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Covalent Polymers Containing Discrete Heterocyclic Anion Receptors

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Abstract

This chapter covers recent advances in the development of polymeric materials containing discrete heterocyclic anion receptors, and focuses on advances in anion binding and chemosensor chemistry. The development of polymers specific for anionic species is a relatively new and flourishing area of materials chemistry. The incorporation of heterocyclic receptors capable of complexing anions through non-covalent interactions (*e.g.*, hydrogen bonding and electrostatic interactions) provides a route to not only sensitive but also selective polymer materials. Furthermore, these systems have been utilized in the development of polymers capable of extracting anionic species from aqueous environments. These latter materials may lead to advances in water purification and treatment of diseases resulting from surplus ions.

Keywords

polymers; anion complexation; molecular receptors; sensing

1 Introduction

The field of polymer chemistry has made tremendous progress since Staudinger first pioneered various polymerization methods in the early 1920's [1,2]. Staudinger proposed structural formulae for natural rubber, polystyrene, and polyoxymethylene, and is also credited with coining the term “macromolecule” which is still commonly used today. The field of synthetic polymers was advanced further in the 1930's when Carothers developed two widely used synthetic polymers, neoprene and nylon [3,4]. The importance of these materials cannot be overstated. For example, nylon and other polyamides are excellent fiber forming materials, and were initially used to make ropes, parachutes, and tents, but applications have since greatly expanded and these and other synthetic polymers can now be seen in almost all aspects of everyday life. This ubiquity has spawned wide-spread efforts to develop new and improved materials. A few areas of advanced focus within this general paradigm include creating synthetic replacements for biological tissues [5,6] and developing macromolecular materials suitable for use in diagnostic and array technologies [7,8].

Another major thrust in polymer chemistry has come from the field of “supramolecular chemistry”, a term coined by Lehn to mean chemistry beyond the molecule [9,10]. As chemists began to exploit the weak non-covalent interactions (which represent the foundation of supramolecular chemistry) to create new molecular receptors and chemosensors, it soon became apparent that the same principles could lead to advances in the field of polymer chemistry [11–14]. A major subset of this latter effort has been devoted to the synthesis of so-

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called main-chain supramolecular polymers, where reversible/dynamic non-covalent interactions within the polymer backbone are used to assemble monomers into larger polymeric structures [15]. Separate from this, a number of researchers began to realize the potential benefits of incorporating small molecule supramolecular receptors into polymeric structures. The vast majority of these latter systems consist of conjugated polymers containing receptors for positively charged or neutral species. One highly utilized approach involves the incorporation of crown ether species for metal ion recognition and sensing [16]. For example, Swager reported how an appropriately designed, conjugated polymer chemosensor containing crown ethers would undergo recognizable changes as the result of potassium induced aggregation [17].

In spite of the above advances, it was only recently that the number of polymers that incorporate receptors for anionic species began to increase. This tardiness in terms of materials development is somewhat surprising given the role anionic species play in the environment and in biological processes. It is now well recognized that many anionic species, such as fluoride, nitrate, phosphate, and cyanide, constitute major environmental pollutants; there is thus a clear, widely appreciated need for materials capable of recognizing, capturing, and detecting these and other anionic species. Furthermore, excesses in phosphate anion levels in patients suffering from end-stage renal failure is a frequent complication that can lead to a disease state known as hyperphosphatemia [18,19]. In most cases dialysis in combination with ingestible anion exchange resins is used to control the level of phosphate in the blood. However, neither of these methods is fully satisfactory, in part because the underlying methodologies are not phosphate selective. The authors thus believe that new materials, such as anion-specific dialysis membranes, could be used to control phosphate anion concentrations for patients on dialysis and lead to clinical advances. The incorporation of supramolecular receptors specific for anionic species into polymeric frameworks represents a first step towards achieving this long-range goal. Related anion-binding macromolecules could also see application in the recognition and sensing of anions of environmental concerns and in the areas of separation and purification. Taken in concert, these various potential benefits provide an incentive to prepare anion receptor-modified polymers. The goal of this chapter is to provide a summary of recent work in the area.

To the best of our knowledge, no reviews have appeared that cover the chemistry of macromolecular systems targeting the problem of anion recognition. The focus of this chapter will be on polymeric systems that incorporate heterocycle-based anion receptors into polymeric structures. Heterocyclic receptors as additives to polymers (Fig. 1A) for applications such as polyelectrolyte development, will be covered, as will be polymers that contain anion receptors either as pendant side-chains (Fig. 1B) or incorporated directly into the polymer main-chain (Fig. 1C). As will become apparent from the present review, the majority of the systems that exist today are conjugated polymers that have been applied as so-called chemosensors. However, it is our hope and expectation that a detailed description of these and related systems will inspire the synthesis of new and improved systems for anion detection, sequestration, extraction, and separations, among other conceivable applications.

2 Anion Receptors as Polymer Additives

According to the principle of Occam's Razor, "entities must not be multiplied beyond necessity," which one can interpret to mean that often the simplest explanation is the correct one. Analogously, in engineering and materials science, one attempts to get the biggest bang for one's buck by using cheap and simple materials to build up complexity and solve pressing problems. Over-complicated syntheses or expensive starting materials can lead to greatly diminished returns and harpoon the chances that the molecule or material will ever see widespread application. Such appreciations may well have inspired early researchers working at

the interface of anion recognition and polymer research. This is because most initial efforts in the area were focused on integrating heterocyclic anion receptors into polymeric systems by simply blending various anion receptors into the polymers. Such approaches, which are akin to blending chocolate chips into cookie dough, are markedly different than synthetic strategies that involve attaching recognition units to the polymer backbone or creating receptors that are functionalized in such a way that they may act as precursors for polymer synthesis. These approaches are thus treated separately in this chapter, with the focus of this particular section being on polymeric materials whose properties have been modified *via* the blending in of anion receptors.

Arguably the most important area where the blending strategy has been successfully applied involves the development of ion-selective electrodes (ISEs). Such analytical tools derive their selectivities from the specificities of the constituent ionophores and their abilities to form stable complexes with analytes that are subsequently transported into electrode membranes. Ideally, an ISE should respond to a specific ion and should not be affected by the presence of other ions in solution. A number of ISEs utilizing polymer matrix liquid membranes have been developed and investigated. As detailed below, the incorporation of appropriately chosen receptors for a target ion into the electrode membrane represents a particularly valuable approach to anion-specific ISE development.

Early work in the development of ISEs for anionic species utilized polyamines. One such example was reported by Carey and Riggan who incorporated cyclic aza-ethers (**1** – **4**) into polyvinyl chloride (PVC) membranes for construction of phosphate selective electrodes (Fig. 2) [20]. The chemical inertness of PVC, combined with its adsorptivity and stability features, has traditionally made it an ideal choice for electrode development. In the particular case of the Carey and Riggan study, ISEs were constructed by dipping an electrode into a membrane-forming “cocktail” which consisted of 20 wt % ionophore (*i.e.*, **1** – **4**), 45 wt % PVC, and 35 wt % dibutyl sebacate in tetrahydrofuran (THF). This resulted in the formation of a PVC matrix with a thickness of 15–30 μm over the open end of the electrode.

The electrode produced using **1** as the enmeshed ionophore showed excellent selectivity for dibasic phosphate (HPO_4^{2-}), exhibiting a near-Nernstian slope of ~ 29 mV per activity decade and a linear range of 10^{-7} – 10^{-1} M at pH = 7.2. Ionophores **1**–**4** demonstrated an inverse relationship between ring size and the linear range of the electrodes made with each ionophore. The electrode developed with **1** was also shown to respond to varying pHs, a finding that led the authors to suggest that this electrode responds specifically to dibasic phosphate anions. Furthermore, the electrode demonstrated selectivity over other interfering anions (*e.g.*, $\text{HPO}_4^{2-} > \text{SCN}^- \approx \text{Cl}^- > \text{NO}_3^- > \text{SO}_4^{2-}$). The selectivity of the electrode is consistent with the so-called Hofmeister bias [21], with the exception that Cl^- gives rise to a greater response than NO_3^- . The authors postulate that possible interactions between chloride and membrane components, such as PVC, could account for this observation. Carey and Riggan reasoned that the inherent selectivity of **1** could be attributed to preferential conformational changes upon binding, according to preliminary modeling results. Gratifyingly, the electrode showed great durability, retaining selectivity and usability over a period of 9 months while being repeatedly used in tests of human saliva and phosphate standards.

