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Conjugated Polymer-Based Chemical Sensors

D. Tyler McQuade,[†] Anthony E. Pullen,[†] and Timothy M. Swager*

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139

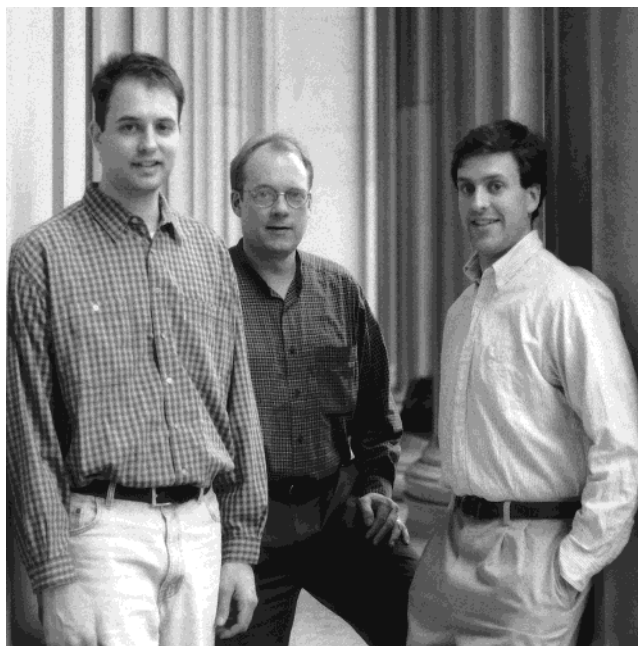
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I. Introduction

When considering new sensory technologies one should look to nature for guidance. Indeed, living organisms have developed the ultimate chemical sensors. Many insects can detect chemical signals with perfect specificity and incredible sensitivity. Mammalian olfaction is based on an array of less discriminating sensors and a memorized response pattern to identify a unique odor. It is important to recognize that the extraordinary sensory performance of biological systems does not originate from a single element. In actuality, their performance is derived from a completely interactive system wherein the receptor is served by analyte delivery and removal mechanisms, selectivity is derived from receptors, and sensitivity is the result of analyte-triggered biochemical cascades. Clearly, optimal artificial sensory sys-



Tyler McQuade (pictured far right) was born in Atlanta, GA, in 1971 and raised (for the majority of his youth) in northern California. He received his B.S. degrees in both Biology and Chemistry from UC Irvine. During his undergraduate education, organic chemistry struck a deep chord; he has pursued this passion under the auspice of Professors Moore (UCI, B.S.), Gellman (Wisconsin, Ph.D.), and Swager (MIT). He is profoundly interested in using the tools of chemistry, biology, and materials science to create and study functional materials. Tyler also enjoys spending time with his wife and two children as well as playing almost any sport imaginable.

Anthony Pullen (pictured far left) was born in 1970 in Muncie, IN. He obtained his B.S. degree in Chemistry from Ball State University and his Ph.D. degree from the University of Florida in Inorganic Chemistry. There, under the direction of Professor John R. Reynolds, he worked on the synthesis of coordination complexes for electrically conducting materials. During his time in Gainesville he also became an avid follower of Gator football. He was awarded a Chateaubriand Postdoctoral Fellowship to work with the group of Dr. Patrick Cassoux at the Laboratoire de Chimie de Coordination du CNRS in Toulouse, France. His research included the synthesis of coordination complexes for magnetic materials applications. He is currently working on derivatized polyanilines and polythiophenes for chemosensing and actuating materials.

Timothy M. Swager's (pictured center) research interests are in design, synthesis, and study of supramolecular systems including organic-based electronic, sensory, and liquid crystalline materials. A native of Montana, he received his B.S. degree from Montana State University in 1983 and his Ph.D. degree from the California Institute of Technology in 1988. After a postdoctoral appointment at MIT, he was on the chemistry faculty at the University of Pennsylvania as an Assistant Professor from 1990 to 1996 and as a Professor in 1996. He moved to MIT in July of 1996 as a Professor of Chemistry.

* To whom correspondence should be addressed.

[†] These authors contributed equally.

tems should also display all of these features. While some elements can be addressed by instrumentation, the design of robust, sensitive, and discriminating sensory materials remains as an emerging frontier.

