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Pyrrole N–H Anion Complexes

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Abstract

Synthetic pyrrole-based anion receptors date back to the 1990s. They have been extensively developed in the context of macrocyclic systems as expanded porphyrins and calixpyrroles, and related systems. The chemistry of open-chain pyrrolic systems is, in many respects, no less venerable. It also has more direct analogy to naturally occurring pyrrole-based anion binding motifs. However, it has not been the subject of a comprehensive review. Presented herein is a summary of efforts devoted to the creation of de novo pyrrole-based receptors, as well as the anion recognition chemistry of naturally occurring pyrrolic systems as prodigiosins and their synthetic analogues.

Keywords

Pyrrole; Anion Binding; Hydrogen-bonding; Prodigiosin; Receptor; Recognition

1. Introduction

Anions play important roles in the environment and in many other biological processes. For instance, an excess of phosphate and nitrate anions lead to eutrophication of lakes and waterways [1], whereas misregulation of chloride concentrations is associated with a number of diseases, including cystic fibrosis [2]. The use of supramolecular systems capable of complexing anions is an area that has its beginnings in the 1970s and has rapidly evolved into the development of sensors, extractants, anion-responsive materials, and anion carriers, among other application areas. One of the building blocks used as a recognition unit for anions is pyrrole. The first reported pyrrole-containing system that acted as an anion receptor was sapphyrin (Figure 1) [3,4]. In this instance, a serendipitous observation in 1990 revealed fluoride bound to the diprotonated form of the macrocycle [4]. Subsequent studies confirmed the ability of sapphyrin to bind the fluoride, chloride, and phosphate anions in solution [5]. Even interactions with the polyphosphate anion, DNA, were demonstrated [6]. Later on in the 1990s, a number of other protonated expanded porphyrins [7,8] and several open-chain analogues [9] acted as anion receptors. In 1996, the non-conjugated tetrapyrrolic

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macrocyclic, calix[4]pyrrole, functioned as a neutral anion receptor (Figure 1) [10]. Expanded porphyrins [11,12], calixpyrroles [13] and their macrocyclic analogues [14,15] have been extensively reviewed in the context of anion and ion pair recognition. In this review we focus on the anion binding properties of neutral and charged acyclic pyrrolic systems.

The first report of a pyrrolic system interacting with an anion came in a 1992 publication by Peter Jordan and coworkers [16]. In this structural report, which appeared two years after the observation that the artificial system, sapphyrin, would recognize anions, revealed a dipyrromethane interacting with a carboxylate anion in the active site of porphobilinogen deaminase [16]. A subsequent milestone in the chemistry of pyrrole-based biological anion recognition came with the proposal by Ohkuma and Wasserman that the open-chain tri-pyrrolic secondary metabolite, prodigiosin, mediated some or all of its biological activity, including its antiproliferative effects, as the result of the co-transport of protons and the chloride anion [17,18]. This suggestion was put forward based in part on appreciation of the fact that a synthetic open chain hexapyrrolic system, formally a covalently linked “bis-prodigiosin”, had been previously characterized structurally in the form of its chloride anion-bound dihydrochloride salt [9]. As detailed further below, the combination of biological activity and a proposed mechanism of action involving anion recognition and transport suggested for prodigiosin served to stimulate considerable effort to understand further the anion recognition features of pyrrole, and to create molecular receptors and carriers capable of efficiently binding and transporting anions [19–21]. For instance, a strapped calix[4]pyrrole transported Cl^- across cell membranes effectively in the presence of functioning Na^+ channels and to induce apoptotic activity in several cancer cell lines (e.g., lung A549 and HeLa) [22]. Many other effective transporters are known and very recently one acted as an inhibitor of autophagy [23]. Several classes of anion transporters have been the subject of separate reviews [24,25].

Beyond the chemistry of prodigiosin there has been considerable interest in the biology of anion recognition. For instance, publication of the X-ray structure of two prokaryotic chloride channels (CIC) by Dutzel *et al.* in 2002 [26] provided information at the molecular level regarding the structure of these channels and their interactions with chloride anions. Based on the structural parameters, both electrostatic interactions and hydrogen-bonding interactions were inferred as being important. This fundamental biological work, thus served to highlight further the importance of non-covalent interactions in anion recognition.

Although less studied, non-cyclic pyrrolic receptors offer some advantages over macrocyclic systems in terms of anion recognition. Potential advantages include, conformational changes that allow the receptor adjust its shape to fit the targeted anionic species, as well as being formed generally in higher yields than the corresponding macrocyclic compounds. Substitution in the α - or β -pyrrolic positions is often easier to accomplish than in the case of macrocyclic systems. This kind of synthetic adjustment has resulted in a number of open chain, pyrrole-containing receptors that associate with anionic species with minimal steric hindrance and with more favorable electrostatic interactions than might otherwise be anticipated. One goal of this review is to provide a survey of accomplishments to highlight

key trends that relate structure to function in the case of both simple and more complex acyclic pyrrole-based anion receptors.

2. Monomeric Pyrrole Anion Receptors

The interaction between a proton donor pyrrole and negatively charged species can lead to the formation of well characterized $\text{N-H}\cdots\text{X}^-$ complexes. In 2001 Gale *et al.* reported the single crystal structure of the chloride complex of pyrrole (with TBA, tetrabutylammonium, as the counterion). This structure revealed the chloride anion hydrogen bonded to two pyrrole rings via $\text{N-H}\cdots\text{Cl}^-$ interactions (Figure 2a), assisted by a weaker hydrogen bond interaction involving the TBA cation [27]. In spite of the $\text{N-H}\cdots\text{Cl}^-$ interactions observed in the solid state, pyrrole itself was not an efficient anion receptor in solution. The lack of appreciable binding was rationalized in terms of other competing factors that can affect anion binding such as ancillary solvent-pyrrole and anion-solvent equilibria. Protonation of the anionic species, which would lead to a loss of the negative charge, could also play a role. A low association constant ($K_a \sim 9 \text{ M}^{-1}$) was also observed by Sessler and coworkers for the complex between 2,5-dimethylpyrrole and F^- when studied in CD_2Cl_2 [10].

Subsequently, the addition of complementary binding sites to the α -pyrrolic positions such as guanidinium or amide groups that can provide either, electrostatic interactions or additional hydrogen-bonding sites, were used to enhance anion binding affinity. Pioneering work by Schmuck and coworkers describes the anion binding properties of a number of positively charged guanidiniocarbonylpyrrole derivatives. These systems have been used in the recognition of amino acids, nucleotides, and even as a part of DNA delivery systems. The amido- and bisamidopyrroles prepared by Gale and coworkers have shown selective oxoanion complexation and have even been employed as transmembrane anion carriers, making anion transport a fast growing subfield of supramolecular chemistry. Since these first reports descriptions of other monopyrrolic anion receptors followed [20,28,29]. Taken in concert, this work provided the antecedents for the preparation of more complex and efficient anion receptors.

