to induce a change in the UV spectrum.

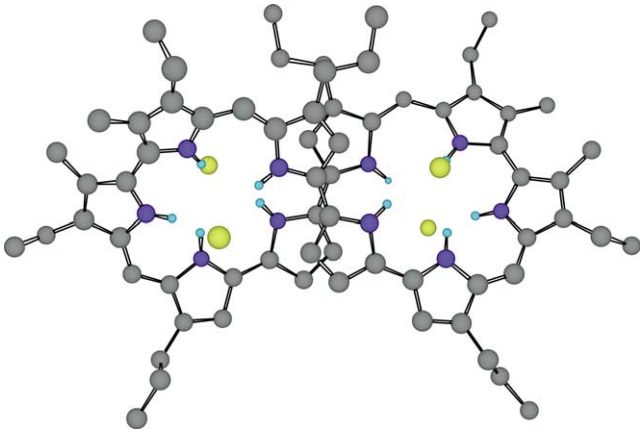
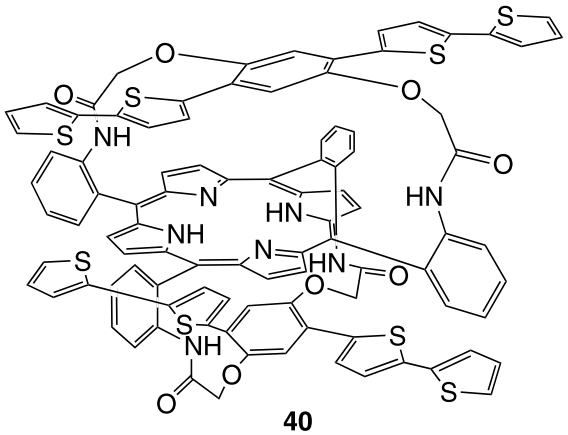


Fig. 24. Single crystal X-ray structure of the tetrakis-HCl salt of turcasarin **39**. This figure was generated using information downloaded from the CCDC and corresponds to a structure originally reported in reference [46]. Key: nitrogen, dark blue; hydrogen, cyan; chloride, yellow; carbon, gray. Selected hydrogen atoms have been omitted for clarity.



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In recent years the chemistry of porphyrins has been enriched, not just by the study of expanded systems as described in Sections 2 and 3, but also by the study of systems that are formally isomers of porphyrins (i.e. containing the same number of pyrroles (4) and *meso* bridges (4)), as well as ones that are "contracted" [5]. Several of the systems produced in the context of this work show promise as anion receptors. For instance, the *N*-fused system of Furuta and Osuka [51], **41**, proved capable of coordinating anionic species with reasonably strong affinities in dichloromethane-d_2 (e.g. $K_a \approx 10^4$ M^{-1} for fluoride anion). Likewise, the dioxacorrole derivative **42** with a protruding furan ring reported by Latos-Grazynski and coworkers in 2002, was found to crystallize as its monohydrochloride salt and display obvious NH–Cl interactions in the solid state (cf. Fig. 25) [52]. At present, no quantitative solution phase anion recognition data is available for this system. However, in a general sense, given the rapidly exploding nature of the porphyrin analogue field, it is likely that if proof-of-principle data is not soon forthcoming for this

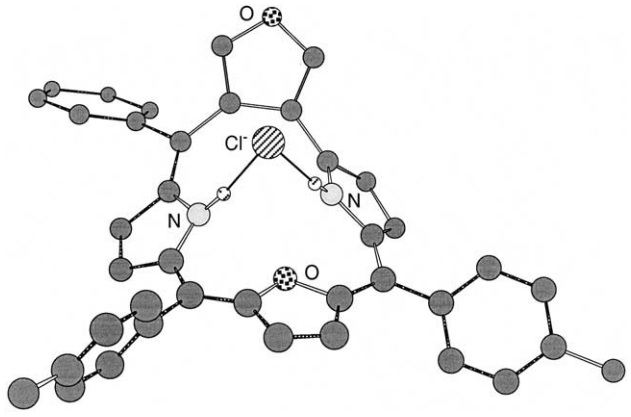
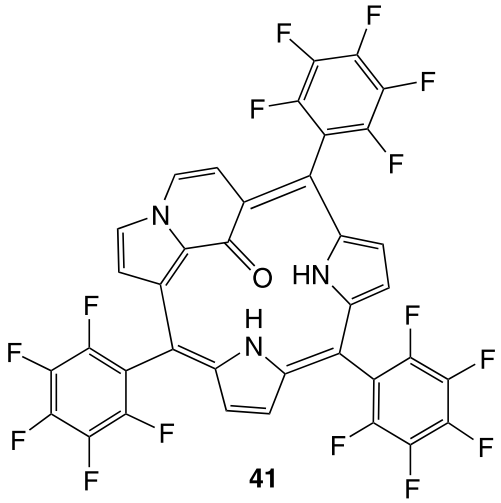


Fig. 25. Single crystal X-ray structure of the HCl salt of dioxacorrole derivative **42**. This figure was generated using information downloaded from the CCDC and corresponds to a structure originally reported in reference [52]. Selected hydrogen atoms have been omitted for clarity.



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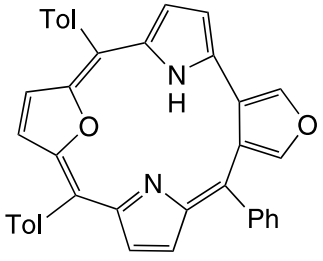


42

system, it will be for a range of others. In other words, the use of non-expanded porphyrin analogues as anion receptors is predicted to be an area of rich, active growth in the coming years.

5. Imine-linked expanded porphyrins

5.1. Texaphyrin and texaphyrinogen

One of the best studied of all porphyrin analogues is texaphyrin [53–55]. This system, in the form of its gadolinium(III) and lutetium(III) complexes **43** and **44**, is currently in advanced clinical trials as an adjuvant for radiation therapy and as a sensitizer for so-called photoangioplasty [54,55]. First prepared in the late 1980s, metallotexaphyrins are prepared by an oxidative insertion process involving reduced, species known as "texaphyrinogens" or "sp^3 texaphyrins" [53]. In 1987, the first such reduced precursor, **45** was characterized structurally in the form of its HSCN salt [56]. Although not appreciated for its significance at the time, the resulting structure revealed a hydrogen bonding interactions between both the SCN^- anion and the protonated imine and pyrrolic NH protons. Five years later, this led to the suggestion that species such as these could function as anion carriers. However, preliminary tests, while confirming the basic viability of the suggestion, revealed that they were less effective than related diimine macrocycles, notably the anthraphyrin system described in Section 5.2 [57] Fig. 26.

Very recently, Sessler and coworkers succeeded in developing an effective synthesis of metal-free oxidized,

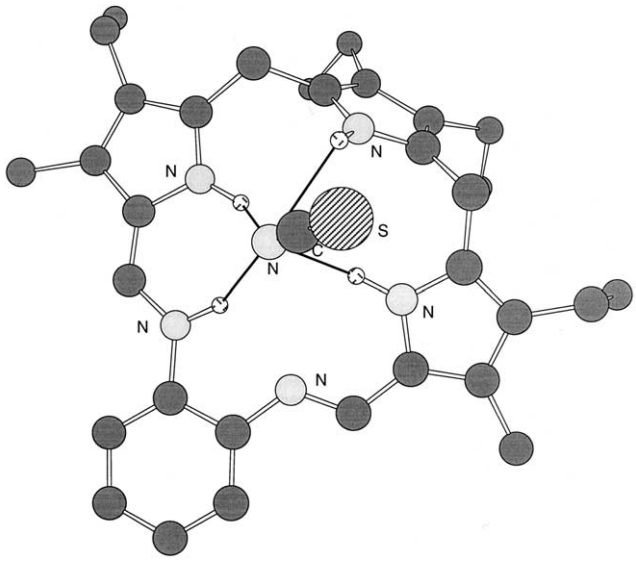
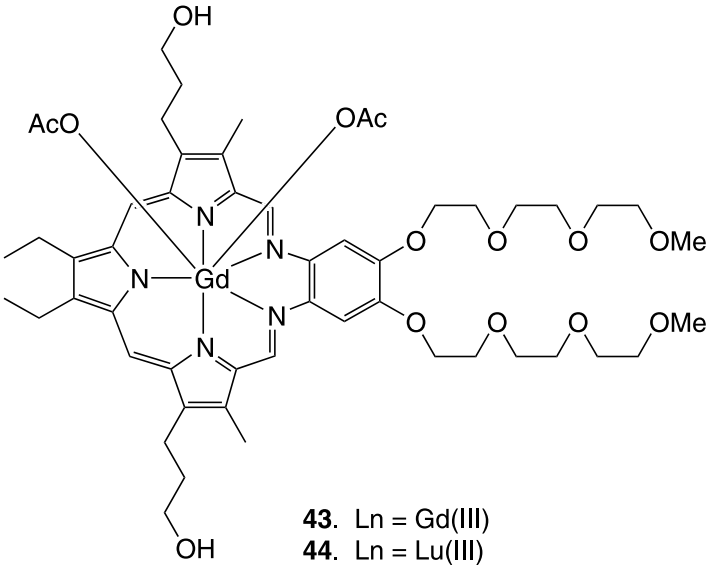
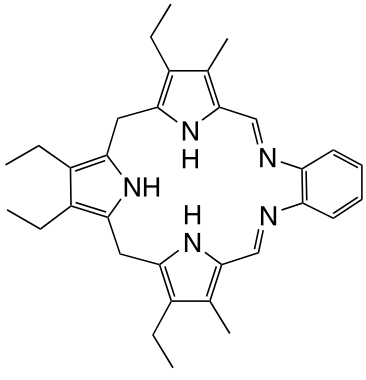


Fig. 26. Single crystal X-ray structure of the mono-HSCN salt of "texaphyrinogen" **45**. This figure was generated using information down-loaded from the CCDC and corresponds to a structure originally reported in reference [56]. Selected hydrogen atoms have been omitted for clarity.

or so-called sp^2 texaphyrins [58]. One of the resulting species, **46** was characterized structurally in the form of its mono-HPF_6 salt. While no direct interactions with the weakly coordinating PF_6^- counter anion were seen in the solid state, the highly basic nature of the system, which was found to be stable in both its mono and diprotonated forms, led to the suggestion that metal-free texaphryins might have a role to play as novel anion receptors Fig. 27.