Conjugated polymers (CPs) offer a myriad of opportunities to couple analyte receptor interactions, as well as nonspecific interactions, into observable (transducible) responses. A key advantage of CP-based sensors over devices using small molecule (chemosensor) elements is the potential of the CP to exhibit collective properties that are sensitive to very minor perturbations. In particular, the CP's transport properties, electrical conductivity or rate of energy migration, provide amplified sensitivity.¹ Polymers are often used in sensory devices as passive supports or structural materials to provide stability. The majority of this review covers CPs as active components mediating or transducing responses that indicate the presence of an analyte.

A cursory summary of the properties of CPs is necessary to understand their properties. In general, CPs in their pristine (neutral) states are wide band gap semiconductors.^{2,3} CPs generally have what is referred to as a direct band gap, exhibiting an efficient (allowed) absorption or emission at the band edge. Depending on the system, a CP can exhibit a strong luminescence. The luminescence efficiency in many cases is related to the delocalization and polarization of the electronic structure. For example, poly(phenylenevinylene) is a strongly luminescent material wherein absorption of photons creates excitons, which are bound electron-hole pairs.^{2,3} A more polarizable and delocalized polymer such as polyacetylene is only very weakly luminescent. In these cases, photogenerated electron-hole pairs can dissociate to generate free carriers that migrate throughout the system. The free carriers can then combine to form triplets or deactivate by other nonradiative processes. The reduced band gap in these latter systems also increases nonradiative processes in accord with the energy gap law, which is well-known in small molecule photochemistry.⁴

CPs generally exhibit semiconductive to insulating levels of conductivity in their pristine state but can be made conductive by doping.⁵ The term doping is derived in analogy to semiconductor systems. However, in contrast to semiconductor systems, doping does not refer to the replacement of atoms in the material's framework. Doping in the case of a CP refers to the oxidation or reduction of the π -electronic system, p-doping and n-doping, respectively, and can be effected chemically or electrochemically. To maintain electroneutrality, doping requires the incorporation of a counterion.

A vast number of studies on oligomers confirms that the electronic states in a CP have limited delocalization, and the electronic structure of a given CP is often determined by 7–13 repeating units.⁶ This is particularly prevalent in systems containing aromatic rings since the aromatic character localizes the electronic wave functions. As a result of this localization, a CP's band gap (HOMO–LUMO gap) is largely determined by its local electronic structure. The injection of charge (oxidation or reduction) cre-

ates local carriers that can exist as cation, cation radical, anion, anion radical, dication, or dianion species. The CP lattice generally allows relaxation around these charged carriers, and the resulting mobile distortions are often described as quasiparticles (solitons, polarons, and bipolarons).⁷ Like band gaps, the electrochemical oxidation and reduction potentials of CPs are local properties. Transduction based solely on these properties will not fully utilize the collective properties of the system.¹

CP-based sensors have been formulated in a variety of schemes. Conductometric sensors display changes in electrical conductivity in response to an analyte interaction. This is a particularly natural sensory scheme for electrically conducting polymers. These measurements are easily performed by connecting two adjacent electrodes (often microelectrodes) with a polymer film and then measuring the film's conductivity (or resistivity) as a function of analyte concentration.^{8–10} Conductometric studies can also be made while maintaining the system at a fixed electrochemical potential. Doping offers a powerful transduction mechanism since the polymer's conductivity often changes by multiple orders of magnitude with even a small amount of charge injection.⁵ The charged nature of the carriers also lends itself to interactions with the surrounding medium, thereby affecting the conductivity. A classic example is the extraordinary sensitivity of n-doped polyacetylene to solvation of the Na^+ ions by THF.¹¹ Strong electrostatic interactions with the alkali metal counterions reduces carrier mobility, and solvation screens these interactions to give dramatic increases ($\sim 10^4$) in conductivity.

Potentiometric sensors rely on analyte-induced changes in the system's chemical potential. The reversible nature of the redox processes in CPs, as well as their sensitivity to conformation and electrostatics, enables the development of sensors based on this principle. In this scheme, the CP need only be immobilized on a single electrode. Potentiometric effects can also be used in hybrid semiconductor systems wherein changes to a CP's work function affect the transport characteristics of a base semiconductor device.¹²

Colorimetric sensors refer to changes in a material's absorption properties. Although the conjugated polymer's absorption characteristics are largely determined by the local electronic structure, the sensitivity of the band gap to the polymer's conformation provides a useful means to create this type of sensor.