Umezawa *et al.* developed a similar ISE based on a modified aza-crown ether, **8** [22], which was obtained by treating a $\text{C}_{16}\text{H}_{33}$ -substituted malonate (**5**) with tetraethylenepentamine (**6**) in absolute methanol for three weeks under conditions of reflux. This produced macrocycle **7** (Scheme 1). The amide linkages were then reduced to amines using $\text{BH}_3 \cdot \text{THF}$. This procedure allowed receptor **8** to be isolated in 40% yield after purification involving recrystallization from a mixture of MeCN and MeOH. The receptor was then used to create a PVC-based ISE. As above, good anion selectivity was seen with this system, in this case towards adenosine

triphosphate (ATP^{4-}) in comparison to phosphate and other biologically ubiquitous anions. In HEPES buffer at pH 6.7, a linear response to ATP^{4-} was found from 10^{-3} – 10^{-7} M with a response slope of -14.5 mV. Additionally, the electrode did not appear to exhibit any memory effect (hysteresis) corresponding to changes in concentration.

At physiological pH, the aza-crown ether derivative **8** was believed to be triply protonated (*i.e.*, existing as a trication). The use of such a charged receptor, as opposed to a neutral receptor, was thought to account for the observed selectivity for ATP^{4-} and/or its monoprotonated form, HATP^{3-} . This finding was considered to be unique at the time since it meant that the neutral form of the receptor (as used to prepare the modified electrode) undergoes protonation at the surface of the ISE, thus producing a more effective, charged receptor. This finding inspired the construction of yet additional ISEs.

In 1998 Umezawa, Sessler, and coworkers conducted a comprehensive study of a variety of aliphatic and heteroaromatic lipophilic amines (Fig. 3) and their potentiometric anionic response to neutral phenols [23]. The amines used in this study included the aza-crown ether derivative discussed above (**8**), tri(decyl)amine (**9**), 4,7-diphenyl-1,10-phenanthroline (**12**), terpyridine (**13**), and sapphyrin (**14**) [24].

The electrodes developed by Umezawa and Sessler utilized PVC matrix membranes. Membranes that incorporated aliphatic amines (**9–11**) exhibited potentiometric selectivities that correspond to the acidity (hydrogen donor activity) as well as the lipophilicity (extractability) of the phenols. The authors explained the anionic response on the basis of a decrease in the amount of charge separated by the protonated amines and counteranions across the membrane. The pH profiles of heteroaromatic amines **12**, **13**, and **14** led the authors to suggest that protonation of these latter species is less facile, but still leads to charge separation across the membrane interface generating a membrane potential. Interestingly, the membrane developed using sapphyrin (**14**) as the ionophore showed selectivity for catechol, reflecting an innate geometrical discrimination.

In a separate study, Umezawa and Sessler studied the potentiometric response of membranes containing expanded porphyrins towards carboxylate anions and inorganic anions [25]. The expanded porphyrins used in this study included sapphyrin (**14**), rubyrin (**15**), and triphenylrosarin (**16**). Prior to using these particular species as ISE elements, Sessler and coworkers had shown that various expanded porphyrins are capable of binding anionic species in their protonated forms through a combination of hydrogen bonding and electrostatic interactions [26]. Specifically, sapphyrin was demonstrated to be an efficient receptor for fluoride, phosphate and phenylphosphate [27,28]. Rubyrin [29], which is a 26 π -electron species, was shown to demonstrate an affinity for chloride and GMP, whereas triphenylrosarin [30], a fully conjugated 24 π -electron macrocycle, was likewise shown to recognize the chloride anion. In both cases, prior protonation of the macrocycle was deemed necessary to achieve efficient anion binding.

Umezawa and coworkers prepared PVC membranes containing expanded porphyrins **14** – **16** using a procedure similar to that used to obtain the previously described systems. In this case, pH titrations involving the resulting electrodes served to demonstrate that protonation of the expanded porphyrins at the surface of the electrode is required for uptake of the targeted anions and to obtain a potentiometric response. This set of electrodes demonstrated a strong response to the benzoate anion, but did not respond well to inorganic anions or saturated aliphatic carboxylate anions. Interestingly, the electrode developed from sapphyrin (**14**) deviated from the Hofmeister series, and showed selectivity for fluoride, a much more hydrophilic anion, over chloride and bromide. The sapphyrin-based electrode in this study appeared to discriminate for fluoride based on size, the specificity of the charge-charge

interactions, and *via* hydrogen bond formation. At the time of the work, a selective potentiometric response based on size represented a new approach to developing analyte-specific ISEs.

In 1999, Král, Sessler, and Gale developed PVC-derived ISEs from neutral anion receptors [31]. This study utilized *meso*-octamethylcalix[4]pyrrole (**17**) and its pyridine containing analogues dichlorocalix[2]pyrrole[2]pyridine (**18**) as well as tetrachlorocalix[4]pyridine (**19**). This series of macrocyclic receptors represents a matched set, wherein it was considered that if the pyridine moieties remain unprotonated they should act as strong (**17**), intermediate (**18**), and weak anion receptors (**19**), respectively. Calix[4]pyrrole is a known neutral macrocycle that binds anionic species through hydrogen bonding interactions, showing selectivity for $F^- > Cl^- > H_2PO_4^-$ when studied as the TBA salts in dichloromethane [32].

ISEs developed from **17** displayed a strong anionic response (negative slope) at lower pH values (*i.e.*, 3.5 and 5.5) in the case of Br^- , Cl^- , and $H_2PO_4^-$. A correspondingly lower response was observed with F^- . However, at higher pH (*i.e.*, 9.0) electrodes derived from **17** displayed a cationic response (positive slope) toward Cl^- and Br^- . Non-Hofmeister selectivity was also seen in the case of an ISE produced from **17** (*i.e.*, $Br^- < Cl^- < OH^- \approx F^- < HPO_4^{2-}$). The authors rationalized this finding by suggesting that **17** acts as a direct anion binding agent at low pH, whereas at higher pH this same receptor acts, at least in part, as a hydroxide anion-complexing receptor. ISEs based on receptors **18** and **19** displayed selectivities in accordance with the Hofmeister series at pH 9.0. The authors also reported that at lower pH values ISEs derived from **18** and **19** displayed increased anionic responses and improved selectivities for hydrophilic anions (*e.g.*, F^- and $H_2PO_4^-$); this observation was rationalized in terms of protonation of the pyridine containing receptors, which led to the higher anion binding effects. These results, when considered in concert, provide initial support for the notion that calixpyrroles, as well as other neutral receptors, may be used in the development of anion specific ISEs and, more broadly, polymeric systems capable of interacting specifically with negatively charged analytes.

The incorporation of heterocyclic receptors into polymeric materials has not been limited to the development of selective electrodes. For example, Anzenbacher and Nishiyabu designed chromogenic anion chemosensors based on calix[4]pyrrole (**17**) that were produced by attaching non-chromophoric dye precursors to the macrocyclic framework [33]. The ease and high yield of the underlying preparation offer obvious advantages over attaching pre-existing chromophores to calixpyrroles. The calixpyrrole derivatives **20** – **22** produced by these researchers were found to display dramatic color changes upon the addition of the fluoride, acetate, pyrophosphate, and phosphate anions.

In an effort to demonstrate the relevance of chemosensors **20** – **22** to health care applications, studies were performed using carboxylates of medical interest (salicylate, ibuprofen, naproxen). Toward this end, Anzenbacher and his group developed a new assay utilizing polyurethane films that contained receptors **20** – **22** embedded non-covalently within macromolecular matrices. According to the authors, the polyurethane support served two purposes. First, the polymer physically acted to screen off various blood plasma protein carboxylates from the active sites. Second, its hydrophobic nature prevented hydrophilic anions (*e.g.*, HCO_3^-) from penetrating into the matrix and biasing the embedded sensor. The actual test experiments involved the use of a multi-well assay that contained the functionalized polyurethane. It was found that relatively lipophilic aromatic carboxylates were able to penetrate films containing **20**, bind with the chemosensor, and produce a response. This response takes the form of a characteristic change in the color of the polymer film (Fig. 7). The affinity for the carboxylate anions was as follows: naproxen $\approx$ ibuprofen $\geq$ salicylate $>$ laurate $>$ acetate (prepared in plasma-like aqueous solution (PLAS)).

A follow up article in 2007 by Anzenbacher *et al.* was concerned with the development of easy to use chemosensors and arrays for anions in water [34]. The low charge to radius ratio and high energy of solvation of various anions (*e.g.*, F^- has an ionic radius of 1.33 Å and $\Delta G_{\text{hydration}} = -465$ kJ/mol [21]) makes sensing in water a particularly challenging task. Anzenbacher utilized eight pyrrole hydrogen bond donor motifs as the chemosensor elements (Fig. 8). These motifs included N-confused calix[4]pyrrole (**23**), calix[4]pyrrole **21** and its derivatives **24** – **28**, as well as the anthraquinone based dipyrrolylquinoxaline (DPQ) **29**.