43. Ln = Gd(III)
44. Ln = Lu(III)



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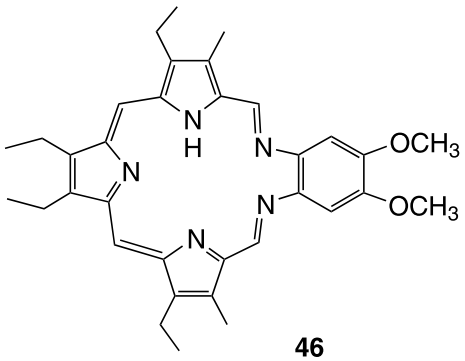

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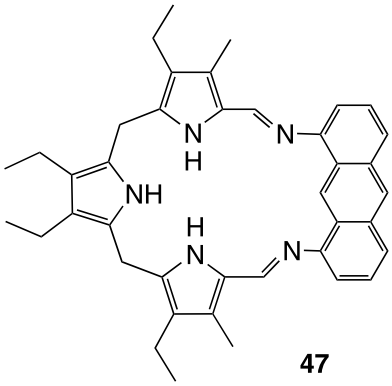


47

5.2. Anthracene-derived expanded texaphyrin analogue

Support for the contention that imine-derived expanded porphyrins could prove useful as anion receptors comes from early studies of the diaminoanthracene-derived "expanded" texaphyrin, **47** [57]. Known as anthraphyrin for short, this system is important in historical terms because it was the first non-sapphyrin expanded porphyrin to be recognized as being a bona fide anion-binding agent. In contrast to sapphyrin, the diprotonated form of this non-aromatic, bis-imine system was found to display a preference for chloride over fluoride anions in CH_2Cl_2 solution ($K_a = 2 \times 10^5$ vs. $1.4 \times 10^4\ M^{-1}$ for Cl^- and F^-, respectively). On the other hand, anthraphyrin was found to transport fluoride anion roughly a factor of three times more efficiently than chloride anion, as judged from standard U-tube model membrane studies. This latter finding was considered consistent with the proposal that overly high anion affinities can lead to reduced transport rates, as the result of inhibiting rates of substrate release [11] and was taken as support for the notion that anthraphyrin is a potentially selective chloride receptor.

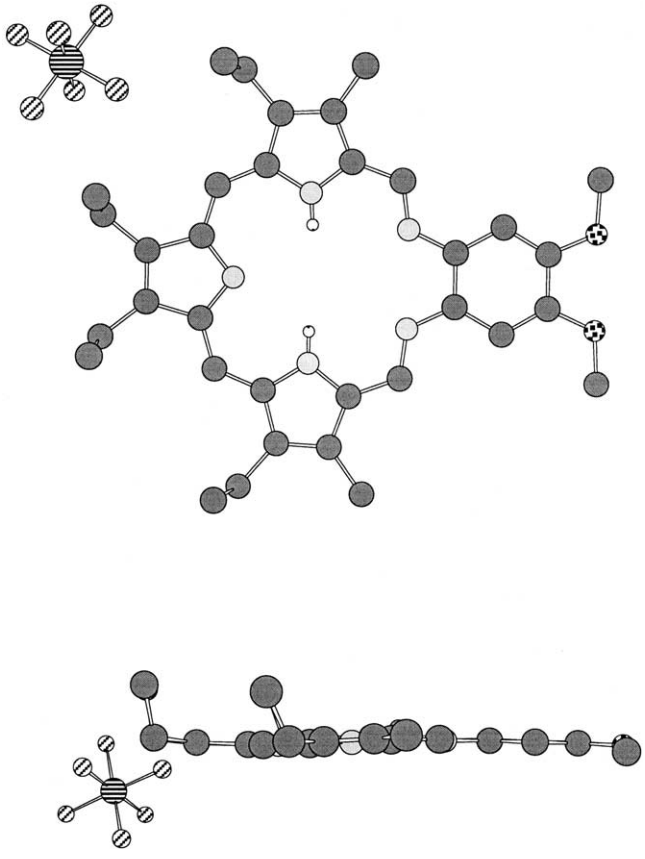


Fig. 27. Top and side views of the X-ray structure of the mono-HPF_6 salt of metal-free texaphyrin **46**. This figure was generated using information down-loaded from the CCDC and corresponds to a structure originally reported in reference [58]. Selected hydrogen atoms have been omitted for clarity.

A solid structural analysis of the HCl–HBF_4 salt of anthraphyrin **47** also supported the proposed chloride anion selectivity [57]. Specifically, this structure (shown in Fig. 28) revealed that the chloride anion is bound to the dicationic expanded porphyrin core via four hydrogen bonding interactions. As such, this structure bears resemblance to both that of the fluoride anion complex of diprotonated sapphyrin, wherein the bound anion is held by five converging hydrogen bonds, as well as that of the HSCN salt of texaphyrinogen in that the anion is not completely bound in the macrocyclic plane. As compared with this latter structure, however, that of anthraphyrin differs in two important ways. First, the macrocycle is diprotonated, as opposed to monoprotonated. Second, the chloride counter anion is encapsulated within the pyrrolic receptor cavity. Specifically, in the mixed anthraphyrin salt, the chloride anion was found to reside but 0.795 Å above the planar portion of the macrocycle [57]. By contrast, in the protonated texaphyrinogen–SCN^- salt, the nitrogen atom of the thiocyanate counter anion rests a full 2.11 Å above the mean plane obtained by considering the four more nearly coplanar nitrogen atoms [56].

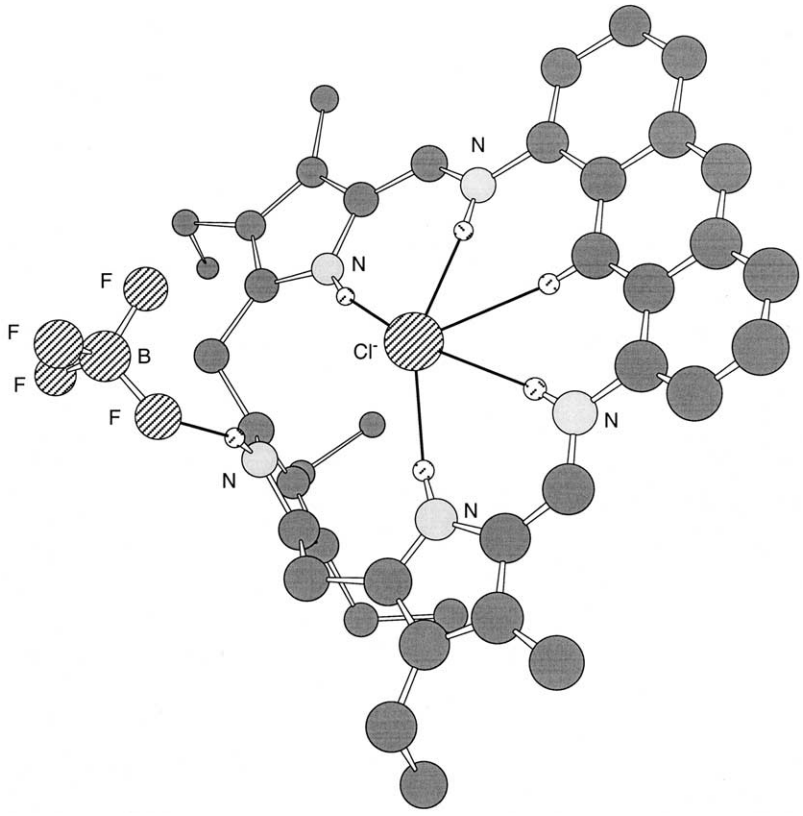
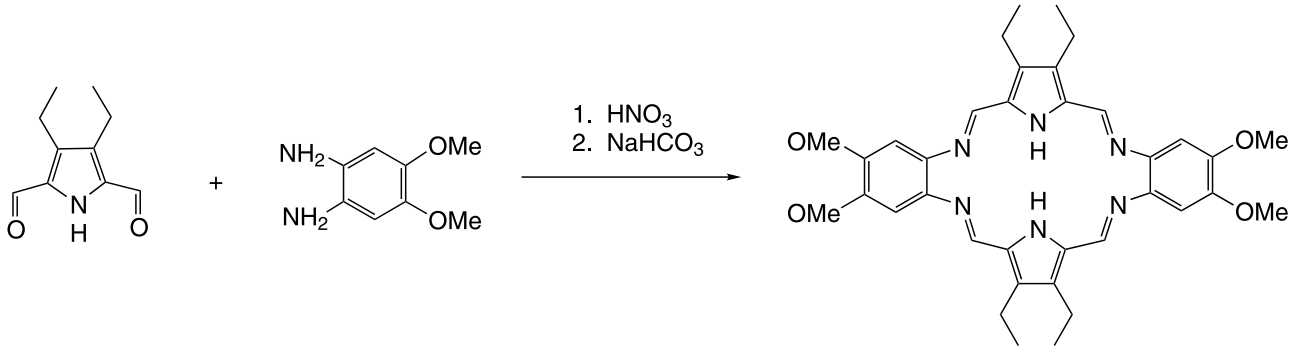


Fig. 28. Single crystal X-ray structure of the mixed salt formed between anthraphyrin **47**, HCl and HBF_4. In this structure the anthraphyrin skeleton is doubly protonated and the chloride anion is bound nearly within the pyrrolic receptor cavity; the BF_4^- counter anion, on the other hand, is not proximate to the macrocyclic ring. This figure was generated using information down-loaded from the CCDC and corresponds to a structure originally reported in reference [57]. Selected hydrogen atoms have been omitted for clarity.

5.3. Anion template effects in alaskaphyrin

In 1992 Sessler and Mody reported the synthesis of the 2,5-diformylpyrrole-derived tetraimine **48** [59]. While proving more useful as a ligand for uranyl cation complexation than as an anion receptor, this system nonetheless warrants mention in the context of anion recognition. This is because it is one of the few polypyrrole macrocycles whose synthesis benefits from a documented anion template effect. Specifically, it was found that the condensation reaction shown in Scheme 1, could be ameliorated in terms of both product yield and purity by using as catalysts Brønsted acids that contain nitrate anions as the corresponding conjugate base [59].



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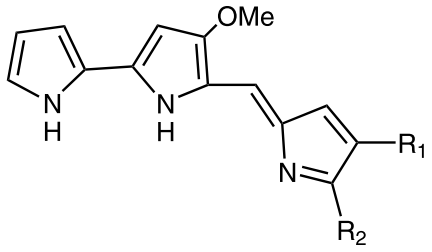
Scheme 1. Synthesis of tetraimine **48**. The condensation reaction used to prepare this product benefits from of a nitrate anion template effect.