Fluorescence is a widely used and rapidly expanding method in chemical sensing. Aside from inherent sensitivity, this method offers diverse transduction schemes based upon changes in intensity, energy transfer, wavelength (excitation and emission), and lifetime. There are advantages to using CPs in fluorescent sensory schemes due to amplification resulting from efficient energy migration. The combination of amplification and sensitivity in CP-based sensors is evolving to produce new systems of unparalleled sensitivity.^{13,14} Other optical methods, such as those based upon changes in refractive index, although not necessarily excluded by conducting polymers, are less developed.

Analyte specificity in CP-based sensors results from the covalent or physical integration of receptors, imprinting, and/or the CP's overall electrostatic and chemical characteristics. CPs are a diverse sensor platform, and a growing number of studies have also made use of biomolecular recognition schemes to elicit sensory responses. Studies of cross-reactive (low specificity) arrays of CPs have also been fruitful, and these "electronic nose" or "electronic tongue" devices mimic mammalian sensory systems. Arrays of CPs are particularly attractive in electrical transduction schemes since semiconductor microfabrication techniques can be easily used to create multielement devices. This review will not specifically address array systems since this topic is covered elsewhere.¹⁵

The goal of this review is to cover CP-based sensors in a comprehensive fashion. In general, we use the term "sensor" liberally. To many, a sensor is a composite device capable of eliciting a response which quantifies the presence of an analyte. Others define a sensor as a chemical system which displays an observable response. Further delineations can be made with respect to the reversibility of the system. Irreversible systems give integrated time-dependent responses and are best referred to as dosimeters. However, we find that the dosimeter specification is not widely used. To elicit a real-time monitoring of an analyte concentration, a reversible response is necessary. In surveying the CP sensor literature, we find a range of reports from purely device-based systems, with little chemical innovation, to those that are based purely on intuitive chemical principles with no device component whatsoever. The embodiment of the sensor varies depending on the perspective of the investigator and the potential application in mind. In many cases, the sensor need only have a relatively nonspecific response. The environment may be controlled to exclude potential interfering species negating the need for sophisticated molecular recognition. In other situations, a CP sensor may be used in an environment which contains a great deal of chemical "clutter" and a highly discriminating device will be best. We have done our best to cover a broad spectrum of CP sensor claims, some of which are little more than an observable change in chemical state. The primary motive of this review is to illustrate the many configurations by which a CP can be harnessed to give a transducible response to analytes.

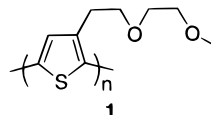
As mentioned earlier, a range of sensory principles are possible with CPs. As some systems can function in multiple capacities, organizing the review by the sensory output or the sensor type would necessarily create overlap. Hence, it has been our goal to minimize any overlap and create an organization that efficiently covers all of the sensing principles. As a result, we have chosen an organization based upon the structure, class of recognition element, or the target analyte. This is not the first review in the field of CP sensors, and for those specific topics with voluminous amounts of research, we focus only on the key studies and recent reports. When appropriate, the interested reader is referred to previous reviews for additional details.^{16–18}

II. Conjugated Polymers with Synthetic Receptors and Functional Groups

The following discussion enumerates the large variety of systems and design parameters that can be harnessed to develop materials based on conjugated polymers. Since the beginnings of the field, CP-based systems have developed into highly sophisticated devices capable of detecting a large variety of metal ions. More recent progress has been made to develop CP sensors to sense neutral and charged organic species.

A. Polyalkyl Ether and Crown Ether Functionalization

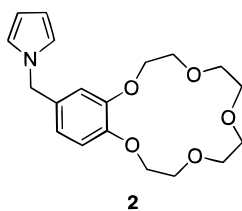
CPs functionalized with polyalkyl ether chains, crown ether, and aza crown ether moieties have been the most thoroughly studied covalently modified systems.¹⁹ In 1989, Roncali and co-workers reported the synthesis of poly[3-(3,6-dioxaheptyl)thiophene] (**1**) and examined its voltammetric properties in the presence of Bu₄N⁺ and Li⁺ electrolytes.^{20,21} This was