As in the previous study, Anzenbacher blended sensing elements **21** and **23** – **29** with a polyurethane hydrogel, and cast the resulting modified polymer into a microwell array. Individual wells were filled with 400 nl of polymer-sensor mixture (approximately 0.08% sensor in polyurethane w/w) in a tetrhydrofuran (THF) solution (5% w/w) and dried to form polymer films (10 μm thick). The use of a hydrogel in these studies lends mechanical support to the sensor ensemble and presumably helps draw the bulk analyte into the matrix and partially remove the hydrate from the anion (all anions were applied in aqueous solutions). Wells prepared in this way produced a naked eye detectable color change upon exposure to the fluoride, pyrophosphate, and acetate anions. Anions were typically added as aqueous solutions (200 nl) of their corresponding TBA salts. The authors observed that the magnitude and dynamic range of the colorimetric response corresponded well with the affinity displayed by the chemosensor molecule in organic solution. Furthermore, multivariate analysis, specifically principal component analysis (PCA), was used to distinguish between 10 different brands of fluoride-containing toothpaste.

The final study considered in this section involves work reported by Ebdon and coworkers in 2004. They were able to improve upon the findings of Carey and Riggan (*vide supra*) by developing an improved phosphate-selective electrode containing receptors as both additives to polymers and as covalently linked side-chain functional elements [35]. This study is important in that it allowed the relative benefits of receptors incorporated as additives into preformed polymers to be compared with those where the receptors are covalently attached to polymers. In prior work, Ebdon *et al.* demonstrated immobilization of quaternary ammonium species containing allyl groups *via* a free radical cross-linking reaction [36]. The resulting membranes were used as receptors for nitrates. They thus employed similar methods as were used by Carey and Riggan to immobilize derivatives of receptor **1** (*vide supra*); this was done by substituting a terminal allyl-bearing alkyl group to the macrocyclic core. However, in contrast to these earlier researchers, Ebdon *et al.* utilized monomers **30** and **31** whose syntheses were based on previously reported procedures [20,36]. These monomers were added to membranes composed of the relatively heat resistant polystyrene-block-polybutadiene-block-polystyrene (SBS); subsequent cross-linking was achieved *via* a hot-pressing process using a Bytec industrial heated press (obtained from Bytec, London, UK) [37].

To test the efficacy of a trapped ionophore in a polymer blend versus an ionophore covalently bound to a polymer, Ebdon and coworkers constructed two electrodes. One of these was a PVC-based membrane akin to that used by Carey and Riggan; the second electrode consisted of the previously mentioned SBS-based membrane containing covalently bound ionophores. Under the conditions of analysis, receptor **30** was found to be too hydrophilic for use as an embedded (*i.e.*, not cross-linked) probe. Specifically, it was found to leach out of the PVC-based membrane during processing, such that no response to phosphate could be detected. On the other hand, the SBS-based electrode incorporating **30** worked well, as long as a hot-pressing process was used to ensure covalent cross-linking between **30** and the SBS backbone. This electrode gave a response slope of -16 ± 3 mV, had a linear range of 2.2×10^{-3} to 5×10^{-6} mol dm⁻³ H₂PO₄⁻ and a limit of detection of 1.0×10^{-6} mol dm⁻³ H₂PO₄⁻. While these results compared favorably to those obtained by Carey and Riggan the nature of the comparison was not identical. Therefore to permit a more accurate assessment of the trapped versus covalently

bound ionophore approaches, Ebdon and coworkers synthesized a more hydrophobic monomer, **31**, which showed improved performance in the PVC matrix electrode. The PVC-**31** electrode showed detection abilities comparable to those of electrodes created using **1** embedded in PVC. Specifically, a response slope of -34.0 ± 2.0 mV, a linear range of $2.2 \times 10^{-3} - 5 \times 10^{-6}$ mol dm⁻³ H₂PO₄⁻ and a limit of detection of 5×10^{-6} mol dm⁻³ H₂PO₄⁻ was seen. Due to **31** being simply embedded in the PVC matrix, the electrode had a response lifetime of merely 4 days, compared to the SBS-**30** electrode. In the latter case, where the ionophore was covalently bound, a lifetime of 20 days was observed.

With these results in hand, Ebdon and coworkers sought to extend further the lifetime and improve the response of their phosphate-selective electrodes. To do this, they turned to clay composites, an approach known for improving stability, as well as altering the backfilling of electrolytes which resulted in significant improvement in the limit of detection in electrode systems [38,39]. By blending in 23.8% (m/m) PoleStar™ 200R (clay-based filler), Ebdon and coworkers found that the lifetime of the electrode could be extended from 20 days to 40 days for the bound electrode. That comparable response behavior was seen for the ISEs based on mobile and bound ionophores is consistent with the notion that ionophore mobility is not necessary to get a working ISE. Nevertheless, it is important to appreciate that the ISEs based on covalently bound ionophores exhibit significantly increased robustness and stability as compared to analogous PVC-membranes containing “trapped” ionophores.

The work of Ebdon and coworkers thus provides an important demonstration of the potential advantages that can accrue from appending receptors covalently to polymeric materials. Taking this a step further, the formation of well-defined polymers with precisely placed receptors can be expected to enhance the performance of the aforementioned devices (and other applications) even further. Along these lines, the following sections will highlight two classes of such receptor functionalized polymers, specifically those where receptors are 1) attached as side-chain appendages to polymeric frameworks and 2) incorporated directly into polymer backbones.

3 Side-Chain Polymers Containing Anion Responsive Heterocycles

The incorporation of anionic receptors into well-defined polymers and other macromolecules is expected to produce materials that offer a number of advantages as compared to their small molecule analogues. For example, polymers often have significantly different solubilities than small molecules, a feature that is likely to be particularly useful in the areas of anion extraction and separation. Attachment to a polymer provides a method for immobilizing anionic receptors and chemosensors and can prevent “leaching”, or loss of the receptor, which can be advantageous in applications involving the use of mixed phases. The use of polymers can also lead to beneficial matrix effects that can serve to decrease the solvation of a targeted anion or its counteraction. Again, this can be useful in any application involving transfer of an anionic species from an aqueous to hydrophobic environment. Finally, polymeric materials can often be used to create mechanically-robust thin films; where the films contain anion receptors, new and practical applications in the areas of *inter alia* membrane technology, filter devices, and sensors can be easily envisioned.

In this section the focus will be on polymeric materials wherein anion receptors are incorporated as pendant side chains. As will be detailed below, several basic strategies have been used to prepare such materials. The use of differing synthetic methods, and the choice of the receptor system in question, has allowed a degree of affinity and selectivity to be designed into polymeric systems. However, the hope and expectation is that yet-improved systems can be obtained. Indeed, as implied in the introductory remarks, one objective of this review is to stimulate additional effort along these lines.

Early functionalized polymer systems targeting the problem of selective anion recognition relied on the use of secondary electrostatic interactions for the detection of anionic species. Indeed, rather than incorporating an anion receptor *per se*, these systems relied on cationic species that would then attract anions as the result, presumably to maintain charge balance. This strategy is elegantly embodied in the work of Leclerc and coworkers who in 2002 reported a polythiophene derivative containing a pendant imidazolium salt [40]. This polymer was prepared by an oxidative polymerization procedure using FeCl_3 as the oxidizing agent (Scheme 2) [41]. The polymer was soluble in aqueous solution and at 55 °C (0.1 M NaCl or 10 mM tris (hydroxymethyl)aminomethane (Tris) buffer/0.1 M NaCl) the solutions were yellow in color ($\lambda_{\text{max}} = 397 \text{ nm}$). The red-shifted absorption maxima was attributed to the random-coil conformation and subsequent decrease in effective conjugation [42].

Polymer **34** was initially used for the colorimetric and fluorometric detection of nucleic acids. The cationic polymer displayed an ability to transduce oligonucleotide hybridization easily, with the specific capture of a 20-mer probe translating into a clear optical output. In a separate study, Ho and Leclerc used the related polymers **35** and **36** as colorimetric and fluorometric chemosensors for the specific detection of the iodide anion [43]. The impetus for this latter study derives in part from the fact that iodide is a biologically relevant anion, mostly known for its role in thyroid functions. In the study itself, electrostatic interactions were thought to result in a conformational change of the polythiophene derivatives causing a change in the effective conjugation of the polymer chain. Iodide anions promote the aggregation and planarization of polymer **35** causing a red-shift in absorbance as well as fluorescence quenching. The optical effects, monitored using absorption and emission spectroscopies were shown to be independent of the corresponding counter cation (*e.g.*, Na^+ vs. K^+). The authors also demonstrated that these systems were dependant on the length and nature of the side chain; for instance, they found that polymer **36** displayed reduced sensitivity under conditions similar to those used to analyze polymer **35**.