Recently, Maeda and coworkers synthesized 3,4-bis-(perfluorohexyl)pyrrole **1** (Figure 2b) [30]. The polarization on the pyrrole NH induced by the electron withdrawing substituents on the β -positions resulted in a stronger chloride anion affinity in the case of **1** than was seen for pyrrole and Cl^- . The binding constant (K_a) corresponding to the formation of $\mathbf{1}\cdot\text{Cl}^-$, as estimated by ^1H NMR spectroscopy in CD_2Cl_2 , was $1.4 \times 10^3 \text{ M}^{-1}$. Optimized theoretical calculations revealed that the more polarized and more acidic pyrrole NH moiety present in **1** supported a longer the N–H bond allowing a shorter $(\text{N}-)\text{H}\cdots\text{Cl}$ contact that translated into the observed higher chloride affinity. Interactions with other anions, particularly Br^- and AcO^- (as their TBA salts), were also observed.

Studies with simple pyrrolic receptors helped to highlight one of the key challenges associated with the design of receptors based on hydrogen bond donors. Specifically, this work helped to reinforce what at the time was an emerging notion, namely that anions susceptible to protonation such as fluoride, can act as Brønsted bases, rather than non-reactive Lewis bases. The resulting protonation equilibria can lead to deprotonation of the

receptor instead of anion complexation. For instance, the pyrrolylindandione **2**, described by Sigalov and coworkers self-associate via intra-receptor hydrogen bonding in weakly polar aprotic solvents (i.e., dichloromethane and chloroform) [31]. In the presence of strongly basic anions (e.g., F^- and AcO^-), the intramolecular hydrogen bond interaction was disrupted and coordination of the anions (as their TBA salts) could be detected by 1H NMR spectroscopy. However, deprotonation of the pyrrole NH proton occurred after anion recognition. This led to changes in absorbance in the UV-vis spectra (Figure 3) [31]. More weakly basic anions (e.g., Cl^- , Br^- , and HSO_4^- , as their TBA salts) did not bind well or to induce deprotonation under identical experimental conditions.

2.1 Guanidiniocarbonyl Pyrrole and Guanidiniocarbonyl Pyrrole-Based Anion Receptors

Creating supramolecular receptors that can emulate the solvent isolated and less polar microenvironments of proteins has been of great interest for researchers for many years. This has been no less true for anion recognition chemists. Since the earliest of days, they have sought inspiration from nature. One of the most abundant anion binding groups in biological systems is the guanidinium group, which is the protonated form of guanidine, an intimate part of the amino acid arginine. In proteins the guanidinium group plays a critical role in recognizing carboxylates and other oxoanions. In pioneering work dating from the 1970s, Lehn and co-workers used bis- and tri-guanidinium salts for the recognition of carboxylate anions [32]. Unfortunately, the interaction between guanidinium and anionic species is typically very weak in aqueous solutions. This results generally in the formation of unstable complexes and ones that are subject to fast dissociation kinetics [33]. On the other hand, strong anion complexes are seen in organic solvents or mixed aqueous-organic solvent media in the case of appropriately designed alkylguanidinium and bicyclic guanidinium cations. This fundamental anion recognition work has been reviewed recently by Schmuck; we encourage the reader to consult this reference for further discussion of guanidinium-based anion binding systems [34].

In 1999, Schmuck and co-workers reported the association of the guanidiniocarbonyl pyrrole (GCP) cation (receptor **3**; Figure 4) with carboxylate anions in mixed aqueous-organic media [35]. For instance, that receptor **3** selectively binds *N*-acetyl- α -amino acid anions (specifically, *N*-acetyl alanyl carboxylate) over other carboxylates (e.g., acetate or alkyl substituted acetates) in solutions consisting of 40% water in $DMSO-d_6$ ($K_a(\text{amino acid}) = 2,790\text{ M}^{-1}$ vs $K_a(\text{acetate}) = 770\text{ M}^{-1}$) [34,35]. In a later report, GCP served as a building block for more complex systems such as the tripodal guanidiniocarbonyl pyrrole **4** (Figure 4). This latter species formed complexes with trianionic species in pure water (e.g., $K_a = 3.4 \times 10^5\text{ M}^{-1}$ and $1.6 \times 10^5\text{ M}^{-1}$, for the benzene-1,3,5-tricarboxylate and citrate anions, respectively). The high association constants observed in the case of these substrates were attributed to the “flytrap” conformation that the receptor adopts during the binding event. In fact, compound **4** is one of the most efficient tricarboxylate receptors currently known. These results led to the conclusion that the interactions governing the selectivity of these type of receptors are the result of cooperative effects, where the GCP receptor provides both 1) electrostatic ion pairing interactions involving the anion and the acyl guanidinium moiety and 2) highly directional H-bond interactions associated with the guanidinium group. In

addition, the recognition effects could be enhanced by incorporating additional H-bond donor groups (e.g., amide groups) into the receptor framework as shown in Figure 4.

Cooperative non-covalent interactions seem to be crucial for the effective anion association seen in the case of GCP-based systems. Indeed, the absence of a hydrogen-bonding site leads to a decrease in the anion affinity. This conclusion is supported by binding studies using the “knockout” analogs of **3** that contain heterocycles that lack hydrogen bond donors (e.g., pyridine and furan); comparisons revealed that **3**, containing a pyrrole NH-binding site, exhibited superior binding affinities than the “knock-out” receptors. This relative increase in the case of **3** was attributed to two factors: The presence of an extra hydrogen-binding site and repulsive interactions between the carboxylates and the lone pair on the heteroatom in the heterocycle used in the case of the “knock-out” analogs.

GCP has been attached to the commercially available PAMAM-G2 dendrimer, **5**, via amide coupling. This produced a vector **6** (Figure 5a) that proved effective as DNA chemical delivery systems [36]. The formation of a hydrogen-bond-assisted ion pair with the phosphate groups of DNA upon exposure to the PAMAM-GCP vector **6** gives rise to tight polyplexes with diameters of *ca.* 100–150 nm (Figure 5a). The association constants for the initial recognition event are in the range of 10^4 to 10^6 M⁻¹ as inferred from ITC studies [36]. In contrast, the unfunctionalized dendrimer, **5**, interacted with DNA but weakly and little in the way of stabilized polyplex formation was observed. The differences in the DNA affinities of **6** and **5** were attributed to two factors: a) The formation of stabilized hydrogen-bonding complexes involving the phosphate and GCP subunits and 2) electrostatic interactions between the GCP moieties and DNA. In contrast, the main interactions involved in the formation of the complex **5** and DNA are purely electrostatic. Of particular note is the observation that vector **6** could be used to transport genetic material into HeLa cells at submicromolar concentrations with negligible toxicity. Such favorable effects could not be reproduced using dendrimer **5** alone; nor were they seen with other commercially available transporters such as the cationic polymer polyethyleneimine, PEI.