said to be the first conjugated polymer system with a covalently attached functional group for ion complexation. In the presence of Bu₄NClO₄ electrolyte in CH₃CN, the CV of **1** displays two redox processes at approximately 0.5 and 0.8 V (vs SCE). Replacing Bu₄N⁺ by Li⁺ resulted in a slight increase of the intensity of the cyclic voltammogram (CV) of the polymer and shifted the *E*_{1/2} values of the two redox systems toward less positive potentials. It was shown that increasing Li⁺ concentration further shifted the peak potentials and narrowed the voltammetric waves. The authors attributed these results to Li⁺ complexation by the pendant 3,6-dioxaheptyl group which changes the conformation of the polythiophene backbone.^{20,21} The pendant ether chains in this case appear to be incapable of discriminating between different ions, and the higher degrees of preorganization available with crown ethers are necessary (vide infra) to produce an ionoselective response. A separate report the same year demonstrated that systematically extending the ethylene oxide ether chain pendant to the polythiophene backbone resulted in further enhancement in the peak current of the first wave (0.40 V vs SCE) in the CV with Li⁺.²² An increase in the ionic conductivity was proposed as the origin of this effect. Hence, it appears that regions of the polythiophene which were electrochemically inactive, due to limited electrolyte penetration (diffusion) into the film, display electroactivity in the presence of Li⁺. In 1991, a more in-depth study of **1** was reported and UV–vis studies showed that replacement of equimolar amounts of Bu₄N⁺ with Li⁺ in CH₃CN produced only a slight red shift of λ_{max} (2–13 nm, dependent upon concentration) and increased the sharpness of the absorption maximum at approximately 550 nm.^{23,24} The authors suggested

that Li^+ complexation by the pendant ether chain in CH_3CN resulted in two effects. The complexation was proposed to planarize the polythiophene backbone and rigidify the network by Li^+ pseudo-cross-linking in **1**. Changing the solvent to H_2O gave a UV-vis spectrum that is significantly blue shifted and less structured. Complexation of Li^+ in H_2O is expected to occur to a lesser extent as a result of solvation barriers for both the Li^+ and alkyl ether side chains. The H_2O -induced blue shift in the UV-vis was attributed to the large effective volume of the solvated ion which results in steric crowding, thereby distorting the polymer backbone from planarity.

Also in 1991, a crown ether covalently linked to a conjugated polymer specifically designed for Na^+ sensing was reported.²⁵ *N*-Substituted 15-(pyrrol-1-yl)methyl(benzo-15-crown-5) (**2**) was electropolymerized, and cyclic voltammetry was carried out in the presence of Na^+ along with Et_4N^+ , K^+ , and Li^+ . No



discernible cation binding effects were observed in the oxidized polymer despite the fact that 15-crown-5 units are well-known to selectively bind Na^+ . This initially was explained as Coulombic repulsion between Na^+ and the charge carriers of the p-doped polymer.²⁵ However, after determining that the neutral polymer does not bind Na^+ , the authors concluded, based upon modeling studies, that there may be a steric barrier between the closely packed crown ether units that prevents complexation of solvated Na^+ .²⁵ An alternative explanation offered here is that the benzylic benzo-15-crown-5 units are partially or totally cleaved in the electropolymerization. Indeed, 4-alkoxy-benzyl moieties are often used as protecting groups for oxygen and nitrogen functionalities that can be readily cleaved.²⁶ When oxidized, the nitrogens in the polypyrrole are effectively benzyl-immonium groups that are expected to be cleaved in the presence of even very weak nucleophiles. FT-IR spectra, although not shown, indicated the presence of benzo crown groups in the reduced polymer films.²⁵ To further resolve the lack of response in this system, quantitative IR measurements and a determination as to whether the crown ether groups are covalently attached or simply entrapped are necessary.