In a more recent study Tang *et al.* employed a different approach towards creating polymers with positively charged appendages [44]. Specifically, with the goal of exploiting the so-called “molecular wire effect” noted for conjugated polymers, these researchers synthesized polyphenylacetylenes (PPAs) containing imidazole moieties attached to the backbone (*i.e.*, as pendant side chains). These materials were prepared *via* post-polymerization functionalization, wherein substitution with imidazole was used to generate polymer **37** (Fig. 10). Polymer **37** displayed poor solubility in THF, chloroform and dimethylformamide (DMF) but was readily soluble in ethanol. This material demonstrated both the strong luminescence (*i.e.*, blue fluorescence) characteristic of disubstituted polyacetylenes, as well as the metal ion-coordinating ability of imidazoles. As such, it was proposed that polymer **37** would provide a new kind of potentially efficient chemosensor.

It was shown that Cu^{2+} could quench the fluorescence of polymer **37** ($1.06 \times 10^{-4} \text{ M}$ solution in ethanol) completely at very low concentration (1.48 ppm) with the corresponding Stern-Volmer constant determined to be $3.7 \times 10^5 \text{ M}$. Tang and coworkers were then able to take advantage of a “turn on” method of anion sensing by employing species that competitively bound Cu^{2+} . In particular, low concentrations of CN^- (*i.e.*, $7.0 \times 10^{-5} \text{ M}^{-1}$ of sodium cyanide) served to “turn on” the fluorescence of the polymer **37**· Cu^{2+} complex. The reactivation of the fluorescence signal was not observed in the presence of other anionic species. The detection of CN^- is highly important given its inherent toxicity to mammals and its common use in industrial applications such as gold mining, electroplating, and metallurgy [45,46].

In 2009, Tang and coworkers utilized polymer **37** to sense α -amino acids *via* a similar “turn on” fluorescence approach [47]. The use of a normal UV lamp allowed histidine to be differentiated from other α -amino acids; in particular, histidine allowed for the visual

observation of a restored blue fluorescence at concentrations as low as 4.0×10^{-5} M. Using fluorescence spectroscopy to monitor the “turned on” fluorescence signal, after exposure of the polymeric complex **37**·Cu²⁺, allowed histidine to be detected at concentrations as low as 2.1 ppm.

Recognizing that the human eye is not generally as sensitive to the blue fluorescence produced by **37** as it is to green light, Tang *et al.* generated a second generation imidazole-pendant PPA (*e.g.*, polymer **38**) [48]. In this polymer the residual halogen groups were completely converted to imidazole substituents (effected synthetically by converting **37** to the corresponding bromide); this yielded a polymer with strong green fluorescence (**38**). The chemosensing behavior of **38** could be observed visually or with the help of a normal UV lamp. This material was capable of detecting copper and cyanide at concentrations as low as 0.85 and 1.38 ppm, respectively.

A novel PPA containing naphthalimide subunits in the side-chain was developed by Tian and coworkers in 2009 [49]. Previous work with naphthalimides demonstrated that these systems act as chemosensors for fluoride ions based on a unique intermolecular proton-transfer (IPT) signaling mechanism (Fig. 11) [50,51]. Polymer **39** was synthesized using [Rh(nbd)Cl]₂ as a catalyst, resulting in a material that was soluble in most common organic solvents.

Upon addition of tetrabutylammonium fluoride (TBAF) to an acetonitrile solution of **39**, a drastic color change from colorless to yellow was observed. The change in the absorption and emission spectra of **39** allowed for a ratiometric detection of fluoride anions in solution. Titrations with other anionic species lead to no spectral changes. Ratiometric fluorescent probes allow for improved reliability and a greater effective dynamic range by providing a built-in correction for environmental effects [52,53]. While there have been a number of ratiometric fluorescent probes developed for cationic species [54,55], there are few reports of ratiometric fluorescent polymers for F[−] anions [56]. Interest in the detection and recognition of the fluoride anion is of growing interest given its association with nerve gas (it is, for instance, a hydrolysis product of Sarin) and the role that UF₆ plays in the enrichment of uranium-235.

Taking a more materials based approach to anion sensing, Li and coworkers developed a novel photonic ionic liquid (IL) system for the detection of various anions (Fig. 12) [57]. Utilizing an imidazolium-based IL monomer (**40**), these investigators performed a photopolymerization of this monomer in 1:1 feed ratio with methylmethacrylate in the presence of the cross-linker ethylene glycol dimethacrylate, and the initiator 2,2'-azoisobutyronitrile (AIBN). The polymerization itself was effected in the presence of silica colloidal crystals in a mixed solvent system consisting of a 1:1 mixture of methanol and chloroform. The silica colloidal crystals were then etched away with 1% HF solution to yield a photonic IL film with an inverse opal structure. The resulting 3D ordered photonic IL was utilized in the naked eye detection of anions (*vide infra*).

It is well known that the hydrophobicity and hydrophilicity of ILs can be tuned by counteranion exchange [58]. In the case of macromolecules containing such species, such tuning was expected to be characteristic of the material. The use of appropriate solvents leads to swelling or shrinking of the films, which should result in a change in the stop gap of the photonic ILs. Similar effects were expected from counteranion exchange. As can be seen from an inspection of Fig. 13, such effects were observed for exposure of the photonic IL films to nitrate (NO₃[−]), tetrafluoroborate (BF₄[−]), perchlorate (ClO₄[−]), phosphorous hexafluoride (PF₆[−]), bis (trifluoromethylsulfonyl)imide (Tf₂N[−]) and bromide (Br[−]). Subsequent monitoring by FTIR served to confirm adsorption of the anions to the films. The most hydrophobic anion, Tf₂N[−],

results in the largest shift in absorbance, 76 nm, while the most hydrophilic, NO_3^- , led to a relatively modest shift of only 18 nm.

Boron-based heterocyclic receptors have also been appended to polymers. Fabre and coworkers in 1999 reported one of the first examples of an immobilized boronate anion receptor [59]. In particular, Fabre *et al.* detail a polypyrrole functionalized with pendant boronate pinacol ester derivatives (**41**) that can function as an electrochemical chemosensor for anions when electrodeposited onto a platinum electrode *via* anodic oxidation performed in acetonitrile. The concentration of anionic analyte was then monitored *via* shifts in the cyclic voltammograms. To synthesize the pyrrolic monomer, Fabre and coworkers began with 1-(phenylsulfonyl)-3-vinylpyrrole. Hydroboration by diisopinocampheylborane yielded the intermediate diethyl boronate derivative. Reaction with pinacol then gave the pinacol boronate derivative. Subsequent deprotection of the phenylsulfonyl group by electrochemical reduction gave monomer **41** in 13% overall yield. Electropolymerization of **41** was achieved in anhydrous MeCN using 10^{-1} M Bu_4NPF_6 as the supporting electrolyte.

In water/acetonitrile mixtures, the polymer-coated platinum electrode based on **41** exhibited a reversible redox process at -0.11 V versus a standard calomel electrode (SCE). Upon addition of a 2 mM solution of potassium fluoride (KF) to the system, a cathodic shift to -0.37 V versus SCE was observed, a result that is consistent with the expectation that the polymer would be easier to oxidize when fluoride is bound. Fabre, *et al.* also reasoned that the negative charge of the fluoride anion might be stabilized by the positive charge created on the polymer backbone as the result of oxidation. Presumably, this adds to the signal response. In contrast to fluoride, very little response was seen when the boronate functionalized polypyrrole was exposed to the chloride or bromide anions, requiring a minimum concentration of 20 mM before a recognizable response was seen in the cyclic voltammetry (CV) traces.

A different set of electrochemical sensors for anion detection was developed by Royal and coworkers, who relied on ferrocene-viologen (4,4'-bipyridinium) based redox active receptors, as well as related polymer films [60]. The stated long-range goal of this research was to develop a sensor for ATP^{2-} that would function in biological milieus. This is a particularly challenging objective given the ubiquity and relatively high concentrations of other anionic species in the human body, including in particular chloride and inorganic phosphate. Cognizant of this challenge, Royal *et al.* first synthesized the small molecule receptors **42** and **43**. These compounds were made so as to test the sensing abilities of the ferrocene-viologen receptors *per se*. Here, it is to be noted that receptor **42** represents a ferrocene with viologens bound at the 1 and 1' positions, while **43** is an *ansa* system wherein two viologens are connected through two ferrocenes to form a macrocycle that is formally analogous to the cyclobis(paraquat-*p*-phenylene) "blue box" made famous by Stoddart [61]. Films of polymer-**44** were deposited onto an electrode surface *via* oxidative electrochemical polymerization of the pyrrole fragment (0.9 V *vs.* Ag/Ag^+ 10^{-2} M in MeCN + TBA salts of perchlorate (TBAP).