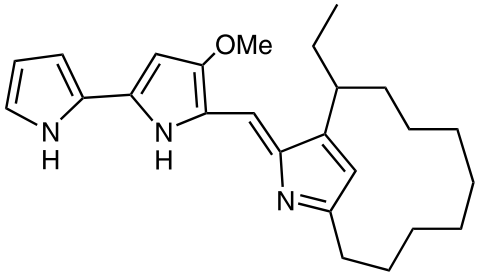
6. Linear oligopyrroles

6.1. Prodigiosin

While there is as yet no evidence that expanded porphyrins exist in nature, it has recently been proposed that an important set of open-chain pyrrolylpyrromethene-type oligopyrroles, the so-called prodigiosins (e.g. **49**–**51**), mediate their physiological effect as the result of effecting the into-cell transport of HCl [60–62]. Isolated from micro-organisms such as *Streptomyces* and *Serratia* [63], the prodigiosins are red pigments, known since the 1930s, that are currently are being studied as potential antineoplastic and immunosuppressive agents [60,64]. They are known to raise the intralysosomal pH [65] and to stimulate apoptosis [64,66], among other effects. Such findings, which are consistent with the proposed protonation-counter anion binding-based mode of action, makes the prodigiosins of interest from a mechanistic, as well as strict drug development, point of view. Certainly, they provide a very clear incentive to synthesize and study the anion recognition properties of open-chain oligopyrrolic systems.



49. R_1 = n-pentyl; R_2 = Me (prodigiosin)
50. R_1 = H; R_2 = n-dodecyl (prodigiosin 25-C)



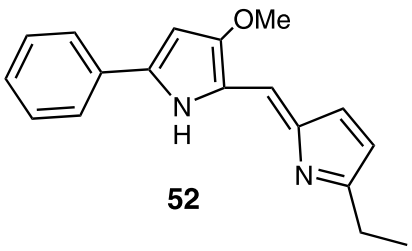
51. metacycloprodigiosin

Given the potential utility of the prodigiosins, it is not surprising that the majority of the open-chain oligopyrroles studied to date have been formally related to this naturally occurring product (cf. **52** and generic structure **53**) [65,67,68]. However, quite recently in the context of this work compound **54** was also reported [65]. In this instance, as in the case of the other analogue synthesis work, the goal was not to study anion recognition per se, but rather to explore the biological mode of action and to find prodigiosin analogues with more favorable physiological properties. Indeed, to the best of the author's knowledge, a reliable K_a value for the binding of chloride (or any other anion) to prodigiosin has yet to be reported in the literature, although the effect of substitution on pyrrole nitrogen basicity has been studied to some extent [68]. Thus, a whole host of critical chemical properties, such as chloride affinity and selectivity, as well as the kinetics of anion binding and transport (i.e. on-off rates, flux values, etc.), remain to be determined, as do correlations between these properties and biological efficacy, assuming such exist. Here, the availability of a greater range of prodigiosin analogues is sure to be useful, as will be studies of other, non-pyrrolylpyrromethene oligopyrroles.

6.2. Anion complexes of pyrrolylpyrromethene and dipyrrolylmethane

While several prodigiosins have been characterized by X-ray diffraction analysis, the authors of this review are unaware of any structures wherein a chloride (or other anion) is observed bound to the protonated form of a pyrrolylpyrromethene of either natural or synthetic origin. On the other hand, Melvin and Manderville and colleagues have recently subjected the HCl salt of the phenyl-substituted dipyrrolylmethene derivative **52** to X-ray diffraction analysis. The resulting structure (shown in Fig. 29) reveals the presence of a single, anisotropic chloride–pyrrole hydrogen bonding interaction in the solid state [68].

Concurrent with the studies of Melvin and Manderville, Sessler and coworkers succeeded in obtaining diffraction grade crystals of the 2:1 receptor-to-anion complex formed between the dipyrrolylmethane **55** and fluoride anion. This structure, shown in Fig. 30, is noteworthy not only because of the unusual stoichiometry, but also because it represents, to the best of the author's knowledge, the first structurally characterized



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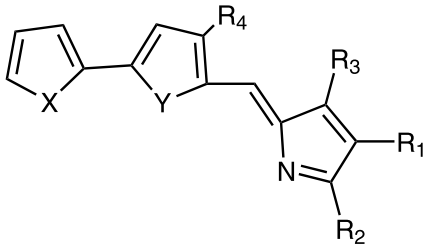
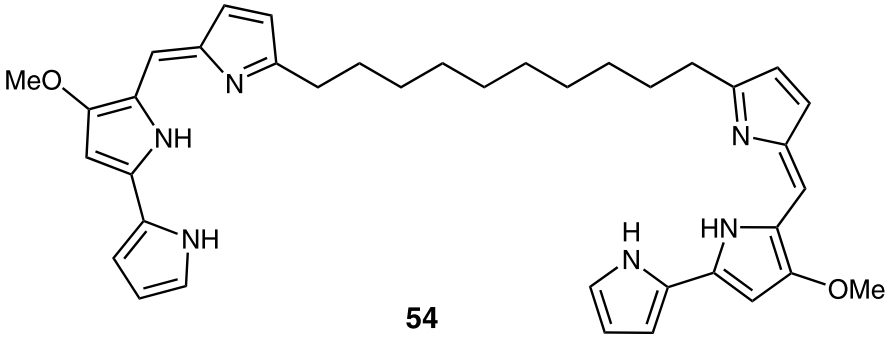
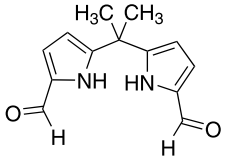


53. X, Y = O, S, NH;
R_1, R_2, R_3 = H, alkyl, cycloalkyl;
R_4 = H, OH, O-benzyl, O-alkyl, etc.



54

anion complex of a dipyrrolylmethane [69]. It thus highlights the role very simple oligopyrroles may play as anion receptors. Supporting this conclusion are the results of preliminary, as yet unpublished, ion thermal calorimetry (ITC) measurements; these confirm that system **55** binds chloride anion in acetonitrile solution, albeit weakly ($K_a < 100\ M^{-1}$).



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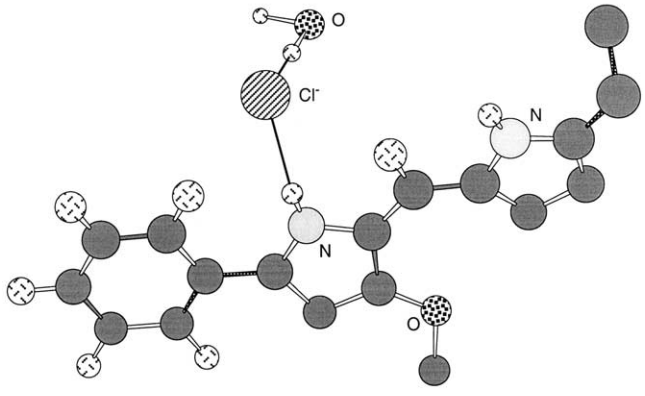


Fig. 29. View of the hydrochloride salt of the pyrrolylopyrromethene prodigiosin analogue **52**. This structure was generated from data down-loaded from the CCDC and corresponds to a structure that first appeared in reference [68]. Selected hydrogen atoms have been omitted for clarity.

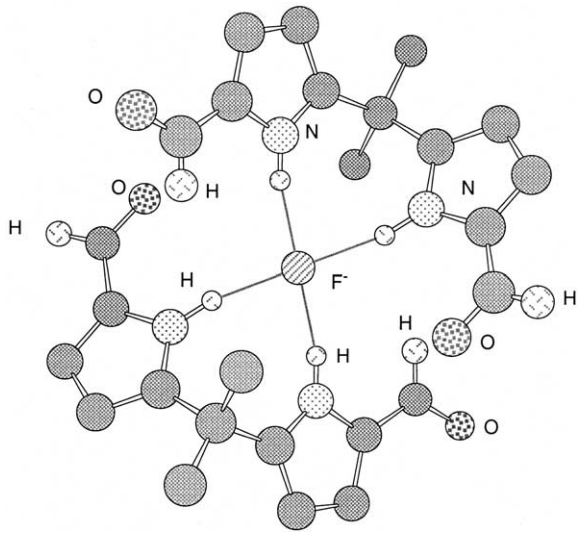
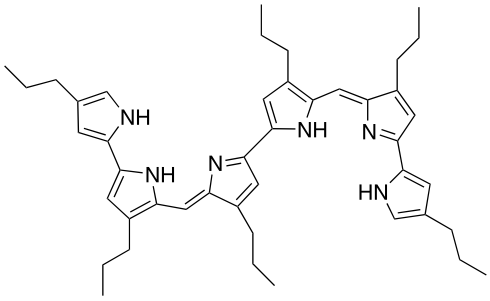


Fig. 30. View of the 1:2 fluoride anion structure formed from the formylated dipyrrolylmethane **55** reported in reference [59]. The TBA counter cation is not shown and selected hydrogen atoms have been omitted for clarity.

6.3. Hexapyrrins

In recent years a number of so-called "open chain" oligopyrroles have been synthesized by Sessler and coworkers, both to study their inherent features and as precursors in the synthesis of new expanded porphyrins. In the course of this work, two hexapyrrolic systems were prepared that bear a direct resemblance to prodigiosin and which show promise as anion receptors. The first of these is the 5,15,25-tris-nor-hexapyrrin **56** [70]. This system is formally an α,α′ linked prodigiosin dimer that contains not one, but two potential chloride anion binding clefts. Consistent with this suggestion is the structure of the bis-HCl salt shown in Fig. 31. It reveals two bound chloride anions tethered to the flat diprotonated hexapyrrin via two sets of three hydrogen bonds thereby providing direct structural conformation for the mode of binding presumed to be operative in prodigiosin and its analogues. Unfortunately, this structure, which dates to 1994, predates the current wave of interest in prodigiosin as a chloride anion receptor and is not apparently appreciated for the important structural precedence it provides.

The second hexapyrrolic system of interest is the bis-terpyrrolylmethene **57** [71]. This system, characterized structurally in the form of its free-base, was found to bind fluoride and chloride anions in a 1:1 fashion in dichloromethane-d_2, albeit weakly ($K_a = 3.5 \times 10^3$ and 12 M^{-1}, for fluoride and chloride, respectively). Such weak binding could make these systems useful as halide anion transport agents or interesting as potential prodigiosin mimics.