In 1993, the groups of Bäuerle, Garnier, and Swager all reported CPs with covalent receptors with ionoselective responses. Bäuerle and co-workers reported a systematic study on the sensitivity of polythiophenes, derived from mono-, bi-, and ter-thiophene polymerized units (**3–6**) substituted with pendant 12-crown-4 receptors tethered with long alkyl chains, to Li^+ , Na^+ and K^+ ions.^{27,28} Control experiments conducted in parallel used 3'-dodecyl-2,2':5',2''-terthiophene (**7**). Electropolymerization experiments of **3** and **4** resulted in soluble, oligomeric products and poorly adhering films which precluded their utility

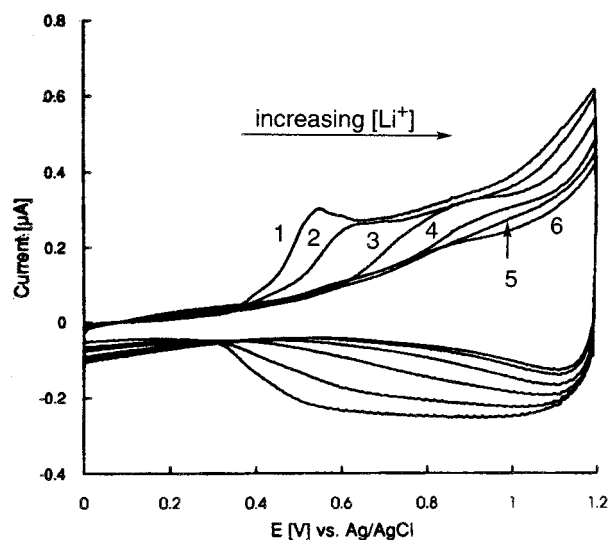
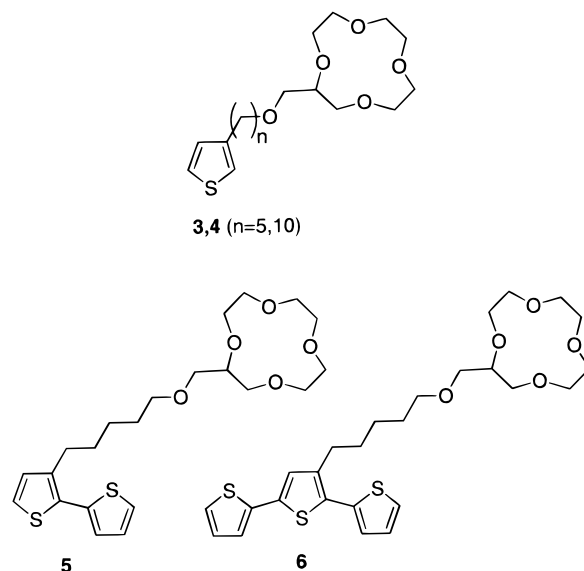


Figure 1. CVs of a film of poly(**5**) in 0.1 M $\text{Bu}_4\text{NPF}_6/\text{CH}_3\text{CN}$. After each scan an equivalent portion of 4×10^{-5} M $\text{LiClO}_4/\text{CH}_3\text{CN}$ was successively added with scan 1 having the lowest and scan 6 having the largest amount of Li^+ present. Each fifth scan is shown for clarity. (Reprinted with permission from ref 27. Copyright 1993 Wiley-VCH Publishers.)

in chemosensing studies. Electropolymerization of monomers **5** and **6** gave quality films as a result of the higher ratio of thiophene units to side chains. Cyclic voltammetry and static applied potential experiments were used to interrogate the sensing properties of **5** and **6**. When increasing amounts of



Li^+ , Na^+ , or K^+ were added, the cyclic voltammetric curves of poly(**5**) lost definition, with both the anodic and cathodic current maxima steadily shifted to higher potentials, and the total current passed decreased. These effects indicate that the polymer was becoming progressively more difficult to oxidize (Figure 1). This effect was also observed to a lesser extent with poly(**6**). Current response measurements at fixed potentials (0.53 V with Li^+ , 0.59 V with Na^+ , and 0.57 V with K^+ vs Ag/AgCl) of a film of poly(**5**) exhibited distinct differences as a function of the alkali metal ion and concentration. As shown in