These investigators chose CV and differential pulse voltammetry (DPV) as the probe methods used to investigate the binding affinities of **42**, **43** and polymer-**44**. In the case of the redox active receptors **42** and **43**, exposure to H_2PO_4^- , SO_4^{2-} , HPO_4^{2-} , CF_3COO^- , F^- and Cl^- produced no significant shifts in the CV or DPV curves. However, the $\text{Fc}^{0/+}$ couple in **42** was found to undergo a shift of -10 mV when exposed to HSO_4^- , $\text{S}_2\text{O}_4^{2-}$ and ATP^{2-} , while a shift of -10 mV in this wave was seen when **43** was exposed to PhPO_4^{2-} and $\text{S}_2\text{O}_4^{2-}$. Of particular note is that the ferrocene linked system **43** experienced a shift in the $\text{Fc}^{0/+}$ wave of -25 mV when titrated with 2 two-molar equivalents of ATP^{2-} , thus revealing a selectivity for this all-important biological analyte. Royal, *et al.* argued that this selectivity can be attributed to **43** forming a hexacationic receptor upon oxidation, increasing the electrostatic interactions with

ATP²⁻. Charge-transfer interactions between the electron rich adenosine ring system and the viologens are also thought to contribute to the anion binding process.

Upon oxidative electropolymerization of monomer **44** in MeCN, an ATP²⁻ selective electrode was produced. When the polymer-coated electrode was titrated against H₂PO₄⁻, PhPO₄²⁻ and halide anions, which had previously caused no shifts or only modest shifts in the CV peaks of receptors **42** and **43**, little in the way of response was likewise observed. On the other hand, exposure to ATP²⁻ over a concentration range of 10⁻⁵ to 10⁻³ M produced a cathodic shift in the Fc^{0/+} peak that increased to a maximum ΔE_p of -35 mV (*i.e.*, from E_p = 460 mV to E_p = 425 mV vs. SCE). This was considered an excellent result that highlights the possible detection of ATP in aqueous environments, which could in due course allow for the use of these electrodes in more biologically-oriented environments.

In this section we have covered polymeric materials that incorporate anion receptors as pendant side chains. These systems have been applied as chemosensors for species such as CN⁻, F⁻, and phosphate derivatives. This approach toward material development is attractive because it allows the beneficial features of various monomeric receptors (*e.g.*, specificity and signal output) to be combined with those of polymers (*e.g.*, solubility and stability). In this section, the receptors discussed derived their selectivity from electrostatic interactions or subsequent de-protonation upon exposure to anionic species. In contrast, the ensuing section will focus on incorporation of neutral heterocyclic receptors with a strong affinity for anionic species.

4 Polymers Containing Neutral, Anion Receptors

The previous section provides an introduction into polymeric materials containing receptors capable of recognizing anionic species. The aforementioned systems incorporate anion responsive or sensing moieties as side-chain appendages. However, the innate functionality of these materials was typically derived from electrostatic interactions or deprotonation after exposure to anionic species. This often resulted in a colorimetric or fluorometric response. In this section, we will look at neutral receptors capable of binding anions with a high affinity, often through multiple hydrogen bonding interactions. In particular, the structural incorporation of calix[4]pyrrole into polymeric systems will be covered, as well as other molecular receptors (*e.g.*, crown ether, DPQ, and diindolylquinoxaline (DIQ)). Earlier in this chapter, polymer matrices containing calix[n]pyrrole, and derivatives thereof, were described. These materials not only represent a creative approach to ISE development, but also are exemplary of initial progress in the development of polymers containing neutral anion receptors. One advantage to the strategies described below is the ability to tune material properties based on choice of receptor as well as polymer design (*e.g.*, alteration of polymer type, cross-linking, or monomer loading levels).

Early progress in this field is represented by two sets of resins prepared by Kaledkowski [62, 63]. In the first of these, calix[4]pyrrole (**45**) and calix[4]pyrrole[2]thiophene (**47**) were attached to cross-linked vinylbenzene chloride/divinylbenzene copolymer beads. A condensation of phenol-substituted calix[4]pyrrole with formaldehyde (**46**) was used to synthesize the second set of resins. Both these materials displayed an ability to “capture” halides and cyanide anions from MeCN (*i.e.*, non-aqueous environments). Furthermore, resins that contained the “expanded” calix[4]pyrrole[2]thiophene unit demonstrated an enhanced affinity for larger anionic species, such as iodide. This result correlates well with the selectivities observed for the stand-alone receptor [64].

In a more recent study, Sessler, Bielawski, and coworkers reported poly(methyl methacrylate)s (PMMA)s containing pendant calix[4]pyrroles [65]. As mentioned in the chapter on calix[n]pyrroles by Gale and Lee, these new polymeric materials were utilized in the extraction of TBAF and TBACl from aqueous environments. The calix[4]pyrrole methacrylate monomer

(**48**) was prepared in 84% yield from treatment of a hydroxymethyl calixpyrrole derivative with methacryloyl chloride in the presence of triethylamine (TEA). Homopolymer (**49**) was prepared *via* treatment of monomer **48** with 1 mol% AIBN in THF solution. The reaction was then stirred at 70 °C for 17 h under a nitrogen atmosphere. The resulting viscous polymer solution was precipitated by dropwise addition into excess cold methanol, and recovered in 66% yield. Analysis using gel permeation chromatography (GPC) revealed a number-average molecular weight (M_n) of 23,600 Da (relative to PMMA standards) and a polydispersity index (PDI) of 2.3. Furthermore, this conventional free radical polymerization technique was also used to generate a calix-pyrrole containing PMMA copolymer (**50**). Using GPC analysis, copolymer **50** was found to possess a M_n of 85,500 Da and a PDI of 2.1. Sessler and Bielawski concluded from the high molecular weight of **50**, compared to **49**, that the steric bulk of the calixpyrrole negatively impacted the growth of the polymer (**48**).

In an effort to explore the anion binding ability of copolymer **50** under interfacial conditions, Sessler and Bielawski utilized NMR spectroscopic techniques. Towards this end, a D₂O solution of TBAF (90 mM) was exposed to a CD₂Cl₂ solution of polymer **50** (effective concentration of calixpyrrole repeat unit = 6.5 mM). The layered mixture was shaken for 20 min and then centrifuged to separate the organic and aqueous layers. Analysis of the organic layer (CD₂Cl₂) *via* ¹H NMR spectroscopy revealed a substantial downfield shift in the pyrrole NH protons ($\Delta\text{ppm} = 0.32$ ppm), which is typically observed upon anion binding. Furthermore, peaks corresponding to the TBA⁺ counter cation (at $\delta = 3.2$ ppm) were observed, confirming that both the anion (F⁻) and the cation (TBA⁺) were present in the organic phase. A greater downfield shift in the NH pyrrole proton signal was observed upon exposure to TBACl under analogous extraction conditions and concentrations. These results are consistent with the ability of polymer **50** to extract chloride over fluoride. This selectivity runs counter to the anion affinities displayed by calix[4]pyrrole in dichloromethane [32]. However, the observed affinities are in agreement with the so-called Hofmeister bias, as chloride is a more hydrophobic anion ($\Delta G_h = -340$ KJ mol⁻¹) than fluoride anion ($\Delta G_h = -465$ KJ mol⁻¹) [21,66]; chloride anion was thus expected to be extracted more readily than this latter, more hydrophilic species. Supporting this rationalization came from the finding that octamethylcalix[4]pyrrole and PMMA were both capable of extracting TBACl, but 35% less efficiently than polymer **50**. In the case of TBAF only polymer **50** was capable of removing fluoride from the aqueous layer.