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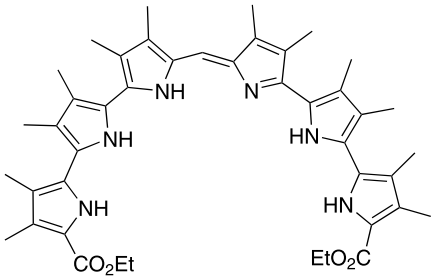

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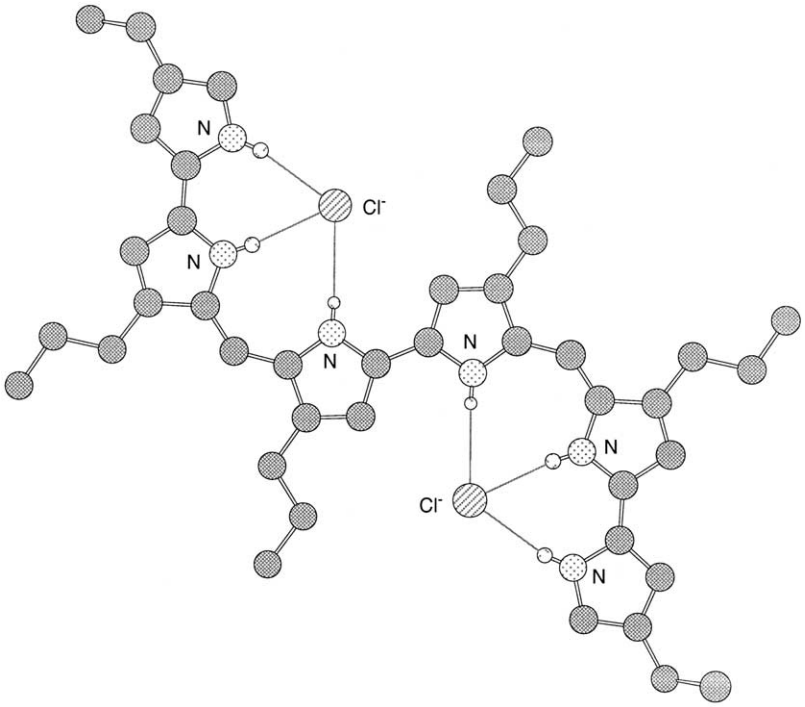
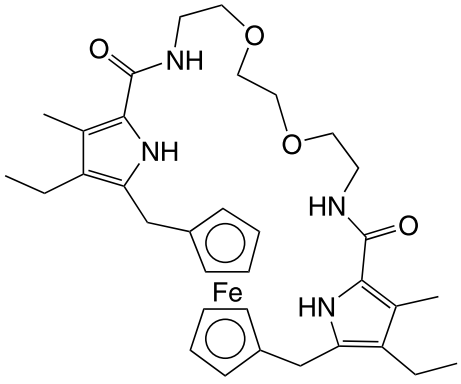


Fig. 31. View of the 2:1 chloride anion complex stabilized in the solid state by the diprotonated form of the tris-nor-hexapyrrin **56**. This structure was generated from data down-loaded from the CCDC and corresponds to a structure that first appeared in reference [70].

7. Amide- and guanidinium based polypyrrolic systems

7.1. Ansa-ferrocene

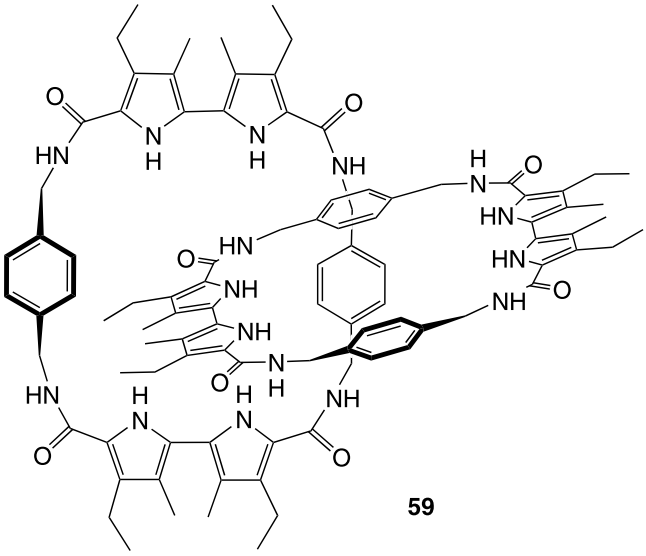
Pyrrole-containing macrocycles represent a class of compounds that have been widely studied by an increasing number of researchers. In addition to their work with expanded porphyrins, open-chain oligopyrroles, and other polypyrrolic systems discussed elsewhere in this review, Sessler and co-workers have generated a number of macrocyclic systems containing more isolated pyrrolic subunits. One of the more interesting of these is the bridged dipyrrole *ansa*-ferrocene **58** [72]. This compound contains two pyrrolic NH and two amidic NH groups that combine to make it and its analogues [73] efficient anion receptors. In the specific case of **58**, the binding stoichiometry was found to be dependent on the size of the anionic guest; Job plots revealed a 2:1 (anion-to-host) binding stoichiometry for the complexation of fluoride anion and a 1:1 ratio for the others anions (viz. chloride, bromide, hydrogensulfate and dihydrogenphosphate). Quantitative ^{1}H-NMR spectroscopic titration studies also confirmed that this macrocyclic receptor possessed an inherent affinity for dihydrogenphosphate, fluoride, and chloride over a range of other studied anions. These findings were corroborated by electrochemistry studies that allowed for the detection of a coordinated anionic species through specific cathodic shift of the ferrocene–ferrocenium redox couple. The largest shift was observed in the presence of dihydrogenphosphate anions (136 mV) followed by fluoride and chloride (80 and 24 mV, respectively). These shifts, it was appreciated by the authors, actually reflect a number of chemical events, including the relative binding affinities for complexation to the oxidized ferrocenium and neutral ferrocene forms of the macrocycle. They were thus not put forward as a direct measure of binding per se. On the other hand, the qualitative correspondence between the electrochemical and NMR spectroscopic analyses was considered pleasing and became the predicate for further work. In this latter context, it is noteworthy that several simple polypyrrole films have recently been prepared by Gale and shown to respond electrochemically to the presence of sub-stoichiometric quantities of anions [74].



58

7.2. A bipyrrole based catenane

In 1998, Sessler, Vögtle, and co-workers reported the first example of a dipyrrole-based [2]catenane [75]. This catenane, compound, **59** was synthesized from the appropriate bipyrrole acyl chloride and *p*-xylenediamine building blocks. ^{1}H-, ^{13}C- and ^{19}F-NMR studies carried out in 1,1,2,2-tetrachloroethane-d_2 provided evidence consistent with this compound being able to bind fluoride anions effectively in solution as the result of it undergoing a change in conformation and thereby providing a more accommodating cavity. Such "induced fit" binding is rare among pyrrole-based anion receptors but even more noteworthy is the fact that larger anionic species, such as chloride, actetate and dihydrogenphosphate, are bound more effectively than fluoride by this receptor (K_a (1,1,2,2-tetrachloroethane-d_2,) $= 3.6 \times 10^6$, 9.6×10^5, $> 1 \times 10^7$ and 1.5×10^5 M^{-1} for Cl^-, $H_2PO_4^-$ and F, respectively). These findings, rationalized in terms of the larger anions being bound between the two rings of the catenane, highlight further how appropriate structural designs can be used to modify the inherent for-fluoride selectivity displayed by most pyrrole-based anion receptors.



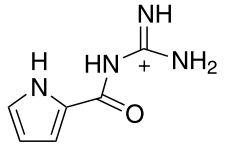
59

7.3. Guanidinium-appended systems

In some respects the simplest approach to generating pyrrole-based anion receptors involves modifying the pyrrole ring with groups capable of increasing the

strength of the receptor–anion interaction. Schmuck and co-workers have produced a variety of receptors containing a guanidinium group attached to a pyrrole (e.g. compound **60**) [76], that are excellent receptors for carboxylates. In DMSO solution, the association constant for the formation of the acetate complex of receptor **60**, proved too high to measure accurately ($K > 10^6$ M^{-1}). By moving to a more polar solvent mixture (50% water–DMSO), however, it proved possible to determine the association constant; it was found to be ca. 10^3 M^{-1} [76].

Schmuck also reported the synthesis of a pyrrole based receptor **61** for *N*-acetyl-α-amino acid carboxylates that functions in aqueous solution [77]. Compound **61** consists of a pyrrole ring substituted in the 2- and 5-positions by an amide group and a guanidinium moiety. In this case, acetate was found to be the best bound of all the carboxylate anions studied (presumably due to the absence of unfavorable steric interactions). A number of *N*-acetyl-α-amino acid carboxylate anions were also studied. The identity of the side chain present in these amino acid derivatives presumably serves to modulate the strength of the anion–receptor complex with, for instance, π-stacking interactions between the acylguanidinium residue of the receptor and the aromatic ring of phenylalanine serving to enhance the stability of the **61**–*N*-Ac–L-Phe complex (Fig. 32).



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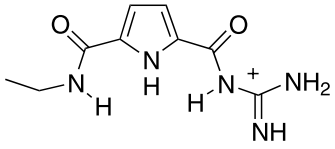


61

7.4. 2,5-Diamidopyrroles

Another approach, taken by Gale and co-workers, to produce an oxo-anion selective receptor, has been to append amide groups to the 2,5-positions of the pyrrole ring. These systems may be regarded as pyrrolic analogues of the isophthalic amide anion receptors

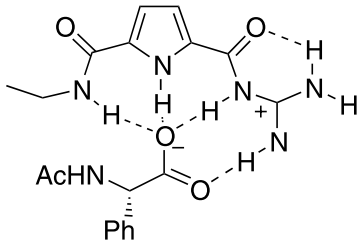
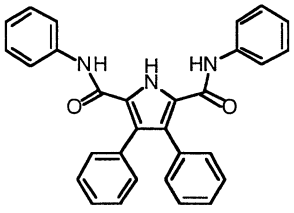


Fig. 32. Schematic representation of the proposed supramolecular complex formed between receptor **61** and *N*-Ac–L-Phe.

produced by Crabtree and co-workers [78]. Receptors **62** and **63** were synthesized by reaction of the corresponding diacid chloride with either aniline or *n*-butylamine [79]. Both compounds proved to be selective for oxo-anions in polar organic solvent (CD_3CN or DMSO-d_6 (0.5% water)). However, they displayed some differences in their individual binding characteristics, with peak association constants of 2.5×10^3 M^{-1} being displayed by compound **63** when binding benzoate anions in acetonitrile-d_3 while a corresponding K_a value of 1.45×10^3 M^{-1} was observed for the binding of dihydrogenphosphate by compound **62** in DMSO-d_6–H_2O 0.5%.



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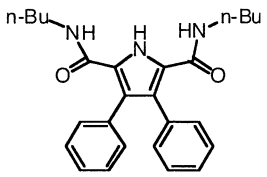
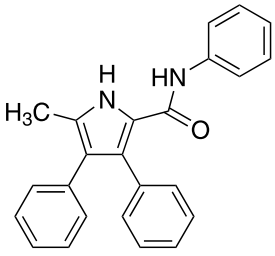


63

The 2-amido-5-methylpyrrole compounds **64** and **65** were synthesized in order to gain some insight into the binding mode adopted by these kinds of compounds in solution. Both compounds show significantly reduced affinities for oxo-anions as compared to their 2,5-diamido analogues (e.g. compound **65** binds benzoate with an association constant of 202 M^{-1} in acetonitrile-d_6, a finding that led Gale to suggest that in the 2,5-diamido systems, all three NH hydrogen bond donors are involved in hydrogen bond donation to oxo-anions [80].