Recently, Schmuck and coworkers reported a nucleotide-binding peptide containing GCP, **7**, as a probe for the imaging of nucleotides in cells. Probe **7** (Figure 5a) consists of a naphthalamide fluorophore from which two symmetric peptidic pending arms, each equipped with GCP anion-binding sites, are appended [37]. Additional functionalization with tryptophan ensured selectivity for nucleoside triphosphates (ATP, GTP, CTP, TTP, and UTP) over diphosphates (ADP and UDP), or monophosphates (HPO₄²⁻, AMP, CMP, GMP), as well as other oxoanions (SO₄²⁻, NO₃⁻, HCO₃⁻, and CH₃COO⁻). A fluorescence enhancement (by more than 4-fold at 540 nm was seen upon addition of 10 μM ATP in a buffered solution at pH = 7.4) was observed when probe **7** was exposed to ATP. Little enhancement was observed for the simple control anions. In fact, the affinity of **7** for nucleoside triphosphates followed the order ATP > GTP > UTP > CTP > TTP > PPi ≫ ADP > UDP, enabling the use of this probe as an ATP turn-on sensor.

The selectivity for triphosphates was attributed to a combination of ion pair interactions between the guanidinium groups in GCP and lysine moieties, and the formation of several hydrogen-bond donor-acceptor contacts involving **7** and the phosphates groups in the

nucleotides. It is also believed that the observed selectivity reflects in part the fact that **7** can adopt a tweezers-like conformation upon binding a nucleotide (Figure 5b). The binding constant obtained for the association of **7** and ATP ($K_a = 2.2 \times 10^5 \text{ M}^{-1}$) [37] surpassed by an order of magnitude the one obtained by Anslyn and coworkers using a very different kind of guanidinium-containing receptor [38].

2.2 Amidopyrrole and Amidopyrrole-Based Anion Receptors

Amide subunits have been combined often with pyrrole groups to produce a wide variety of receptors that run the gamut from very elegant macrocyclic designs that display high selectivities and affinities for anionic species both in solution and the solid-state to more simple acyclic molecules involving pyrroles functionalized with amide-containing functionality; many display quite efficient anion recognition features [39,28,24]. The first effective receptors in this class, described in 2001 by Gale and co-workers, involving the 2,5-diamidopyrrole **8** and 2-amidopyrrole **9**. Both systems displayed selectivities for oxoanions over halide anions in polar aprotic solvents such as acetonitrile (Figure 6a) [39]. The bisamidopyrrole **8** displayed higher affinities than the monoamidopyrrole **9**. This observation was ascribed to the participation of all three convergent hydrogen-bonding NH sites participating in the binding event. A subsequent X-ray analysis of the single crystal structure of the complex of **8** with benzoate (**8**•BzO[−]), as shown in Figure 6b [39,40]. Gale has published a detailed review on various derivatives containing the amidopyrrole moiety, as well as their anion binding properties [28]. However, a summary of recent progress regarding amidopyrrole receptors is appropriate.

Sessler and coworkers prepared receptor **10** using amidopyrrole as a building block (Figure 7). This bisamidopyrrole receptor selectively bound benzoate and acetate (as TBA salts) in nonpolar solvents such as 1,2-dichloroethane ($K_a = 4.3 \times 10^4$, $1.9 \times 10^4 \text{ M}^{-1}$, respectively), over other oxoanions (i.e., NO₃[−], HSO₄[−]) and halides such as chloride and bromide, for which no appreciable interaction was observed [41]. In the solid state intramolecular hydrogen bonding interactions between pyrrole NH and the carbonyl group of the amide group were seen. Similar interactions were proposed to occur between the carboxylates and **10** in solution, account for the observed selectivity for the carboxylate anions over the anionic substrates tested in these studies [41].

Anzenbacher and coworkers reported the tripodal sensor **11** (Figure 7). This species contains amidopyrrole moieties on two arms and gave rise to a roughly 10-fold turn-on fluorescence response upon exposure to dihydrogen phosphate, methyl phosphonate (MP), and isopropyl phosphonate (IMP), in DMSO. The corresponding binding constants of 1.4×10^4 , 3.1×10^4 , and $2.9 \times 10^4 \text{ M}^{-1}$, respectively, were determined [42]. Receptor **11** produced a stronger response when exposed to anions possessing C₃ symmetry (i.e., H₂PO₄[−], MP, and IMP) over spherical anions such as, fluoride and chloride. The fluorescence enhancement and strong selectivity were ascribed to the combination of two factors: 1) The suppression of the rotation of the side arms in the receptor resulted in a locked cup-like conformation upon anion binding, and 2) geometrical complementarity for phosphate and phosphonates species, many of which were expected to fit nicely into the cavity. Consistent with the latter

explanation, a lower association constant ($K_a = 5.1 \times 10^3 \text{ M}^{-1}$) was obtained with a bulkier anions such as $\text{HP}_2\text{O}_7^{3-}$ under the identical test conditions [42].

Recently, Ortuño, Curiel and coworkers used the carbazole derivative **12** (Figure 7) for the construction of a dicarboxylate-selective electrode [43]. When incorporated into an ionophore membrane, receptor **12** produced a good potentiometric response upon exposure to the glutarate, oxalate, malonate, and succinate anions with very good detection limits (LD) with that for glutarate being $4.4 \times 10^{-7} \text{ M}$, for instance. Proton NMR and fluorescence titrations provided support for the notion that receptor **12** is selective for the glutarate anion. The high affinity of this and other dicarboxylates was ascribed to the pre-organized cavity that is spacious enough to host large molecules, along with the presence of up to four hydrogen bond donors provided by the pyrrole rings and the carbazole units.