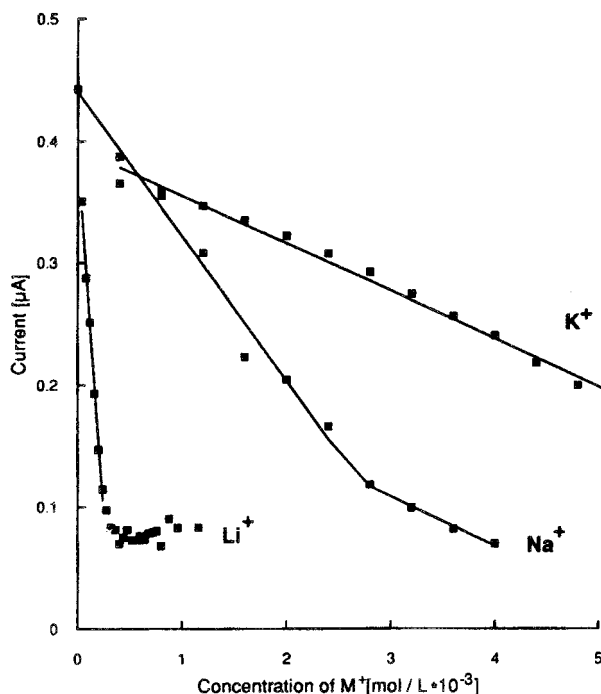
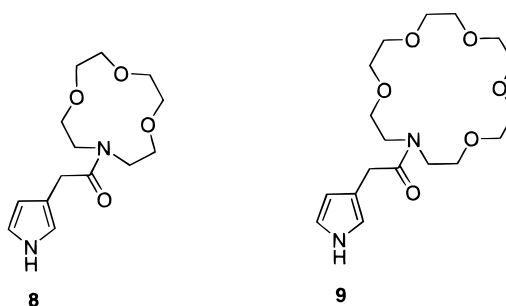


Figure 2. Current versus concentration of the various alkali cations (Li^+ , Na^+ , K^+). Currents were taken from each set of CVs of poly(**5**) at a fixed potential (Li^+ at 532 mV; Na^+ at 590 mV; K^+ at 570 mV) and plotted versus the different concentrations of alkali cations. (Reprinted with permission from ref 27. Copyright 1993 Wiley-VCH Publishers.)

Figure 2, poly(**5**) was most sensitive to Li^+ and least sensitive to K^+ . Small amounts of Li^+ produced a drastic decrease in current, while Na^+ displayed a more gradual current reduction, and K^+ showed the smallest response over the range measured.^{27,28} These results are consistent with the presence of the 12-crown-4 moiety which is known to be selective for Li^+ .²⁹ The same effects in poly(**6**) were also observed but again to a much lesser extent. The electrochemistry of the control polymer, poly(**7**), was completely unaffected by additions of alkali metal ions or a mixture of 12-crown-4 and alkali metal ions, thereby confirming the role of the crown ether.

The explanations for the sensory response of **5** and **6** posed by the authors begin with the assertion that a positively charged "shell" of crown ether-complexed alkali metal ions surrounds the polymer. The shell is thought to impede the diffusion (i.e., kinetics) of charge compensating anions during redox cycling of the polymer. The authors further conjectured that in poly(**6**) a weaker electrochemical response was due to a dilution of the crown ether moieties relative to poly(**5**). A less dense crown ether/ion "shell" would result, lowering the barrier for ion diffusion to the conjugated polythiophene backbone.^{27,28} The fact that the CV changes shape and remains reversible requires a thermodynamic explanation. It is likely that ion complexation alters the polymer's ability to change conformation or restricts the degree of π -stacking between polymer chains. Hence this system is best considered as a potentiometric sensor. It is likely that conductivity changes also take place, however studies of the type have not been performed.

Also in 1993, Garnier and co-workers reported polypyrroles with pendant monoaza-12-crown-4 and monoaza-18-crown-6 entities.^{30–32} Both monomers **8** and **9** were electropolymerizable in 0.5 M $\text{LiClO}_4/\text{CH}_3\text{CN}$ to yield black robust films of poly(**8**) and poly(**9**) with conductivities of approximately 1 S/cm. The