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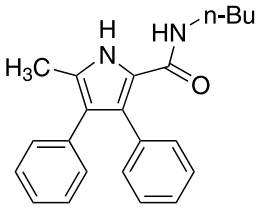


65

Very recently, the crystal structure of the benzoate complex of receptor **63** was elucidated and it revealed that all three hydrogen bond donors are indeed involved in hydrogen bonding to the anionic guest (Fig. 33) [81]. The benzoate anion was found to be coordinated within the cleft formed by the pyrrole and amide moieties by three NH–O hydrogen bonds in the range 2.771(3)–2.864(3) Å. One of the oxygen atoms of the benzoate is in the plane of the pyrrole ring and one of the amide groups bound in a similar fashion to DMSO solvates previously observed [80]. The other amide group is

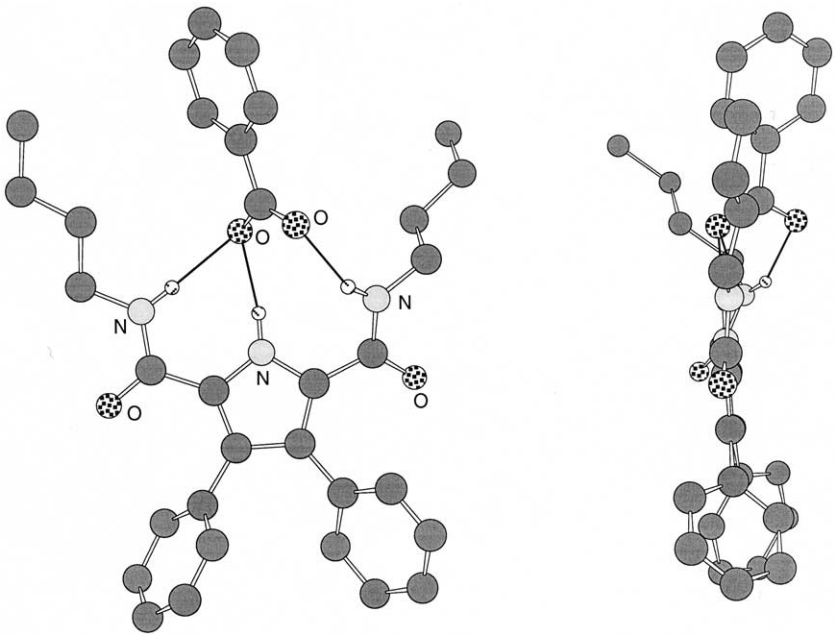
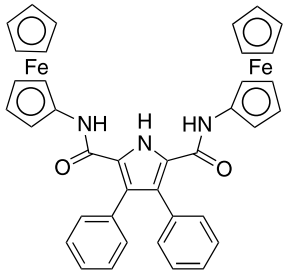


Fig. 33. Front and side views of the benzoate anion complex of receptor **63**. This structure was generated from data down-loaded from the CCDC and corresponds to a structure that first appeared in reference [81]. Selected hydrogen atoms have been omitted for clarity.

twisted out of the plane by 38.03(10)° to accommodate a hydrogen bond to the other benzoate oxygen atom.

By appending ferrocene groups to the 2,5-diamido skeleton, Gale has shown that these compounds may also be used as electrochemical sensors for anions [82]. Compounds **66** and **67** each contain two ferrocene moieties linked either directly to the amide group (**66**) or via a methylene carbon (**67**). As with other 2,5-diamido cleft receptors, the two compounds crystallize as dimers linked via NH–OC hydrogen bonds [80]. The crystal structure of compound **66** (obtained from crystals grown from a dichloromethane–diethylether solution of the receptor) also shows this binding motif and in addition a CH–O interaction from the substituted ferrocene cyclopentadienyl ring to an amide oxygen atom (Fig. 34).



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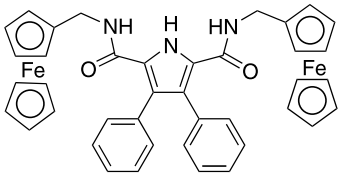


67

The electrochemical behavior of these compounds was investigated by cyclic voltammetry in dichloromethane using a platinum disk microelectrode. Significant shifts of the ferrocene–ferrocenium redox couple were observed upon addition of a variety of anions to solutions of the receptor, however, in a number of cases the voltammetric wave was found to be seriously distorted as the product of the electrochemical reaction passivates the electrode (Table 2).

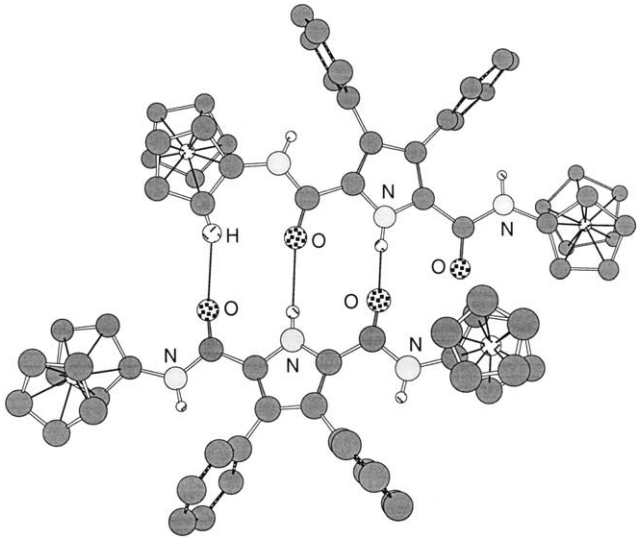
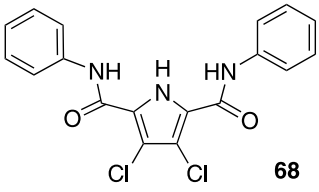


Fig. 34. X-ray crystal structure of **66** showing dimer formation in the solid state via NH–O and CH–O hydrogen bonds. Certain atoms have been omitted for clarity. This structure was generated from data down-loaded from the CCDC and corresponds to a structure that first appeared in reference [82]. Selected hydrogen atoms have been omitted for clarity.

Table 2
Association constants of receptors **66** and **67** with various anions (added as their TBA salts) in dichloromethane-d_2 and voltammetric shifts in ferrocene–ferrocenium redox couple of receptors in the presence of three equivalents of the anion in dichloromethane

	Compound **66**		Compound **67**	
	K_a (M^{-1})	ΔE (mV)	K_a (M^{-1})	ΔE (mV)
F^-	705	−125 and −255 [b]	170	−130
Cl^-	70	−55	<20	−75
Br^-	<20	−10	<20	0
$H_2PO_4^-$	145	[a]	45	[a]
HSO_4^-	75	−40	45	[a]
Benzoate	1820	−120	35	−60

[a] With some anions, the voltammetric wave is seriously distorted as the product of the electrochemical reaction passivates the electrode.
[b] Two waves are observed.



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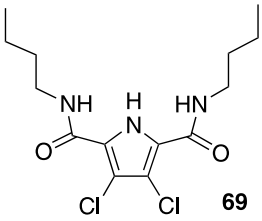


69

In order to enhance the affinity of this class of receptor for anions, compounds **68** and **69** analogues of compounds **62** and **63** containing chlorine substituents in the 3- and 4-positions of the pyrrole ring, were synthesized. The electron withdrawing chlorine groups in compounds **68** and **69** serve to enhance the acidity of the pyrrole NH groups and hence allow the receptor to form stronger hydrogen bonds to the putative anionic guest [83]. In fact, chloride was found to bind to these receptors over an order of magnitude more strongly than to the 3,4-diphenyl analogues **62** and **63**. However,

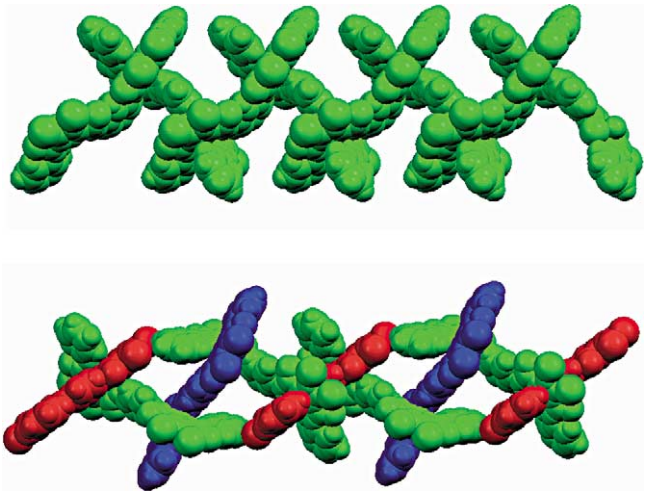


Fig. 36. A space filling representation of the crystal structures of the TBA salts of (top) $[\mathbf{70}–2H^+]^{2-}$ and (bottom) $[\mathbf{71}–2H^+]^{2-}$ (counter cations omitted for clarity). Colors represent crystallographically equivalent anions. Copyright 2002, American Chemical Society, reproduced with permission.

unusual titration profiles obtained upon addition of sub-stoichiometric quantities of more basic anions (such as fluoride) suggested that the increase in the acidity of the pyrrole NH proton was such that the proton could be removed by the anion. Solid-state evidence for this deprotonation process was obtained by obtaining crystals of receptor **68** by slow evaporation of a dichloromethane solution of the receptor in the presence of excess tetrabutylammonium (TBA) fluoride. No fluoride was observed in the crystal structure. Instead the crystals were found to be the TBA salt of the deprotonated pyrrole. The anion forms a 'narcissistic dimer' whereby the N^- is stabilized by the formation of two amide NH–N– hydrogen bonds from another anion

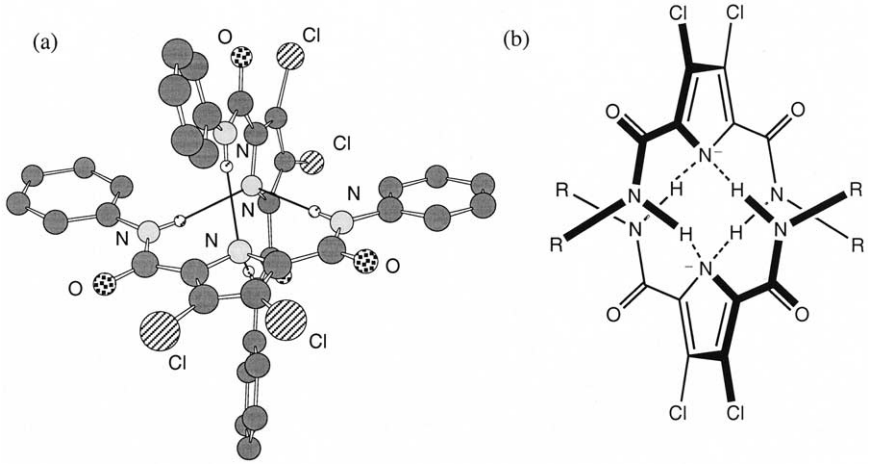
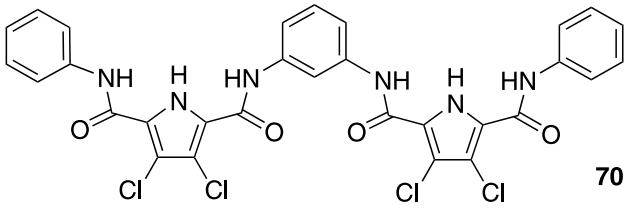


Fig. 35. (a) Crystal structure of the narcissistic dimer formed by the TBA salt of compound **68**. The pyrrole NH proton has been removed allowing the formation of amide NH···N– hydrogen bonds between the two 2,5-diamidopyrrole anions. Selected hydrogen atoms and the TBA counter cations have been omitted for clarity. This structure was generated from data down-loaded from the CCDC and corresponds to a structure that first appeared in reference [83]. (b) Structure of the dimer.