In 2013, Hof and coworkers reported the anion binding properties of the α -substituted pyrrole-tetrazole hybrids **13** and **14** (Figure 8). These systems displayed better affinities for chloride ($K_a = 3.3 \times 10^3 \text{ M}^{-1}$ and $2.63 \times 10^4 \text{ M}^{-1}$ for **13** and **14**, respectively, in CD_3CN) than the mono- and bisamidopyrroles **8** and **9** ($K_a = 28 \text{ M}^{-1}$ and 138 M^{-1} for **8** and **9**, respectively) under the same measurement conditions [44]. In an effort to improve the binding affinity beyond that provided inherently by the tetrazole heterocycle, the amido-tetrazole-pyrrole hybrid **15** was prepared. The chloride anion affinity calculated on basis of a ^1H NMR spectroscopic titration ($K_a = 3.1 \times 10^4 \text{ M}^{-1}$ in CD_3CN) [44] proved comparable to those obtained for analogous receptors lacking the amido group (e.g., **14**). Analysis of the amide NH chemical shift revealed that the inclusion of an amide subunit in **15** contributed minimally to the binding of chloride anion. These observations lead to the conclusion that the capacity of substituents in simple receptors that could potentially serve as hydrogen bond donor (in this case amide group on the tetrazole core) not always results in higher binding affinities. Presumably, this reflects competition between various receptor-substrate and receptor-receptor interactions.

3 Dipyrin-, Dipyrinone-, and Dipyrromethane-Based Anion Receptors

3.1 Dipyrin and Dipyrinone Receptors

Dipyrins are molecules consisting of two pyrrole rings linked by a methene fragment [45]. Generally, the linkage is through the 2 and 2' positions. Dipyrins are important building blocks that are constituents in a number of synthetic and naturally occurring macrocycles such as porphyrin, chlorin, and bacteriochlorin. They are also components of various bile pigments. The neutral form of dipyrin possesses one pyrrole NH group. Once protonated, two NH groups are available for potential interaction with anions and this form can function as anion receptor. In 1978, Becker *et al.* published the single crystal structure of 1,9-dibromo-3,7-diethyl-2,8-dimethyl-dipyrin showing a protonated dipyrin complexed to a bromide anion in the solid state [46]. Sessler and coworkers reported the NH hydrogen bonding-based complexation between the protonated dipyrins **16** and **17** (Figure 9) and for chloride anion (added as a TBA salt). In CH_3CN solution, association constants of 8.8×10^5 and $3.0 \times 10^5 \text{ M}^{-1}$, respectively, were determined by isothermal titration calorimetry (ITC) [47]. Other examples of complexation of anionic zinc salts were published by Dolphin and coworkers [48]. Dipyrins have also been used extensively as complexants of boron and

metal cations. These latter topics, although great practical and preparative utility, lie outside the scope of this review.

Dipyrinones, oxo-derivatives of dipyrins, are neutral species that can function as anion receptors. Dipyrinones are components of bilirubin, a pigment that is responsible for giving bile its characteristic yellow-brownish color. As a general rule, they self-associate as a result of forming four intramolecular hydrogen bonds between the pyrrole N-H and the lactam carbonyl NH moieties. In 2007, Huggins and coworkers described the anion binding properties of dipyrinone **18** [49]. Receptor **18**, as shown in Figure 10, displayed selectivity for HSO_4^- ($K_a = 1,680 \text{ M}^{-1}$) over other anions (i.e., Cl^- , Br^- , and NO_3^- , added as TBA salts) in CDCl_3 . The preference for HSO_4^- was ascribed to the formation of an additional hydrogen bond interaction between the carbonyl oxygen of **18** and the OH in the hydrogen sulfate anion, $\text{OH}\cdots\text{O}=\text{C}$, as observed in the single-crystal X-ray analysis of the complex **18**• HSO_4^- (Figure 10) [49].

3.2 Dipyrromethane Receptors

Dipyrromethanes have been both widely used as anion receptors, either on their own or as building blocks within more complex systems such as calix[4]pyrroles. The popularity of dipyrromethanes in the context of anion recognition is due to the availability of two pyrrole NH hydrogen bond donor sites that can interact with anionic species. Anion binding studies performed in CD_2Cl_2 solutions (added as TBA salts) reported by Sessler and coworkers revealed that the dipyrromethane **19** itself was not an effective anion receptor (Figure 11) [50]. The association constants calculated for Cl^- and Br^- , and oxoanions were in the range of $\sim 10^1 \text{ M}^{-1}$. In fact, a somewhat high affinity was observed only in the case of F^- ($K_a = 2.1 \times 10^3 \text{ M}^{-1}$) [50]. The higher affinity for fluoride was ascribed to the strong hydrogen bonding between the pyrrolic NHs in **19** and the highly basic fluoride anion. However, the low affinities obtained for the majority of anions supports the conclusion that unsubstituted dipyrromethanes such as **19**, are unlikely to be useful as generalized anion receptors.

The substitution of dipyrromethane with additional hydrogen bond donors in the α -pyrrolic positions has proved to be an effective mean of enhancing the anion binding affinities. For instance, the 5,5'-bisamidodipyrrolylmethanes **20** and **21** reported by Gale and coworkers in 2004 (Figure 11) acted as receptors for a number of halides including, F^- , Cl^- , and Br^- , as well as oxoanions such as HSO_4^- and benzoate (added as their TBA salts) [51]. The binding constants obtained from ^1H NMR spectroscopic titrations carried out in 5% water/ $\text{DMSO}-d_6$ solutions revealed that **20** and **21** bind fluoride anion selectively ($K_a = 8.99 \times 10^3$ and $7.56 \times 10^3 \text{ M}^{-1}$ for **20** and **21**, respectively) over Cl^- , and Br^- ($K_{a(\text{Cl})} = 43$ and 23 , and $K_{a(\text{Br})} = 10$ and 13 M^{-1} for **20** and **21**, respectively), and HSO_4^- and benzoate ($K_{a(\text{HSO}_4)} = 128$ and 44 , and $K_{a(\text{benzoate})} = 424$ and 354 M^{-1} for **20** and **21**, respectively) [51].

In 2010 Mlinari -Majerski reported the incorporation of adamantane into the *meso* position of a dipyrromethane with the goal of restricting the rotational mobility of the pyrroles and thus enhance the anion binding properties [52]. The resulting system, receptor **22** (Figure 11) displayed higher association constants for Cl^- , Br^- , HSO_4^- , H_2PO_4^- , and AcO^- , as TBA salts, with receptor **22** (e.g., $K_a = 80, 22, 65, 150$, and 110 M^{-1} , respectively) than the ones

observed for the same anions in the case of the corresponding diphenyl analogues **23** (e.g., $K_a = 22, 4.8, 6, 32$, and 31 M^{-1} , respectively) in CDCl_3 (all anions studied as their TBA salts) [52]. In the case of the more basic anions (i.e., F^- and AcO^-) receptor **22** supported the formation of 2:1 complexes, wherein all four pyrrole NH protons were hydrogen bonding one anion.