The results described above represent one of the first examples of a molecular receptor functionalized polymer capable of extracting anionic species from aqueous environments. However, polymer **50** displayed a low affinity for “hard” salts containing hydrophilic cations (*e.g.*, K⁺ and Na⁺). In 2008, Sessler, Bielawski, and coworkers addressed this issue by appending benzo-[15]-crown-5-ether, a subunit known for its ability to complex cationic species [67], as a pendant group to the calix[4]pyrrole functionalized PMMA polymer backbone [68]. The resulting copolymer (*i.e.*, **51**) was prepared by the previously described free radical polymerization. Initial quantitative evidence that copolymer **51** could extract chloride salts came from a visual extraction test utilizing water-soluble dye **52** (Fig. 18). An aqueous solution of **52** was extracted with a CH₂Cl₂ solution of copolymer **51**, as well as control solutions of octamethylcalix[4]pyrrole (Fig. 18B), benzo-[15]-crown-5-ether (Fig. 18C), and a mixture of both receptors (Fig. 18D). Only the organic layer containing copolymer **51** displayed evidence of successful extraction of dye **52**, as observed by a light blue colored organic phase.

The amount of dye (**52**) removed from the aqueous layer, upon exposure to copolymer **51** and control compounds, was quantified with the use of UV-Vis spectroscopy. Analysis of the aqueous layer, post-extraction, confirmed that copolymer **51** was able to extract dye **52** into the organic phase 54% more effectively than octamethylcalixpyrrole, benzo-[15]-crown-5-ether, or the mixture of receptors.

The promise of the results described above, led Sessler and Bielawski to explore whether or not copolymer **51** was capable of extracting two hard ions, namely potassium fluoride (KF). Thus, a 3.4 M D₂O solution of KF was exposed to a CD₂Cl₂ solution of copolymer **51** (effective concentration of the calix[4]pyrrole and crown ether repeat units 6.25 and 4.86 mM, respectively) and extracted *via* the previously describe procedure. This resulted in the appearance of a signal at $\delta = -121.7$ ppm in the ¹⁹F NMR spectrum of the organic phase. The fluoride anion concentration in this phase was quantified *via* addition of fluorobenzene (final concentration: 14.21 mM) as an internal standard ($\delta = -114.3$ ppm) to the aforementioned extraction experiment. Comparative integration showed copolymer **51** was capable of extracting KF (7.55 ± 0.04 mM) more efficiently than copolymer **50** (5.71 ± 0.03 mM). The extraction efficiencies determined by ¹⁹F NMR were further supported by flame emission spectroscopy (FES), which was used to quantify the amount of potassium extracted into the organic phase (6.84 ± 0.05 mM).

In more recent collaborative work involving the Sessler and Bielawski groups, the above strategy was applied to the development of polymeric chemosensors. In this work, quinoxaline derivatives known as dipyrrolylquinoxaline (DPQ) and di-indolylquinoxaline (DIQ) were utilized as the anion chemosensor elements. DPQs contain pyrroles appended through an α -pyrrolic position to the 5 and 6 positions of the quinoxaline. First developed by Oddo [69] in the early 20th century, DPQs were later “rediscovered” by Sessler and coworkers in 1999 as an efficient fluorometric and colorimetric small molecule chemosensors for anions, *e.g.*, fluoride (F⁻), dihydrogen phosphate (H₂PO₄⁻), *etc.* [70]. The 6-nitro derivative (nitro-DPQ) showed remarkable affinity and selectivity for the fluoride anion, exhibiting a binding constant of $118,000 \text{ M}^{-1}$ in dichloromethane. It also produced an easily discernible yellow-to-red color change. On the other hand, DIQ demonstrated a high affinity and selectivity for dihydrogen phosphate, with the nitro derivative exhibiting a binding constant of $20,000 \text{ M}^{-1}$ in dichloromethane[71].

A two step modification was used to synthesize methylacrylamide monomers of DPQ (**53**) and DIQ (**55**). Subsequently, free radical polymerization, using the previously described synthetic method, resulted in methylmethacrylate copolymers of DPQ (**54**) and DIQ (**56**). The resulting copolymers showed relatively high molecular weights (*ca.* 40,000 Da) and polydispersities on the order of 2.1 to 2.5, similar to previously observed systems.

Thin films of the DPQ polymer **54** (ratio of DPQ to MMA repeat units = 1:10; unpublished results) were prepared using Langmuir-Blodgett techniques. Upon exposure to HF vapors (generated from a 48% aqueous solution of HF) a colorimetric response from bright yellow to red was observed (*cf.* Fig 19b). After two minutes the red color began to fade (Fig. 19c), and was no longer observable after 10 minutes.

Likewise, thin films of copolymer **54** were prepared and used as a “dip-stick” test (*i.e.*, direct exposure to solutions of HF). Exposure to a 48% solution of aqueous HF resulted in a drastic colorimetric change from yellow to dark purple (Fig. 19e). Upon exposure to a 25% aq. solution of HF a change from yellow to red was observed. However, control studies using HCl as the acid solution showed similar colorimetric changes, suggesting that the observed color changes are a result of protonation of the imine in the DPQ, rather than binding of the F⁻ anion. Incorporating DPQ and DIQ sensing moieties into polymeric systems allows for potential application in material-based devices, and demonstrates the tunability of this approach based on monomer selection.

5 Polymers Containing Anion Receptors Conjugated to Their Main Chains

As previously mentioned, polymeric materials often provide advantages beyond those generally displayed by their constituent monomers. One such advantage, displayed by certain

polymers (particularly conjugated polymers), is their ability to conduct charge. This type of conductive polymer can be used to transform a chemical signal into an easily detectable optical or electrical event [72]. The incorporation of anion receptors into such materials should facilitate sensing applications *via* signal amplification. With this goal in mind, it was considered useful to incorporate discrete receptors into the main-chain of covalent polymers. An excellent example of this strategy was reported by Lee *et al.*, who in 2007 succeeded in incorporating quinoxaline receptors into a set of derivatized polyfluorene copolymers (Fig. 20) [73]. The polymer in question, poly[*ortho*-diaminophenylene-fluorene)-co-(quinoxaline-fluorene)] (**57**), was prepared by effecting polymerization of 4,7-dibromo-2,1,3-benzothiadiazole, 9,9-dihexylfluorene-2,7-bis(trimethyleneborate), and 5,8-dibromo-2,3-diphenylquinoxaline through Suzuki coupling, followed by reduction to the *ortho*-diamino group using lithium aluminum hydride. The authors suggested that a selective interaction between the *ortho*-diamino group and the fluoride anion results not only in a colorimetric change, observable by the naked-eye, but also in fluorescence quenching as the result of a photoinduced electron transfer process (PET).

In 2008, Lee and coworkers reported a new set of azomethine-containing conjugated polymers containing fluorene and/or quinoxaline units that are closely attached to their main chains; as above, these systems, represented by canonical structures **58** and **59**, were synthesized by Suzuki-coupling reactions followed by hydrogenation and condensation with cyclohexanone (Fig. 21) [74].

Polymers **58** and **59** were used in the naked-eye detection of acid vapors. Towards this end, the polymers were deposited onto filter paper and exposed to acid vapors. This led to a dramatic color change from bright red to bluish violet (Fig. 22). This color change, which is thought to result from protonation of the imine unit, as opposed to a structural alteration, was found to be reversible, with the color fading when the deposited polymer was left exposed to air for 5 minutes. Protonated versions of polymers **58** and **59**, obtained by pre-exposure to TFA, were also used to prepare a set of anion-induced colorimetric sensors. Specifically, exposure of these TFA-treated polymers to iodide and acetate ions resulted in drastic chromatic changes, which allowed for naked eye detection of these particular negatively charged species.

As previously mention, DPQ is a highly effective receptor for the fluoride anion, thus several groups have developed polymeric systems that rely on this quinoxaline derivative as the anion chemosensor element. Sun and coworkers prepared a DPQ-containing poly(phenylene ethynylene) backbone *via* palladium-catalyzed Sonagashira cross-coupling reactions, producing polymer **60** (Fig. 23) [75]. These systems were found to undergo a bathochromic shift in the UV-Vis absorption spectra when exposed to TBAF in CH₂Cl₂ solution. A quenching of the fluorescence intensity was also seen.

Based on careful ¹H NMR spectroscopic titrations, Sun *et al.* attributed the bathochromic shift in the UV-Vis absorption spectra, as well as the fluorescence quenching, to deprotonation of one of the pyrrolic units, rather than hydrogen bonding of the pyrrolic N-H protons. From UV-Vis absorbance titrations, they were able to calculate an effective binding constant (per DPQ subunit) of $2.52 \times 10^3 \text{ M}^{-1}$ for I⁻ and $1.44 \times 10^3 \text{ M}^{-1}$ for pyrophosphate (HP₂O₇³⁻).