(Fig. 35). The N^- center on the second anion is also stabilized by two NH–N^- hydrogen bonds from the first so forming a dimer. It is interesting to note that in this hydrogen bonding array the two components are orthogonal, in contradistinction to systems such as DNA wherein the two hydrogen bonding bases that constitute a base pair are almost co-planar.

Gale has used this unusual bonding motif to construct anionic coordination polymers [84]. Molecules **70** and **71** (contain two 3,4-dichloro-2,5-diamidopyrrole units) linked via a 1,3- or 1,4-susbtituted phenyl ring. When crystallized in the presence of TBA fluoride, the pyrrole groups once again deprotonate allowing the formation of unusual anionic polymers in the solid state (Fig. 36).



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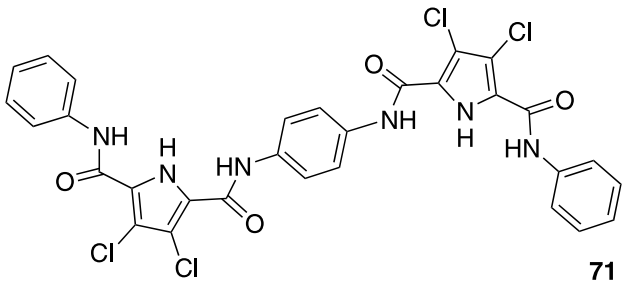


71

The effect of adding electron-withdrawing groups to the groups attached to the amide links was then investigated. Compounds **72** and **73** (containing 4-nitrophenyl and 3,5-dinitrophenyl groups were synthesized by condensation of 3,4-diphenyl-2,5-bis acid chloride with 4-nitroaniline or 3,5-dinitroaniline in dichloromethane in the presence of triethylamine and DMAP in 43 and 11% respective yields [85]. In the case of the 3,5-dinitrophenyl derivative **73**, an unusual titration profile was again observed (Fig. 37). A downfield shift up to one equivalent of fluoride followed by an upfield shift and then another downfield shift upon increasing fluoride concentration has been interpreted by Gale as being due to initial fluoride binding, followed by deprotonation and then subsequent fluoride binding to the deprotonated receptor. The deprotonation process has been used to colorimetrically sense fluoride anions in acetonitrile solution. Addition of TBA fluoride to an acetonitrile suspension of the receptor gives rise to a deep blue color (whilst a yellow color is observed upon addition of other anions such as dihydrogen phosphate or benzoate). The blue solution was allowed to evaporate yielding colorless crystals that proved to be the deprotonated receptor binding an adventitious chloride ion via two amide NH hydrogen

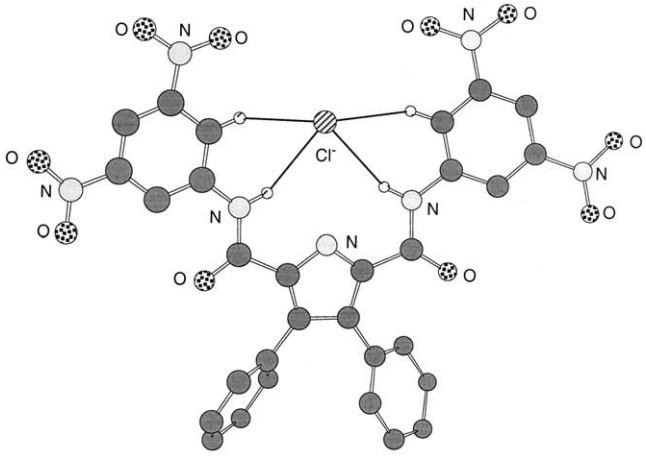


Fig. 38. (a) Crystal structure of the chloride complex of deprotonated receptor **73**. Selected hydrogen atoms and the TBA counter cations have been omitted for clarity. This structure was generated from data down-loaded from the CCDC and corresponds to a structure that first appeared in reference [85].

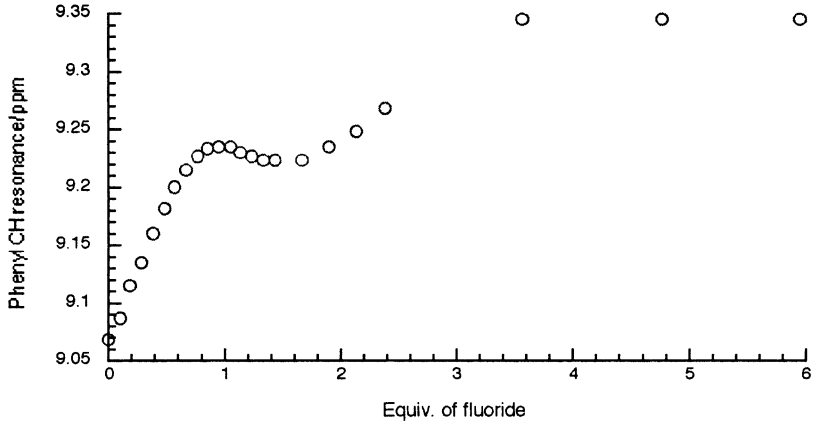
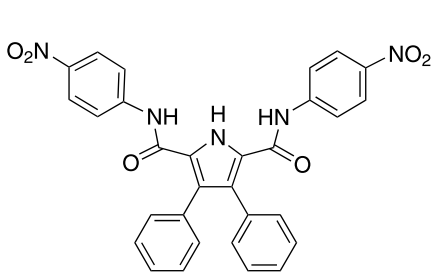


Fig. 37. NMR titration curve of compound **73** with fluoride anions in DMSO-d_6–0.5% water. Copyright RSC 2003, reproduced with permission.



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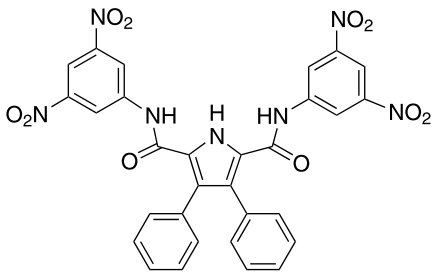


73

bonds and two phenyl CH–Cl interactions (Fig. 38). The TBA salt of **73** was prepared by addition of TBA hydroxide to **73**, and the salt obtained as red crystals. When these were dissolved in acetonitrile they produced a blue solution (with an identical UV–vis spectrum to that obtained upon addition of fluoride) suggesting that the blue color is due solely to the pyrrole anion. In fact the crystal structure of the TBA salt of **73** was solved revealing the formation of a pyrrole anion dimer analogous to that produced by deprotonation of compound **68**.

8. Pyrrole as an anion receptor

Gale and coworkers have recently demonstrated that pyrrole itself can stabilize an anion complex, at least in the solid state. Specifically, these latter workers succeeded in elucidating the crystal structure of a pyrrole–chloride complex prepared by crystallizing tetramethylammonium chloride from pyrrole (Fig. 39) [86]. In this structure, direct hydrogen bonding interactions between the chloride anion and two pyrrole NH protons were seen (N···Cl = 3.241 Å), as well as ones involving the tetramethylammonium cation. Unfortunately, these interactions were found not to persist in dichloromethane solution for simple pyrroles at least not to an appreciable extent [87]. These findings thus underscore the need to incorporate pyrrole into a complementary host framework in order to bind anions effectively in solution.

9. Calixphyrins

9.1. Macrocyclic systems

In 2000 Sessler et al. reported the synthesis of several so-called calix[n]phyrins, macrocyclic compounds that may be regarded as hybrids of calixpyrroles and porphyrins [88]. Representative of this class of compounds, recently reviewed elsewhere [7], is the hexapyrrolic system **74** that was prepared via the reaction of pentafluorobenzaldehyde with an appropriate tripyrrane precursor (obtained, in turn, from the TFA acid-catalyzed condensation of pyrrole and acetone). The crystal structure of calixphyrin **74** reveals a molecule of water bound to the pyrrolic NH protons (Fig. 40), a finding that led to the suggestion that this system could function as an anion receptor. However, no evidence of anion binding was seen when compound **74** was treated with a range of targeted anions (chloride, bromide, iodide, nitrate, hydrogensulfate), at least when it was studied in its neutral form. On the other hand, solid-state structural analysis revealed that chloride anion was bound within the cavity of $[H\cdot\mathbf{74}]^+$ (Fig. 41). On the other hand, the anion was found to be disordered, leading to the suggestion that chloride anion was too small to be an ideal substrate for this receptor.

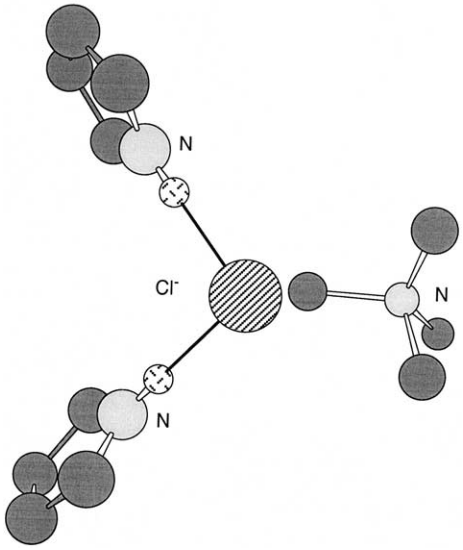


Fig. 39. X-ray crystal structure of the complex formed between tetramethylammonium chloride and pyrrole. Selected hydrogen atoms have been omitted for clarity. This structure was generated from data down-loaded from the CCDC and corresponds to a structure that first appeared in reference [87].