In 2013, the same research group reported receptors **24** and **25** that bear aryl groups directly attached to the pyrroles and noted that these systems could be used as anion sensors (Figure 11) [53]. In particular, changes in absorbance and fluorescence emission features were seen upon the addition of TBA salts of F^- , AcO^- , and H_2PO_4^- in CH_3CN [53]. In particular, upon addition of F^- to the CH_3CN solution of **25** resulted in fluorescence quenching and the appearance of a new signal at higher wavelengths. This was taken as an indication of deprotonation of the pyrrole NH by the fluoride anion forming the HF_2^- species. In contrast, exposure to less basic anions such as Cl^- , Br^- , and HSO_4^- , produced negligible changes in the UV-vis and emission spectra [53]. Although other acyclic dipyrromethanes and even tripyrromethanes have been synthesized, the effective binding of oxoanions such as H_2PO_4^- and HSO_4^- by acyclic dipyrromethane receptors remained a challenge. This is because these anions (e.g., F^-) are sufficiently basic so as to induce proton transfer under certain conditions. When pyrrole NH-to-anion transfer takes place, the key NH-anion hydrogen bonding interactions that underlies pyrrole-based anion recognition are destroyed. True anion recognition is not taking place. On the other hand, the change in the electronic features of the receptor can lead to very dramatic color changes and hence a readily discernible chemosensing response.

In 2012 Sessler and coworkers reported the affinity of the tripods **26** and **27** (Figure 11) for oxoanions such as H_2PO_4^- and HSO_4^- in CH_3CN . ITC analyses revealed that **27** strongly bound H_2PO_4^- and HSO_4^- (as TBA salts) in a similar order of magnitude. Control analysis using receptor **26** indicated selective binding with H_2PO_4^- over HSO_4^- anions ($K_a = 1.38 \times 10^5$ and 10^3 M^{-1} for H_2PO_4^- and HSO_4^- , respectively) [54]. In contrast, receptor **27** containing three additional hydrogen bond donors bound H_2PO_4^- and HSO_4^- with similar affinities with binding constants of 6.54×10^6 and $1.33 \times 10^6 \text{ M}^{-1}$ for H_2PO_4^- and HSO_4^- , respectively under the same conditions [54]. The greater affinity for hydrogen sulfate by receptor **27** relative to **26** was ascribed to additional solvent effects that influence the selectivity.

The bisdipyrromethanes **28** and **29** can form complexes with the TBA salts of H_2PO_4^- and $\text{HP}_2\text{O}_7^{3-}$ in chloroform (Figure 12a), with association constants of $8 \times 10^6 \text{ M}^{-1}$ for both, **28**• H_2PO_4^- and **29**• H_2PO_4^- [55]. The success of these systems was ascribed to the substitution of the dipyrromethane moiety in the α -pyrrolic positions with the formyl group, which leads to the modification of the electronics of the bispyrromethanes. X-ray diffraction analysis of the complex **28**• H_2PO_4^- showed that the formyl groups were assisting the binding of $^-$ dihydrogenphosphate salt via $\text{C}=\text{O} \cdots \text{HO}$ interactions between the formyl group and the H_2PO_4^- anionic guest (Figure 12b) [55,56]. In contrast, in the solid-state no appreciable involvement of the formyl substituents in the binding of the guest was seen in the case of the pyrophosphate complex, **29**• $\text{HP}_2\text{O}_7^{3-}$ (Figure 12b). Instead, a 2:2 complex is

observed wherein two receptor-bound pyrophosphate anions interact with one another via hydrogen bonds to produce a self-associated dimer [55,56].

In 2016, Kataev prepared the 2,2'-bisamidodipyrrolylmethane receptor (**30**, Figure 13). This system bears two naphthalimide subunits and two pH-responsive 1,2-phenylenediamine fragments. It proved effective for the recognition of sulfate anions with selectivity over phosphates being observed [57]. Upon exposure to anions, receptor **30** displays a turn-on fluorescence response. The selectivity for HSO_4^- was ascribed to the ability to interact with the 1,2-phenylenediamine subunits without appreciable proton transfer, whereas the addition of more basic anions such as H_2PO_4^- and AcO^- , induced considerable deprotonation of these subunits [57]. Proton NMR spectroscopic binding studies provided support for these observations and revealed that HSO_4^- (as its TBA salt) binds to **30** in a 1:2 fashion in a 4:1 v/v mixture of DMSO- d_6 and D_2O .

Receptor **30** was also tested using a number of biologically important oxoanions, including H_2PO_4^- , $\text{HP}_2\text{O}_7^{3-}$, ATP, ADP, and AMP (tested as their Na^+ salts); however, no appreciable change in the emission signature was seen in the case of these anions. In contrast, a turn-on in the fluorescence signal was observed upon addition of Na_2SO_4 . Based on curve fits to the binding isotherm, a 1:1 stoichiometry and a binding constant of $1.025 \times 10^3 \text{ M}^{-1}$ were inferred [57]. The selectivity of **30** for the sulfate anion was ascribed to the combination of both hydrogen bonds and electrostatic interactions.

4 Aryl- and Diketone-Bridged Bispyrrole-Based Anion Receptors

Several research groups have described methods for preparing aryl-bridged bispyrrole derivatives. The synthesis and anion binding properties of a number of these systems were reviewed in a book chapter by Maeda [29]. Aryl-bridged bispyrroles have also been used extensively as building blocks in the construction of macrocycles [11] and for preparing low molecular weight compounds with membrane permeability [58]. A full summary of this work is not possible here. However, some limited discussion of the anion recognition features of aryl-bridged bispyrroles is deemed appropriate.

In 2005, Sessler and coworkers reported the anion binding properties of the aryl-bridged bispyrrole **31** (Figure 14a). Binding constant values at 2.3×10^3 , 4.3×10^3 , 1.1×10^3 , 1.3×10^3 , 190, 290, 280, and 32 M^{-1} corresponding to the formation of the F^- , Cl^- , Br^- , H_2PO_4^- , I^- , HSO_4^- , NO_3^- , and ClO_4^- complexes, respectively, were obtained from ^1H NMR spectroscopic analysis in CD_2Cl_2 . Compared with the dimethyl dipyrromethane receptor **19**, receptor **31** exhibited stronger affinities for the anions studied. This increased affinity was ascribed to the larger bite angle provided by **31**, which it was suggested allowed anions such as chloride, bromide, and dihydrogenphosphate, to be accommodated readily.