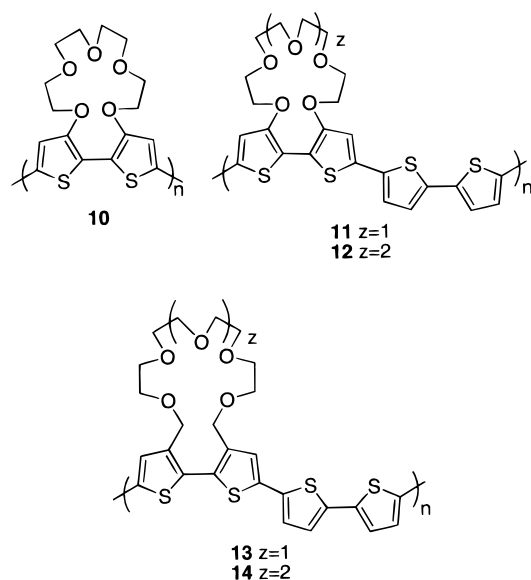


sensitivities of the polymers to Li^+ , Na^+ , and K^+ were examined using cyclic voltammetry. For poly(**8**), no change was detected in the CV (in CH_3CN or aqueous solutions) when exposed to the series of ions. This was attributed to the size mismatch of the monoaza-12-crown-4 (ca. 1.0 Å) and the alkali metal ions, of which Li^+ has the smallest diameter (1.36 Å).^{30–32} The fact that poly(**9**) did not exhibit a response in aqueous solutions was proposed to be a result of the inability of the monoaza-18-crown-6 to desolvate and complex the ions (i.e., low binding constant). However, poly(**9**) did show interesting behavior in CH_3CN . Poly(**9**) was first electropolymerized in a Li^+ -based electrolyte. However, when Na^+ - or K^+ -based electrolytes were added to the solution, progressive shifts in the anodic peak current (I_{pa}) initially at 0.1 V (vs SCE) to a higher potential (0.48–0.52 V) occurred with successive redox cycling. Little effect was seen in the peak cathodic current (I_{pc}). This process was shown to be irreversible, and the initial CV is not reestablished by switching back to a Li^+ -based electrolyte. The final anodic peak potentials from cycling in Na^+ or K^+ -based electrolytes (0.48–0.52 V) were obtained directly when poly(**9**) was electropolymerized in these electrolytes. The lack of sensitivity to Li^+ was attributed to the large diameter of the monoaza-18-crown-6 and its ability to selectively bind the larger Na^+ and K^+ ions versus the smaller Li^+ ion.^{30–32}

Also in 1993, Marsella and Swager reported systems with bithiophene units integrated into crown ethers. The resulting polymers displayed an ion-specific UV-vis response.^{33–37} In polymers **10–12**, the crown ether oxygens are attached directly to the thiophene backbone, whereas **13** and **14** have a methylene spacer inserted between the crown and the polymer. In contrast to the other polymeric systems discussed previously, polymers **10–14** were polymerized by chemical coupling reactions and not electropolymerized. The methods employed in these step-growth polymerizations were a Pd-catalyzed Stille coupling of halide and organotin monomers for **11–14** and a new $\text{Fe}(\text{acac})_3$ oxidative coupling-polymerization of organolithium intermediates for **10**. For these materials, the macrocyclic monomers were first isolated and their binding constants with Li^+ , Na^+ , and K^+ determined (Table 1).

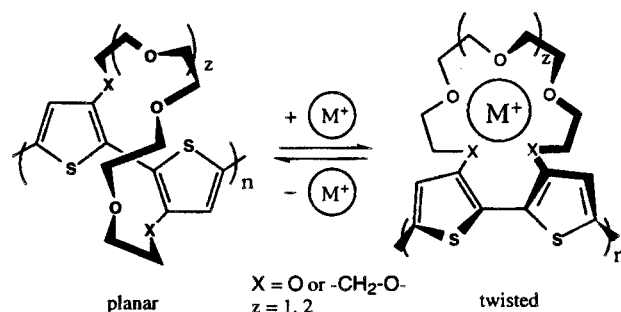
Table 1. Binding Constants for the Crown Ether–Bithiophene Units of Polymers 10–14³²

metal ion	10, 11	12	13	14
Li ⁺	1.2×10^5	1.9×10^5	9.2×10^4	negligible
Na ⁺	2.8×10^5	2.3×10^5	1.7×10^5	1.4×10^5
K ⁺	8.6×10^4	1.1×10^5	7.5×10^4	1.8×10^5



Structures **10–14** were chosen to demonstrate two new design principles. First, they show that a binding event can directly control the conformation of the polymer backbone. In the system under study, a twist (Figure 3) from the preferred planar structure was expected with ion complexation. The magnitude of this twist depends on the size of the metal ion and the macrocycle. The twisting mechanism will reduce both intrachain and interchain conductivity, the former by reducing the conjugation length and the latter by reducing the CP's ability to pack efficiently and thereby increasing the interchain spacing. Second, this study investigated the electronic and electrostatic influence of ion complexation on the oxygens conjugated with the polymer's π system. This latter feature was expected to affect the material's sensory properties since M^+ complexation to the oxygens will reduce their donation ability and give unfavorable electrostatic effects. Both factors will raise the local redox potential of the polymer. A reduction in donation by the oxygens is also expected to increase the CP's band gap by lowering the HOMO energy.