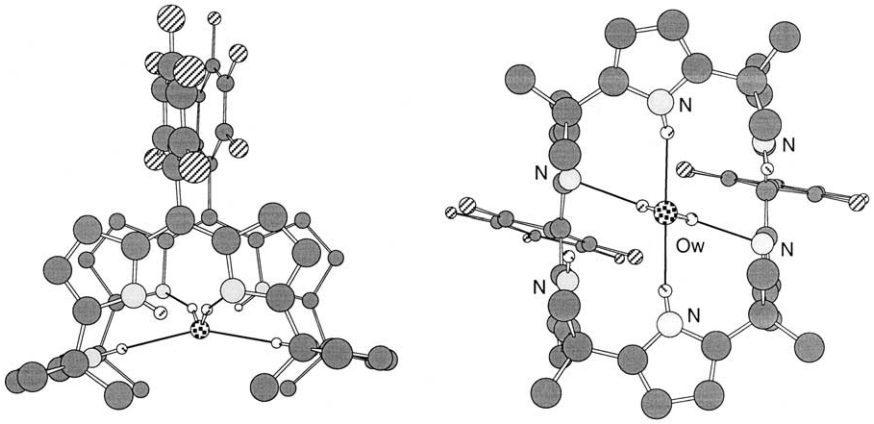


Fig. 40. View of **74**·H_2O showing the hydrogen bonding interactions between the centrally bound water molecule and the pyrrolic NH donor and N acceptor sites. Selected hydrogen atoms have been omitted for clarity. This structure was generated from data down-loaded from the CCDC and corresponds to a structure that first appeared in reference [88].

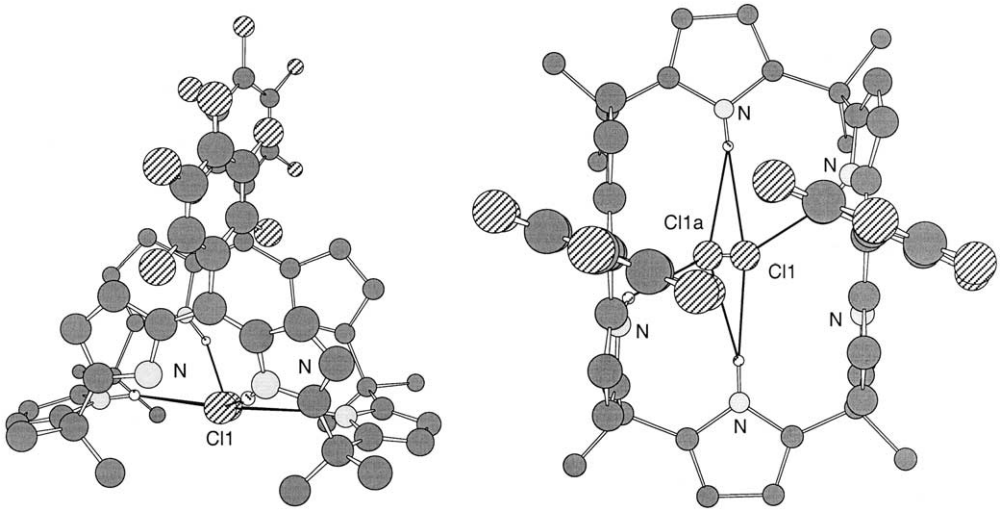
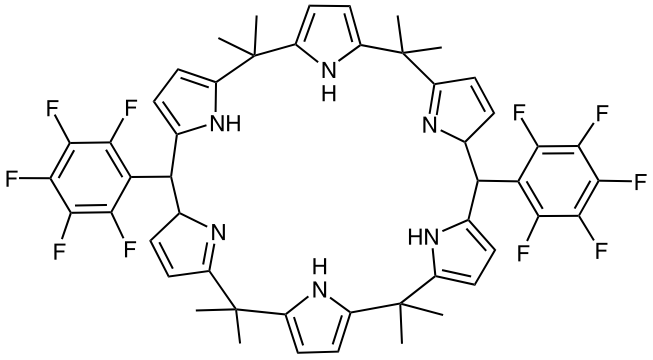


Fig. 41. View of the hydrochloride salt of **74** showing the disordered, centrally bound chloride anion. Selected hydrogen atoms have been omitted for clarity. This structure was generated from data down-loaded from the CCDC and corresponds to a structure that first appeared in reference [88].

Consistent with this suggestion was that fewer equivalents of bromide anion were required to effect a saturation-level change in the optical properties of diprotonated **74** than either chloride or iodide anions. Unfortunately, only in the case of the latter anion and only when **74** was fully (i.e. di-) protonated was evidence for the formation of a clean 1:1 anion–receptor complex obtained; in this instance an association constant of ca. 8×10^7 M^{-1} was estimated for a binding process involving the interaction between iodide anion and diprotonated **74** in acetone solution.



74

9.2. Cryptand-type oligopyrroles

Recently Sessler and co-workers reported the first example of a cryptand-like calix[4]pyrrole **75** [89]. Compound **75** provides three identical binding cavities and was found to bind solvents in these cavities in the solid state (Figs. 42 and 43). This led to the suggestion that it could stabilize anion–receptor complexes of 1:1, 1:2 or 1:3 stoichiometry in solution. In point of fact, ^{1}H-

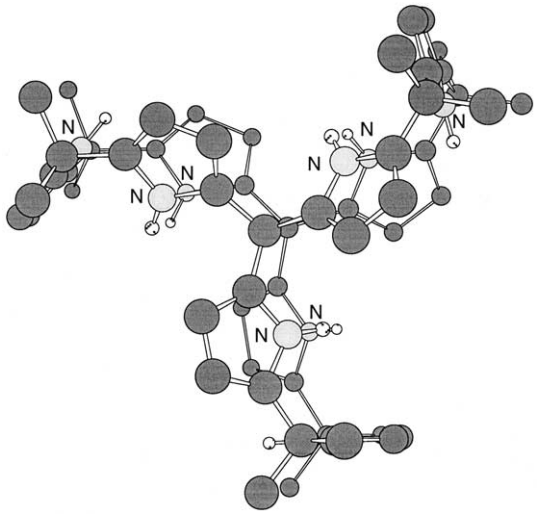
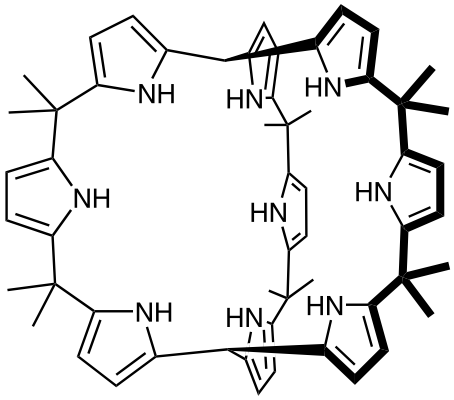


Fig. 42. View of **75** showing several potential binding pockets. Selected hydrogen atoms have been omitted for clarity. This structure was generated from data down-loaded from the CCDC and corresponds to a structure that first appeared in reference [89].

NMR experiments carried out in dichloromethane-d_2 and THF-d_8 revealed host–guest stoichiometries that were even more complicated and which depended directly upon the anion considered. For instance, fluoride, when added as an anionic guest, was found to be bound to six of the nine pyrrolic subunits, presumably in a 1:1 fashion. By contrast, it was proposed that the chloride anion interacts with two molecules of receptor **75** in solution (i.e. 2:1 host-to-anionic guest binding stoichiometry) and is bound with a stability constant of 3.08×10^6 M^{-2} in dichloromethane-d_2 solution. Finally, a 1:2 (host to guest) stoichiometry was observed instead observed upon addition of nitrate with the stability constants K_1 and K_2 being 1740 and 420 M^{-1}, respectively, in dichloromethane-d_2 solution.



75

10. Dipyrrolylquinoxalines

In 1999 Sessler and coworkers reported a new approach to anion sensing that is predicated on the use of DPQs [90]. These acyclic, neutral systems are readily available in two steps from simple commercially available materials (e.g. pyrroles, oxalyl chloride, *o*-phenylenediamines) using a procedure first reported in the literature in 1911 [91]. They also contain a built-in

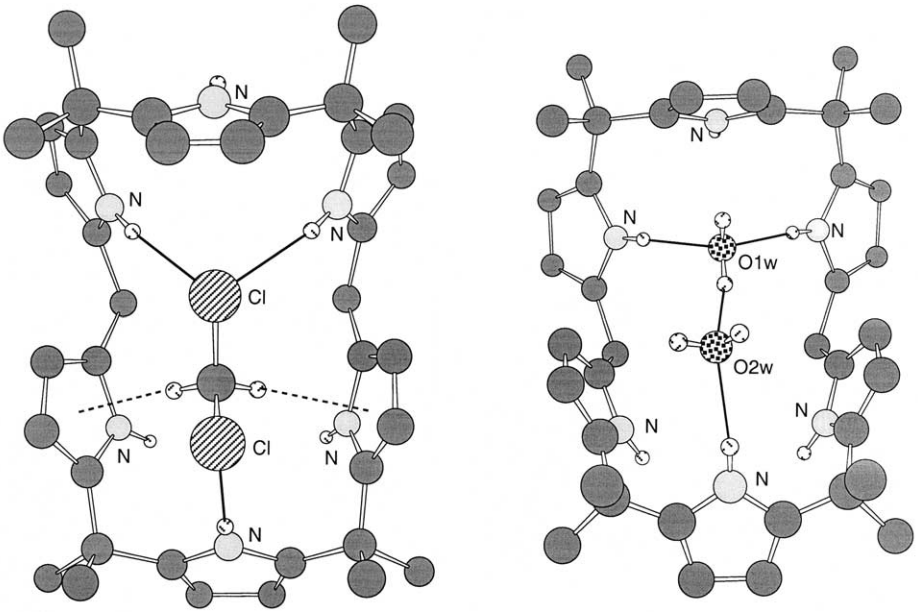
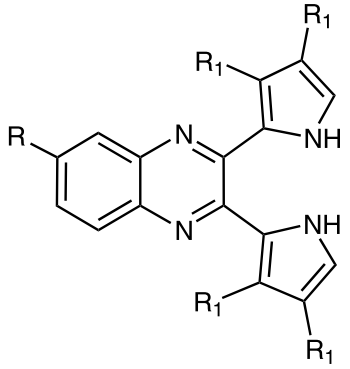


Fig. 43. Partial views of two of the three cavities present in **75**, showing bound dichloromethane and water molecules. Selected atoms have been omitted for clarity. This structure was generated from data down-loaded from the CCDC and corresponds to a structure that first appeared in reference [89].

chromophore, the quinoxaline subunit, whose optical properties can be readily modified through further substitution as detailed more fully in a recent review [6].

The first DPQ systems reported by Sessler and co-workers consisted of the unsubstituted system **76** and its mono-nitro derivative **77** [90]. In the absence of anions, dilute dichloromethane solutions of these two DPQs were pale yellow and deep yellow, respectively, and were found to be highly fluorescent. Addition of 100 molar equivalents of TBA fluoride trihydrate led to an immediate quenching of the fluorescence intensity and to dramatic color changes, from yellow to yellow–orange in the case of **76** and from dark yellow to purple in the case of **77** (Fig. 44). This proved true not only in dichloromethane, but also in DMSO. By contrast the addition of equivalent quantities of TBACl or $TBAH_2PO_4$ did not induce an appreciable quenching of the fluorescence intensity. Nor, did it lead to a discernable color change. These findings were rationalized in terms of fluoride, but not chloride or dihydrogenphosphate, binding to the pyrrolic receptor portion of the DPQ system and modifying the orbital overlap between the pyrrole and the quinoxaline subunits, although alternative mechanisms of action, including ones based on charge transfer and partial or complete deprotonation of the pyrrolic protons could not be ruled out.