In 2014, Jurczak and coworkers used a methoxy-substituted bispyrrolebenzene motif similar to **31** as a building block for the preparation of the receptor **32** (Figure 14b) [59]. Anion binding studies performed in 5% aqueous DMSO- d_6 solutions revealed that **32** binds all the anions studied (i.e., Cl^- , AcO^- , BzO^- , and H_2PO_4^- , as TBA salts) in a 1:1 fashion except for F^- anion. Relatively high affinities were for H_2PO_4^- ($K_a = 1.037 \times 10^3 \text{ M}^{-1}$) and F^- ($K_{a1:1} =$

66 and $K_{a2:1} = 1.456 \times 10^3 \text{ M}^{-1}$) [59]. Two binding modes were observed with F^- anion (1:1 and 1:2 host-guest stoichiometry), with the dominant complex formed being dependent on the concentration of the anion. Detailed ^1H NMR spectroscopic analyses led to the conclusion that at low fluoride concentrations the pyrrole and amide NH protons point towards a single fluoride anion with the receptor thus adopting a *syn-syn* conformation. However, at higher fluoride concentration a *syn-anti* conformational change was observed supporting a 1:2 binding mode. In fact, the authors suggest that receptor **32** could accommodate an additional (i.e., third) fluoride anion by adopting an *anti-anti* conformation as shown in Figure 14b [59]. This capacity to change conformation led the authors to suggest that receptor **32** could function as a supramolecular switch.

The use of polarized C–H bonds that can act as hydrogen bond donors assisting the binding of anion species was described by Van Rossom and Hill [60]. The use of CH-derived hydrogen bonding as a motif for anion recognition was first demonstrated experimentally using other classes of receptors [61].

Receptor **33** (Figure 15) possesses an electropositive cavity and displays improved anion binding properties relative analogous compound containing triazoles instead of pyrroles. In particular, a strong association between **33** and AcO^- ($K_a = 2.4 \times 10^5 \text{ M}^{-1}$, as TBA salt in CH_3CN) in a 1:1 stoichiometry was observed. The binding constants obtained with other anions studied (Cl^- , H_2PO_4^- , and HCO_3^-) under the same conditions proved to be lower by more than one order of magnitude (e.g., $K_a = 9.3 \times 10^3$, 7.9×10^3 , and $1.9 \times 10^4 \text{ M}^{-1}$ for Cl^- , H_2PO_4^- , and HCO_3^- , respectively) [60]. A single crystal X-ray structural analysis of the complex **33**• AcO^- confirmed aryl C–H and pyrrole NH hydrogen bonding interactions with the bound acetate anion (Figure 15) [60]. The preference for AcO^- over H_2PO_4^- was ascribed to a better size match between the cavity and the acetate anion than in the case of H_2PO_4^- , as well as a corresponding minimization of repulsive steric interactions.

In 2005, Maeda and coworkers introduced the BF_2 adduct of 1,3-dipyrrolyl-1,3-propanedione (dipyrroldiketone) **34** as a motif for anion sensing [62]. This planar π -conjugated system underwent a change in its optical properties upon coordination to halide and oxoanions. The coordination of the BF_2 moiety to the diketone moiety in **34** locks the conformation of the pyrrole rings allowing favorable C–H hydrogen bonding interactions with negatively charged species, as shown in Figure 16. Binding constants obtained by UV-vis spectroscopy titrations in CH_2Cl_2 , revealed greater affinities for F^- and H_2PO_4^- , as compared to Cl^- , Br^- , and HSO_4^- , as ($K_a = 8.1 \times 10^4$, 2.0×10^3 , 3.3×10^2 , 1.3×10^4 , 80 M^{-1} for F^- , Cl^- , Br^- , H_2PO_4^- , and HSO_4^- , respectively; all anions studies as their TBA salts) [62]. Modification of the available α -positions present in **34** with aryl rings afforded a series of compounds (e.g., **35**) that form stacked structures upon coordination with chloride complexes.

Further modification with long aliphatic groups on the aryl rings allowed formation of supramolecular gels upon interacting with planar cations. For instance, the chloride complex with **36** (**36**• Cl^-), as TBA salt, and 4,8,12-trialkyl-4,8,12-triazatragulenium (TATA) [63] forms alternating stacks through π – π staking and electrostatic interactions, as shown in Figure 17a. In the presence of TATA, the alkyl chains in **36** enhanced the stability of the gel

formation and column-like structures were observed in a charge-by-charge assembly fashion (i.e., stacking of alternating charged species; Figure 17b). However, **36** exhibits gelation behavior on its own. In contrast to **36**, the substituted β -fluorinated **37** forms gels only in the presence of TBACl salt and TATA; in this case, charge-segregated assemblies (i.e., stacking of identically charged species; Figure 17c) are formed [64]. This latter association behavior was ascribed to the steric-based distortion of the pyrrole rings by the substituents, which prevents an effective stacking. Interestingly, the charge-segregated arrangement displayed higher charge-carrier mobility than the charge-by-charge columnar assemblies. The high charge mobility behavior of these supramolecular gels was suggested as being potentially useful in the development of liquid crystalline materials possessing electric-transporting properties [65,66].

Recently, Yamakado *et al.* reported assemblies of **38** ($[\mathbf{38}]_2 \cdot \text{Cl}^-$) that from interlocked [2 + 1]-type complexes with chloride and bromide anions (as TBA salts), under controlled guest concentration and less polar solvents such as dichloromethane (Figure 18) [67]. The authors suggested that charge-segregated assemblies observed and their formation could be rationalized in terms of possible cooperative π -electronic interactions involving the α -arylethynyl substituents in **38**. These substituents isolate the anions and allow electrostatic repulsions to be avoided. The net result is a stable assembly [67,68]. By manipulating the crystallization solvent (i.e., using racemic alcohols vs chiral alcohols) the assemblies could be modulated making it possible to obtain either charge-by-charge or charge-segregated type assemblies (Figure 18). Furthermore, investigation of the role of the arylethynyl substituent in the formation of these [2 + 1]-type complexes revealed that a cooperative intramolecular interaction between two arylethynyl moieties is necessary for the stabilization of the [2 + 1]-type complexes [67,68].