Anzenbacher *et al.*, have also prepared conjugated polymers containing DPQs. These systems were prepared from monomers of DPQ functionalized with ethylenedioxythiophenes (EDOTs) which were then electropolymerized and subsequently doped (Fig. 24) [76]. The polymeric systems prepared in this way (**61** and **62**) allow for two forms of anion sensing, namely by following the anion-induced color changes *via* UV-Vis absorption spectroscopy, or using a bipotentiostat to monitor the changes in current produced by the addition of anions. Polymer **61** demonstrated good affinities for the fluoride and pyrophosphate anions, yielding effective

binding constants of 48,000 and 61,100 M⁻¹, respectively. Polymer **62** is similar to **61** but contains chlorides in the α pyrrolic position of the pyrrolic subunits. The chloride modified polymer showed selectivity toward dihydrogen phosphate, exhibiting an effective per DPQ binding constant of 90,000 M⁻¹. This polymer also displayed an affinity for fluoride and pyrophosphate, although reduced compared to that displayed by the dihydrogen phosphate anion (the effective affinity constants were 24,000 and 11,000 M⁻¹ for fluoride and pyrophosphate, respectively).

A somewhat different class of conjugated polymers containing neutral heterocycles as anion chemosensors was reported by Wang *et al.*; these researchers produced polyphenylenes copolymerized with phenol-substituted oxadiazoles (systems **65** and **66**) as efficient fluorescent sensors for fluoride anions [77]. Wang and coworkers began by first synthesizing the small molecule model compounds 2,5-bis(2-hydroxyphenyl)-1,3,4-oxadiazole (**63**) and 2-(2-hydroxyphenyl)-5-phenyl-1,3,4-oxadiazole (**64**), systems that they found to act as colorimetric and fluorescent chemosensors of F⁻ and H₂PO₄⁻ (Fig. 25) [78].

It was demonstrated that **63** exhibited a high affinity for dihydrogen phosphate and fluoride anions ($K_a = 7.9 \times 10^5$ and 8.6×10^4 M⁻¹, respectively) in DMF, while **64** exhibited a slightly higher affinity for dihydrogen phosphate ($K_a = 1.8 \times 10^6$ and 4.1×10^4 M⁻¹ for H₂PO₄⁻ and F⁻; studied as the respective TBA salts in DMF). The ability of the small molecule model systems to bind dihydrogen phosphate in organic media led to the assumption that polymeric systems would follow suit. However, contrary to this expectation, Wang *et al.* reported that polymers **65** and **66** (Fig. 26) exhibited higher affinities for fluoride over dihydrogen phosphate when studied in chloroform solutions (5 μ M concentrations). The emission intensity of polymer **65** decreased up-to 380-fold upon exposure to F⁻, which was accompanied by an emission red-shift of up to 15 nm. However, the addition of H₂PO₄⁻ led to only a 6-fold reduction in emission intensity (both anions studied as the respective TBA salts). The anion binding properties of **66** were similar to **65** but a significant reduction in sensitivity for F⁻ was observed. This latter finding was attributed to the different number of hydroxyl binding sites in each repeat unit. The more global change in affinity, namely selectivity for fluoride over dihydrogen phosphate, was ascribed to the fact that the polymers exist in coil conformations. Such structures were expected to limit access to the hydroxyl sites in the case of bulky anions such as dihydrogen phosphate, while still permitting smaller, more charge dense anions, such as fluoride, to bind. Based in part on further studies (*vide infra*) from the Wang group, it is likely that this “binding” involves at least partial deprotonation of the hydroxyl protons.

In a separate study involving conjugated fluorescent polymers as anion sensors, Wang *et al.* prepared hydroxyl-functionalized polyquinoline-derived macromolecules (PQOH, **68**; cf. Fig 27) [79]. Polymer **68** was prepared *via* a nickel-catalyzed coupling of a methoxy-protected precursor followed by demethylation (BBr₃ followed by water) [80]. A hydroxyl-containing quinoline, **67**, was synthesized as a small molecule control.

Both the model compound **67** and the polymer **68** (Fig. 22) were found to undergo naked-eye detectable color changes, as well as fluorescence “turn-on” in the presence of TBAF in DMSO. Upon addition of this fluoride anion salt, solutions of **67** were found to change from colorless to yellow, with even larger changes, from colorless to red, being seen in the case of polymer **68**. Other anionic species, namely chloride, bromide and dihydrogen phosphate (all studied as their TBA salts), did not produce color changes in the case of polymer **68**. Exposure of polymer **68** to TBAF, but not to other anions, was also found to engender a new fluorescent emission peak at 620 nm. This observation is most easily rationalized in terms of the hydroxyl groups undergoing deprotonation when exposed to F⁻ (an anion recognized for its basicity in organic milieus) a chemical change that was expected to give rise to an intramolecular charge transfer interaction.

Deprotonation also likely accounts for the efficacy of a set of polyhydroxybenzoxazole-based colorimetric and fluorometric chemosensors for fluoride (*cf.* structure **71**) introduced by the Lee group, whose other contributions are featured elsewhere in this chapter [81]. In this case, a Suzuki cross-coupling polymerization strategy was employed (Scheme 4). Specifically, palladium-catalyzed polymeric coupling of the dibromo-benzoxazole monomer (**69**) with a dialkoxyphenylene di-boronic acid precursor (**70**), followed by deprotection of the benzyl groups, gave rise to the desired polymer, namely poly[2-(2'-hydroxyphenyl)benzoxazole] (**71**). This polymer, a grayish-white powder with $M_n = 5090$ Da and a polydispersity of 1.56, proved soluble in most organic solvents.

Polymer **71** exhibited a UV-Vis absorbance maximum at 331 nm, and upon excitation at 330 nm, was characterized by a fluorescence emission maxima at 414 nm and 518 nm (both spectra being observed in chloroform). The unique fluorometric results are attributed to excited-state intramolecular proton transfer (ESIPT) of the enol form and the excited state of a polar tautomeric keto form [82,83]. Furthermore, naked eye and spectroscopic analysis of polymer **71** in DMF in the presence of various anionic salts demonstrated the use of this macromolecular system as a fluoride chemosensor. Specifically, upon the addition of TBAF, DMF-polymer solutions were found to undergo a naked-eye detectable shift from colorless to yellow. This process, when followed by UV-Vis spectroscopy, is characterized by the emergence of a new maximum at 420 nm. Unfortunately, Lee *et al.* did not quantify these results to determine binding selectivities or limits of detection.

A different class of polymeric anion chemosensors containing receptors within the main-chain are those that rely on the use of bipyridyl moieties as the anion recognition motif. An excellent example of this type of material was reported by Lee and coworkers [84]. These researchers carried out a Knoevenagel condensation of 5,5'-bis(cyanomethyl)-2,2'-bipyridine (**72**) and 2',5'-didecyloxy-*p*-terphenyl-4,4''-dialdehyde (**73**); this gave rise to a bipyridine polymer linked by cyanostyryl groups (**74**, *cf.* Scheme 5). This polymer proved to be a dark yellow solid with an $M_w = 12,500$ Da and a polydispersity of 1.47.

Lee *et al.* tested a number of anions against polymer **74**, including chloride, sulfate and dihydrogen phosphate (all anions tested as their corresponding TBA salts using DMF as the solvent). However, only the hydroxide anion appeared to induce any significant colorimetric shift in the UV-Vis spectrum or fluorescent amplification. Initial fluorescence spectral analyses of polymer **74** in DMF revealed a broad emission peak at 535 nm when excitation was effected at 404 nm. Upon addition of TBAOH, the photoluminescence intensity increased with a strong new emission peak at 480 nm and bright, blue-green fluorescence visible by the naked-eye also being observed. In the case of the UV-Vis absorption spectrum, the initial absorption maximum at 404 nm seen for **74** was found to disappear as TBAOH was titrated into the DMF solution. A blue-shift in the absorption maximum (to 354 nm) takes place, resulting in a color shift from orange to colorless. These results were rationalized in terms of changes in the electronics of the system that occur as the hydroxide anion binds to the bipyridine subunits. Interestingly, the authors did not report having tested fluoride or cyanide; both of these anions are relatively basic and may be capable of being bound by the bipyridine recognition sites present in polymer **74** as well.

Valijaveetil and coworkers developed a series of poly(*p*-phenylene carbazole) copolymers that enabled the colorimetric and fluorometric detection of iodide anions (Fig. 28) [85]. Carbazole is an interesting functional group for incorporating into polymers given its high thermal stability and moderately high oxidation potential [86,87]. The polymerization reactions used to produce polymers **75** – **79** relied on the use of a Suzuki polycondensation process carried out in the presence of potassium carbonate, a palladium catalyst, and cetyltriethylammonium bromide (CTAB) used as the chain transfer reagent (40 mol%).

Thermal gravimetric analyses of **75** – **79** revealed that these polymers were stable up to 390 C.