76. R = R_1 = H
77. R = NO_2; R_1 = H
78. R = H; R_1 = F

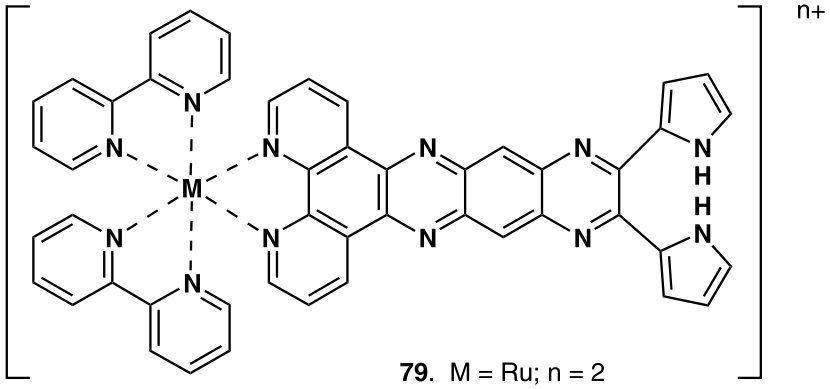
Fig. 44. Color changes (if any) induced by the addition of anions (100 equivalents). From left to right (dichloromethane solutions): **76**; **76**+Cl^-; **76**+F^-, **77**; **77**+Cl^-; **77**+F^-. The anions were used in the form of their commercially available TBA salts. This figure was reproduced with permission and corresponds one first appearing in reference [90].

With the basic utility of the DPQ approach demonstrated, attention has turned to the development of DPQ-based systems with improved affinities and modified selectivities. The first set of efforts in this regard involved the synthesis of the tetrafluoro DPQ derivative **78**. This system displayed an increased affinity for the three test anions studied in the case of **76** (e.g. K_a (CH_2Cl_2) = 61 600 for F^- and 17 300 for $H_2PO_4^-$ vs. 18 200 for F^- and 60 for $H_2PO_4^-$, in the case of **78** and **76**, respectively) as well as a higher dihydrogenphosphate:chloride selectivity ratio (96 vs. 1.2 in the case of **78** and **76**, respectively) [92]. These quantitative findings were underscored by the fact that the fluorinated DPQ **78** was observed to undergo a naked-eye-detectable yellow-to-orange color change when exposed to 100 molar equivalents of either TBA fluoride or TBA dihydrogenphosphate in dichloromethane solution, while failing to undergo a discernable color change when exposed to an equivalent concentration of chloride anion.

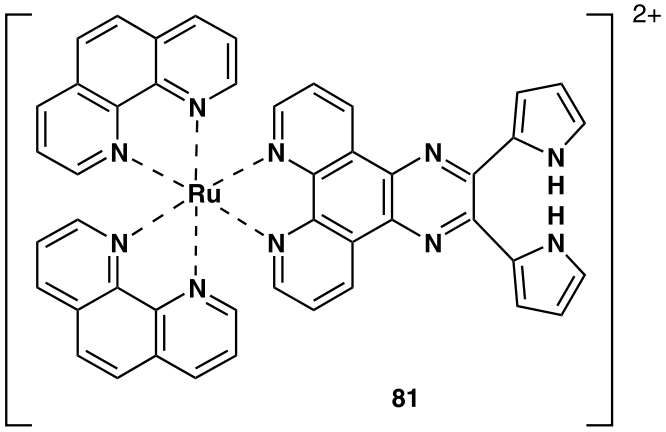
Appreciating that the presence of electron withdrawing substituents served to increase the affinity of DPQ-type anion receptors, Sessler and, independently, Anzenbacher prepared systems, specifically **79** and **80** [93] and **81** [94] that contained phenanthroline metal complexes "fused" onto the quinoxaline core. Although tested in differing solvents (DMSO and dichloromethane in the case of the Sessler and Anzenbacher systems, respectively), taken in concert these two studies confirmed the validity of this approach, underscoring in particular the fact that it could be used to increase the inherent anion affinities of DPQ sensors by several orders of magnitude in the most favorable of cases.

Another approach to augmenting the intrinsic affinity of DPQ sensors, that shows promise of having general utility in the area of pyrrole-based anion receptor design, was recently introduced by Sessler; it involves the "attachment" of ancillary pyrrolic anion binding motifs to produce species such as **82** and **83** [95]. Rationalized in terms of an ability to form bowl-like binding pockets that favor larger anions as illustrated graphically by supramolecular structure **84**, this strategy proved very successful, in terms of not only raising the absolute affinities (to greater than 10^6 M^{-1} for fluoride binding to **83** in dichloromethane) but also increasing the relative affinities of both phosphate and chloride as compared with what is observed in the case of simple DPQs (e.g. K_{F^-}/K_{Cl^-} and $K_{F^-}/K_{H_2PO_4^-}$ (CH_2Cl_2) = 58 and 7.4 vs. 360 and 300 for **82** and **76**, respectively).

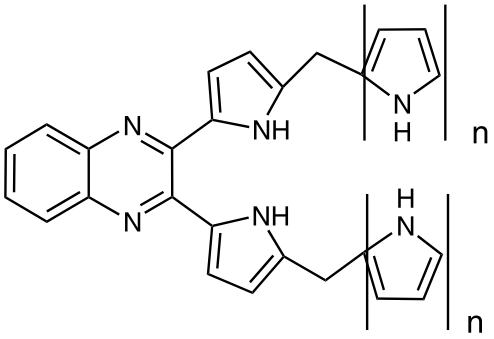
A very different approach to modulating the affinities of DPQ-type systems involves incorporating this subunit into macrocyclic systems. A first successful application of this strategy has recently been demonstrated by Sessler and co-workers. Specifically, these researchers reported the synthesis of the imine-bridged, 1,8-diaminoanthracene-derived systems **85**–**87** and were able to



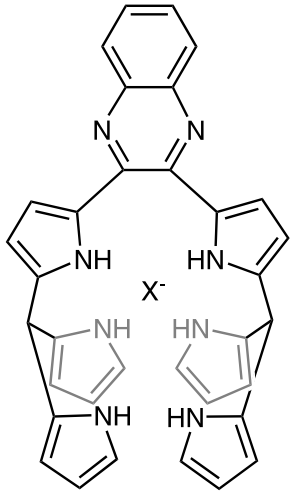
79. M = Ru; n = 2
80. M = Co; n = 3



81



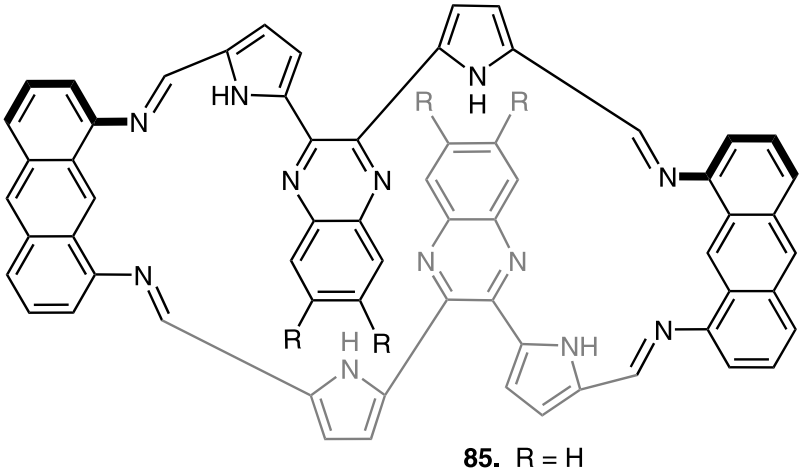
82. n = 1
83. n = 2



84. $X^- = F^-, Cl^-, H_2PO_4^-$.

demonstrate that these receptors bound fluoride and phosphate anions in a cooperative 2:1 fashion in dichloromethane [96]. On the other hand, little affinity was displayed towards a range of other anionic substrates, including Cl^-, Br^-, NO_3^-, and HSO_4^-, a set of findings that presumably reflects both the intrinsic selectivity of the DPQ core and the modulating influence imposed by the receptor design.

As highlighted in this review, for largely historical reasons, namely the serendipitous discovery that diprotonated sapphyrin bound fluoride anion in the solid state, early work in the area focused on the use of so-called expanded porphyrin systems. These systems, which remain of interest and which are being complemented by the study of new porphyrin analogues, are characterized by a high degree of preorganization and



85. R = H
86. R = OCH_3
87. R = OCH_2CH_3

11. Conclusion

Over the last decade pyrrole has emerged as an important anion recognition motif that provides a ready source of hydrogen bond donor functionality. Its great stability and general lack of protonation–deprotonation reactivity has made it amenable to use over a wide range of effective pH and in a number of different solvents. Making pyrrole especially attractive in the context of anion recognition is the fact that, in and of itself, it does not contain any built-in hydrogen bond acceptor sites. On the other hand, it is easy to functionalize. This means pyrroles can be incorporated synthetically into a range of elaborated structures, including ones that contain ancillary recognition or sensing elements. Pyrroles can also be oxidized under appropriate circumstances, leading (generally) to conjugated systems that, like the naturally-occurring prodigiosins, contain basic, pyridine-like pyrrolic centers. The net result of this synthetic and chemical flexibility has been an impressive array of receptor systems and the promise of yet more sophisticated ones to come in the years ahead.

binding that is abetted by the presence of an intrinsic, protonation-derived positive charge. Protonation, concurrent with anion binding is also a hallmark of the prodigiosins and open-chain conjugated oligopyrrole receptors, whose synthesis and study is still in an incipient stage.

In recent years, increasing attention has turned to the study of neutral, pyrrole-based anion receptors. As a general rule, these systems are far simpler to prepare than expanded porphyrin-type systems and conjugated acyclic oligopyrroles. However, they often display reduced anion affinities and inherent for fluoride selectivities that can only be modified through clever receptor design. As a result, effort continues to be devoted to the synthesis and study of increasingly elaborate macrocyclic and polycyclic systems. Meanwhile, the ready accessibility of many neutral pyrrolic systems is leading to their being taken forward in increasingly sophisticated tests of their applicability in various "real world" applications, including sensing, transport, waste remediation, and tailored drug development. This perceived utility, in turn, is inspiring the

synthesis and study of other new systems while providing an important incentive to develop further the chemistry of pyrrole-based anion recognition.

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