5 Prodigiosin-, Tambjamine-, and Perenosin-Based Anion Receptors and Anion Carriers

The development of receptors capable of transporting anions across the cellular membrane has become a subject of interest in recent years. This has put additional emphasis on the chemistry and biology of prodigiosins and its analogues. In living organisms, ion channels embedded in the membrane actively transport charged species, mechanisms that help maintain both intracellular and extracellular ion concentrations at physiological levels. Functional failures in these transport proteins can lead to a series of disorders and underlie a number of well-recognized disease states, including cystic fibrosis (CF) [69], Batter's syndrome [70], Dent's disease [71], and idiopathic epilepsy [72], among other diseases. Many of these diseases are characterized by high intracellular chloride anion concentrations and effects on other anions, including the bicarbonate anion [73]. In contrast, low levels of intracellular chloride anion concentrations have been associated to trigger programmed cell death (i.e., apoptosis) mechanism [74]. In addition, cancer cell proliferation, apoptotic resistance, and cancer cell migration have been related to a dysregulation of ion concentration and fluxes as a result of defective ion channels [75,76]. Over the last decade, a number of reviews describing anion transport and summarizing many of the diverse

synthetic systems developed to influence cellular ion concentrations have been published [24,77–83].

Prodigiosins are naturally occurring acyclic pyrrolic molecules characterized by a pyrrolylpyrromethane core. These red pigments were isolated in the 1930's from the microorganisms *Serratia* and *Streptomyces* [84] and identified as secondary metabolites. They have been actively pursued for their immunosuppressive [85], antimalarial [86], antimicrobial [87], and anticancer properties [88]. Protonated prodigiosin **39** can bind chloride anions via hydrogen bonding interactions with the three convergent pyrrole NH sites (Figure 19). Early transport studies with **39** provided support for the suggestion that this compound passively transports H^+ and Cl^- ions across the cellular membrane and can mediate Cl^-/NO_3^- and Cl^-/HCO_3^- exchange [89]. Unfortunately, in spite of its diverse biological activity of prodigiosin the clinical development of this compound as a potential therapeutic agent has been limited by its high inherent toxicity. This has prompted the synthesis of other synthetic analogues.

Quesada and coworkers have carried out fundamental studies of the prodigiosin derivative Obatoclax **40** (GX15-070; Figure 19) [90] and have reported its chloride and bicarbonate anion transport properties using POPC (i.e., 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine) membrane models. This open chain system (**40**) was a particularly efficient chloride anion transporter. Its high biological activity led to it being studied in clinical trials as potential anti-cancer drug. Unfortunately, due to concerns about side effects, **40** did not advance past Phase II clinical trials [91].

In 2005, Sessler and coworkers reported the chloride transport properties of the synthetic prodigiosin **41** through vesicle membranes via a co-transport H^+/Cl^- mechanism [47]. An X-ray diffraction analysis of **41** revealed a chloride anion hydrogen bonded to three NH sites [47]. It thus provided the first solid state support for Ohkumo and Wasserman's original contention that the protonated form of prodigiosin could act as an open-chain chloride anion receptor [17]. Analogue **41** induced apoptosis in several cancer cell lines, behavior that was attributed to changes in the intracellular pH resulting from the through-membrane co-transport of H^+ and Cl^- ; again, this provided support for the mode of action put forward by Ohkumo and Wasserman [17]. However, alternative mechanisms of action for prodigiosin, involving cleavage of intracellular DNA mediated by Cu^{2+} [92,93], phosphate inhibition [94], and/or modification of the intracellular pH by Cl^-/OH^- [95] exchange have been proposed. Thus, the original studies by Sessler and coworkers should be considered supportive of a transport mechanism, but not conclusive.

Mechanistic studies conducted by Davis, Thompson, and coworkers with modified prodigiosins in the C [96] and B-rings [97] (e.g., **42** and **43**; Figure 20) provided insights into the effect of the substituent in the anion binding. For instance, the presence of an electron withdrawing groups on the B or C ring resulted in a lowered chloride transport efficiency in liposomes made up from egg yolk phosphatidylcholine (EYPC) bilayers [98]. In this case, the electron withdrawing group leads to an inductive effect that lowers the pK_a values of these prodigiosin derivatives. This militates against chloride anion complexation due to a reduction in the effective concentration of the protonated receptor at any given pH.

However, good antiproliferative activity was seen for many of these prodigiosin derivatives. This antiproliferative activity correlated well with the observed transport effects, leading to the conclusion that mechanisms more complex than simple anion transport are responsible for the observed biological effects.

The tambjamine alkaloids are a class of pyrrolic systems that are structurally related to prodigiosins, (e.g., **44**; Figure 21). They contain bipyrrole core and, like other natural and semi- synthetic acyclic anion receptors have received increasing attention as anion carriers in recent years [97,99]. Tambjamines are typically easier to prepare than the prodigiosins and generally possess higher pK_a values (i.e., $pK_a \approx 10$ vs. 7.2, for tambjamines and prodigiosins, respectively); thus, unlike prodigiosins, tambjamines remain largely protonated at physiological pH.

Quesada and coworkers described transmembrane anion transport studies of the tambjamine alkaloid derivative **44a** and reported that these compounds are potent anion transporters capable of effecting $\text{NO}_3^-/\text{Cl}^-$ and $\text{HCO}_3^-/\text{Cl}^-$ exchange in liposomes at low concentrations [99]. The lower intracellular pH levels observed *in vitro* correlated with antitumor activity in the human melanoma (A375) and human mammary epithelial (MCF-10A) cell lines. Further studies were carried out by Frey, Quesada, and Gale using tambjamines bearing alkyl substituents (i.e., **44b** and **44c**; Figure 21). Based on their results, it was concluded that the tambjamine lipophilicity is actively correlated with transmembrane anion transport activity [100].

Van Rossom, Gale, and coworkers reported a new class of anion carrier consisting of a pyrrole linked through an imine to an indole, benzimidazole, or indazole subunit. These so-called perenosins **45–47** (Figure 21) are easily protonated at physiological pH values and can bind Cl^- anions in a 1:1 stoichiometry via three hydrogen bond interactions [101]. In the case of the perenosins **45**, bearing an indole group, relatively high chloride anion affinities [101] were observed (i.e., $K_a = 4.3 \times 10^3$, 2.32×10^3 , and $1.65 \times 10^3 \text{ M}^{-1}$ for **45a**, **45b**, and **45c**, respectively). In the case of H_2PO_4^- and HCO_3^- (as the corresponding TBA salts) only deprotonation of the receptor was observed. Based on transport studies involving POPC, cholesterol liposomal models at different pH values (pH 4.0, 6.2, 7.2, and 8.2) it was concluded that only the protonated forms are capable of functioning as anion carriers.

Despite their higher chloride anion affinities perenosins containing electron withdrawing groups (i.e., **45a** and **45b**; Figure 21) were poor chloride transporters. In contrast, **45c** containing an alkyl group displayed good HCl transport properties [101]. The more lipophilic species displayed good *in vitro* activity ($\text{IC}_{50} = 4.39 \text{ }\mu\text{M}$) and relatively high selectivity (~5.5 fold) for the invasive MDA-MB-231 breast carcinoma over the non-invasive MCF-7 normal breast cancer cell lines [101].