Polymers **75** – **79** proved to be highly fluorescent displaying quantum yields in the range of 0.58 – 0.78 when studied in THF; these values are significantly higher than those of typical polycarbazoles [88], and led to the consideration that these polymers could be used as fluorometric anion chemosensors. In fact, spectral changes were only observed when these systems were exposed to iodide (*e.g.*, TBAI, LiI, NaI, and KI) among other common anions, including fluoride, chloride, bromide, nitrate, perchlorate, dihydrogen phosphate, and hydrogen sulfate (all studied as the TBA salts in THF solution). The polymers were colorless in solution; however, upon addition of iodide salts a change to yellow was observed. A red shift in absorbance and emission was also observed upon addition of iodide salts. The red shift in absorbance is attributed to the lower level of carbazole loading present in polymers **78** and **79**. In all cases, the nature of the iodide counter cation was found to have no influence on the observed color change.

6 Conclusions

This chapter provides a summary of polymeric systems that contain heterocyclic anion receptors. The polymeric materials covered within this chapter are diverse and cover a broad range of applications. The ability to incorporate neutral receptors (and/or charged species) into different varieties of polymers is beginning to be translated into a corresponding ability to tune the anion recognition properties of macromolecules to meet specific needs. A number of these needs were discussed, including applications involving the use of receptor-polymer combinations as additives for ion-selective membrane development, in the extraction of ions from aqueous environments, and the selective sensing of anionic species. Likewise, a broad range of anion receptors, including aza-crown ethers, calix[4]pyrrole, carbazole, and quinoxalines were reviewed in the context of highlighting these applications. The anion specific receptors can be directly blended with existing polymers as so-called “additives” to enhance material properties. Furthermore, synthetic design also allows for the incorporation of anion receptors into the polymers themselves, either as pendant side-chains or directly included as part of the main-chain polymer backbone. The examples given in this chapter are meant to provide a general overview of the field of anion specific polymers and provide a summary of the current state-of-the art. As such, it is expected that the present review will make it clear to the reader that there is much left to do within this fast-evolving area of materials chemistry.

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Abbreviations

NMR	nuclear magnetic resonance
TBA	tetrabutylammonium
ISE	ion-selective electrode
PVC	polyvinyl chloride
THF	tetrahydrofuran
MeCN	acetonitrile
MeOH	methanol

ATP	adenosine triphosphate
GMP	guanosine monophosphate
HEPES	(4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
PLAS	plasma-like aqueous solution
BSA	bovine serum albumin
PCA	principal component analysis
SBS	polystyrene-block-polybutadiene-block-polystyrene
PPA	polyphenylacetylene
DMF	dimethylformamide
IPT	intermolecular-proton transfer
AIBN	2,2'-azoisobutyronitrile
IL	ionic liquid
CV	cyclic voltammetry
SCE	standard calomel electrode
DPV	differential pulse voltammetry
DPQ	dipyrrolylquinoxaline
DIQ	diindolylquinoxaline
PMMA	poly(methyl methacrylate)
GPC	gel permeation chromatography
PDI	polydispersity index
TEA	triethylamine
PET	photo-induced electron transfer
ESIPT	excited-state intramolecular proton transfer
CTAB	cetyltriethylammonium bromide
nbd	norbornadiene

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Fig. 1. Schematic representation of heterocyclic anion receptors incorporated into polymeric materials A) as additives in polymers B) *via* attachment as appendages on the side-chains of polymers and C) by direct incorporation into the main-chain of the polymer backbone.

Fig. 2. Cyclic polyamines of varying sizes that have been used as ionophores for phosphate-selective electrodes.

Fig. 3.
Aliphatic and heteroaromatic amines used as ionophores to construct ISEs.

Fig. 4.
Expanded porphyrins rubyrin and triphenylosarin.

Fig. 5. Calix[4]pyrrole (**17**), dichlorocalix[2]pyrrole[2]pyridine (**18**), and tetrachlorocalix[4]pyridine (**19**). As described in the text, these anion receptors were incorporated into ISE membranes.

Fig. 6.
Calix[4]pyrrole derived chemosensors from non-chromogenic dye precursors.

Sensor **20**-polyurethane film / Anions **Fig. 7.**

Polyurethane films in which chemosensor **20** is embedded. PLAS solutions of anions (10 mM), bovine serum albumin (BSA), and blood plasma were applied to polymer films at pH = 7.4. This figure, which originally appeared in *J. Am. Chem. Soc.* **2005**, 127, 8270–8271 (copyright Am. Chem. Soc.), is reproduced with permission [33].

Fig. 8.
Hydrogen bonding chemosensors for anions based on pyrrole hydrogen bond donor motifs.

30 **31**

Fig. 9.
Cyclic amine monomers **30** and **31**.

37 **38**

Fig. 10.
Polyphenylacetylenes functionalized with imidazole moieties.

Fig. 11.
PPA containing naphthalimide as a pendant side-chain.

Fig. 12.
Photonic ionic liquid monomer based on imidazolium.

Fig. 13.

Photonic IL polymer shifts its stop gap as a function of counter anion leading from a shift from pink to blue. This figure, which originally appeared in *Adv. Mater.* **2008**, 20, 4074–4078 (Copyright Wiley-VCH GmbH & Co. KGaA), is reproduced with permission [57].

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Fig. 14.
Pinacol-based boronate derivatized pyrrole monomer.

Fig. 15. Ferrocene-viologen based receptors developed for polypyrrole-based ATP²⁻ sensing.

Fig. 16. Polymer resins containing calix[4]pyrrole (**45** and **46**) and calix[4]pyrrole[2]thiophene (**47**) receptors.

Fig. 17.

Calix[4]pyrrole methacrylate monomer (**48**), calix[4]pyrrole methacrylate homopolymer (**49**), calix[4]pyrrole-co-methylmethacrylate polymer (**50**), and the calix[4]pyrrole-co-benzocrown[5]-co-methylmethacrylate polymer (**51**) developed by Sessler, Bielawski, and coworkers.

Fig. 18.

Aqueous solutions of water-soluble chloride salt (**52**) after extraction with CH_2Cl_2 (bottom layer) solutions of: a) blank with CH_2Cl_2 b) octamethylcalix[4]pyrrole c) benzo-[15]-crown-5-ether d) a mixture of octamethylcalix[4]pyrrole and benzo-15-crown[5]ether e) and polymer **51**. This figure, which originally appeared in *Angew. Chem. Int. Ed.* **2008**, 47, 9648–9652 (Copyright Wiley-VCH GmbH & Co. KGaA), is reproduced with permission [68].

Fig. 19.

Thin films of DPQ copolymer **54** as they appear upon: a) Pre-exposure to HF vapors, b) post-exposure to 48% aq. HF vapors, c) 2 min after exposure to 48% aq. HF vapors, d) pre-exposure to aqueous solutions of HF (*i.e.*, “dip-stick” method), e) after dipping film of copolymer **54** into 48% aq. HF, and f) after dipping a film of copolymer **54** into 25% aq. HF.

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Fig. 20.
Poly[*ortho*-diaminophenylene-fluorene)-co-(quinoxaline-fluorene)].

Fig. 21. Azomethine-containing conjugated polymers containing linked fluorene and quinoxaline subunits.

Fig. 22.

Changes of polymer **58** upon exposure to acid gas in the solid state; (a) polymer **58** embedded onto filter paper (b) after exposure to acid vapors for 10 sec. and (c) regeneration after exposure to air for 5 min. This figure, which originally appeared in *React. Funct. Polym.* **2008**, 68, 1696–1703 (Copyright, Elsevier) is reproduced with permission [74].

Fig. 23.
DPQ-based poly(phenylene ethynylene).

61 R= H
62 R= Cl

Fig. 24.
Structure of DPQ-based polymers used as sensors.

Fig. 25.
Structures of oxadiazole-based small molecule chemosensors.

Fig. 26.
Polyphenylenes containing phenol-substituted oxadiazole moieties.

Fig. 27.
Small molecule model hydroxylated diquinoxaline control and corresponding polymer system.

Fig. 28.
Carbazole containing conjugated polymers.

Scheme 1.

Aza-crown ether derivative **8** developed by Umezawa *et al.*

Scheme 2.

Synthesis of cationic polythiophene derivative containing imidazolium salts.

Scheme 3.

Free radical polymerization of DPQ (**53**) and DIQ (**55**) acrylamide monomers used to generate DPQ (**54**) and DIQ (**56**) methyl methacrylate copolymers.

Scheme 4.
Suzuki cross-coupling reaction to yield poly[2-(2'-hydroxyphenyl)benzoxazole] (**71**).

Scheme 5.
Bipyridine containing polymer synthesized *via* Knoevenagel condensation.