6 Conclusions

This review has highlighted the use of pyrrole NH motifs for the production of anion receptors. Being easier to synthesize than their macrocyclic congeners, acyclic pyrrole derivatives have been widely used as building blocks for the creation of more complex

receptors. They have also been modified with additional recognition sites in an effort to create system that display enhanced anion affinities. In certain instances, the use of C–H moieties as hydrogen bond donor groups leads to systems possessing greater specific anion selectivity than seen in similar systems bearing only pyrrole and amide NH recognition sites. Pyrrole-based systems capable of stabilizing intermolecular assemblies were seen in the case of anion complexes of dipyrrolyldiketones. Several columnar assemblies exhibiting charge-carrier mobility properties were obtained. Finally, prodigiosins and their derivatives such as tambjamins and perenosines, have emerged in recent years as potential transmembrane anion carriers and as possible anticancer agents underscoring the practical importance of anion recognition in the case of acyclic pyrrole-based systems. Thus, even though macrocyclic, pyrrole-based anion receptors, extractants, and carriers have received much more attention it is likely that acyclic pyrrole- and polypyrrolic systems may emerge as cost effective alternatives. We thus expect this will be an area that witnesses significant growth in the years to come.

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7 Abbreviations

ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
ATP	Adenosine triphosphate
CMP	Cytidine monophosphate
CTP	Cytidine triphosphate
GMP	Guanosine monophosphate
GTP	Guanosine triphosphate
PAMAM	Polyamido amine dendrimer
PPi	Pyrophosphate
POPC	1-palmitoyl-2-oleoyl- <i>sn</i> -glycero-3-phosphate
TBA	tetrabutylammonium cation
TTP	Thymidine triphosphate
UDP	Uridine diphosphate
UTP	Uridine triphosphate

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Figure 1. Structures of synthetic polypyrrolic anion receptors, sapphyrin and calix[4]pyrrole, and the crystal structure of the fluoride complex of the diprotonated sapphyrin reported by Sessler, et al. [4]. This figure was reproduced using the data downloaded from the Cambridge Crystallographic Data Centre (CCDC # 1184078); the PF_6^- counterion was removed for clarity.

Figure 2.

a) Single crystal X-ray diffraction structure of the Cl^- complex of pyrrole (as its TMA (tetramethylammonium) salt) reported by Gale [27]. This figure was reproduced using the data downloaded from the Cambridge Crystallographic Data Centre (CCDC # 173101). b) Schematic representation of the chloride anion complex of receptor **1** as reported by Maeda [30].

Figure 3.
Schematic representation of the initial complexation of the fluoride anion by receptor **2** followed by deprotonation of the pyrrole NH proton.

Figure 4. Anion complexation by GCP-based receptors **3** and **4**, and the primary interactions thought to be involved in carboxylate anion recognition.

Figure 5.

a) Structures of the PAMAM-G2 dendrimer **5** and the GCP-based dendrimer **6**, and the nucleotide sensor **6**. b) Schematic representation of the fluorescence turn-on of **7** upon exposure to ATP. The figure was partially reproduced with permission from the one that first appeared in ref [37]; copyright, the Royal Society of Chemistry.

Figure 6.

a) Structures of bisamidopyrrole **8** and monoamidopyrrole **9**. b) Single crystal X-ray diffraction structure and of the **8**•BzO⁻ complex reported by Gale [40]; the TBA cation was omitted for clarity. This figure was reproduced using the data downloaded from the Cambridge Crystallographic Data Centre (CCDC # 187422).

Figure 7.
Structures of receptors **10**, **11**, and **12**.

Figure 8.
Structures of tetrazole-pyrrole hybrid receptors **13–15**.

Figure 9.
Structures of protonated dipyrins **16** and **17** reported by Sessler [47].

Figure 10.

Dipyrinone **18** and the single crystal structure of the hydrogen sulfate complex **18**·HSO₄⁻ reported by Huggins [49]. This figure was reproduced using the data downloaded from the Cambridge Crystallographic Data Centre (CCDC # 655346). The TBA cation molecule has been omitted for clarity.

Figure 11. Structures of anion receptors **19–25** based on dipyrromethane moiety and structures of the tripodal receptors **26** and **27**.

Figure 12.

a) Bisdipyrromethanes **28** and **29** and b) single crystal structures of the complexes **28**·H₂PO₄⁻ and **29**·HP₂O₇³⁻ reported by Sessler [56]. This figure was reproduced using the data downloaded from the Cambridge Crystallographic Data Centre (CCDC # 1444560 and 1444559). The TBA cation molecule has been omitted from both crystal structures for clarity.

Figure 13.

Structure of the sulfate selective receptor **30** reported by Kataev [57].

Figure 14.

a) Structure of the aryl-bridged bispyrrole receptor **31**. b) Schematic representation of the different binding modes of fluoride anion to receptor **32**. This scheme was redrawn from the original in ref [59].

Figure 15.

Structure of receptor **33** and the single crystal structures of the complex **33**•AcO⁻ reported by Van Rossom and Hill [60]. This figure was reproduced using the data downloaded from the Cambridge Crystallographic Data Centre (CCDC # 975510). The TBA cation molecule has been omitted for clarity.

Figure 16.

Structures of dipyrrolyldiketones **34** and **35** and the single crystal structures of the complex **34·Cl⁻** reported by Maeda [62]. This figure was reproduced using the data downloaded from the Cambridge Crystallographic Data Centre (CCDC # 270297). The TBA cation and solvent molecules have been omitted for clarity.

Figure 17.

a) Structures of aryl-substituted dipyrrolyldiketones chloride complexes **36**•Cl⁻ and **37**•Cl⁻,
 b) charge-by-charge assembly mode, and c) charge-separated assembly mode that these
 complexes can form in the presence of 4,8,12-trialkyl-4,8,12-triazatrangulenium (TATA)
 cation.

Figure 18.
Structures of **38** and the [2 + 1]-type complex [38]₂•Cl⁻.

Figure 19.

Structure of protonated prodigiosin **39** and Obatoclax **40**, and structure of **41** and single crystal of **41·Cl⁻** complex, reported by Sessler [47]. The crystal structure was reproduced using the data downloaded from the Cambridge Crystallographic Data Centre (CCDC # 271587).

Figure 20.
Structures of B-ring substituted prodigiosins **42** and C-ring substituted prodigiosins **43**.

Figure 21.
Tambjamine structure **44** and perenosin structures **45–47**.