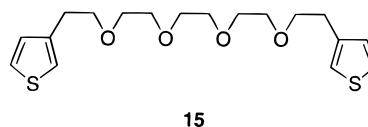
Solutions of polymers **10–14** were exposed to alkali metal ions. UV–vis measurements were carried out in CH_3CN to measure λ_{max} changes with respect to analyte. Before introduction of ions to the polymeric solutions, polymers **10–12** showed longer λ_{max} values (lower band gaps) than polymers **13** and **14**, which have a methylene spacer unit. This difference is consistent with lower conformational restrictions in the backbone for polymers **10–12** than **13** and **14**. The lower band gap for **10–12** also reflects the lower steric requirements of the oxygens as compared to α -methylenes. Diluting the backbone with nonsterically hindered unsubstituted bithiophene units in **11** and **12** resulted in less conformational restrictions and a greater amount of planarity (longer λ_{max}) for

**Figure 3.** Illustration of polymer backbone conformational changes induced by metal ion complexation. (Reprinted with permission from ref 33. Copyright 1993 American Chemical Society.)**Table 2. Ionochromic Responses of Polymers 10–14 When Exposed to 0.1 M Salt/ CH_3CN Solutions³²**

polymer	λ_{max} (nm)	$\Delta\lambda_{\text{max}}$ (nm)		
		Li ⁺	Na ⁺	K ⁺
10	497	46	91	22
11	510	15	63	10
12	524	13	30	45
13	434	3	3	–4
14	432	4	3	1

10 as compared to its homologue **11**. The ionochromic effects when exposed to 0.1 M salt/ CH_3CN solutions were found to be consistent with measured binding constants for the macrocycles and unequivocally demonstrate the proposed polythiophene conformational changes imposed by ion complexation. As listed in Table 2, polymer **10** showed the largest response to Na^+ ($\Delta\lambda_{\text{max}} = 91$) followed by **11** (63 nm). The observed differences in $\Delta\lambda_{\text{max}}$ are consistent with the fact that **10** has a higher concentration of receptors than **11**, which results in more out-of-plane distortions of the polythiophene backbone. The next largest ionochromic response for polymers **10** and **11** was for Li^+ (46 and 15 nm, respectively). Polymer **12** showed the greatest response to K^+ , as predicted from binding studies. Polymers **13** and **14** displayed meager ionochromic responses. This lack of sensitivity was attributed to poor binding affinities (Table 1) and the lack of electrostatic interactions between the alkyl ether chain and polythiophene backbone due to the methylene spacer unit.

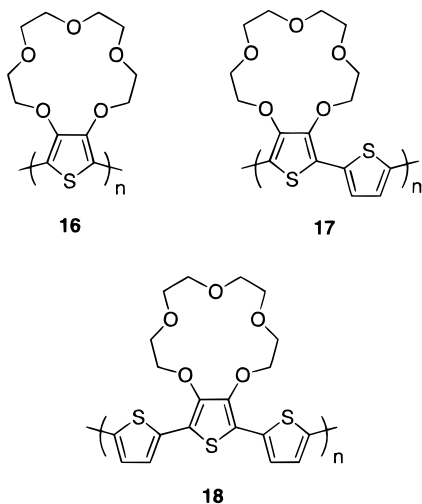
In a related effort, Roncali et al.³⁸ previously investigated a monomer with two thiophenes connected in the β -position by a 3,6,9,12-tetraoxatetradecane spacer (**15**). The electropolymerization of **15**



was conducted in the presence of Li^+ in an effort to template intramolecular coupling and macrocycle closure. Nevertheless, a significant amount of cross-linking probably occurred. Conductivities of only 10^{-2} S/cm were reported for electropolymerized films. The sensing properties of the polymer were not reported.

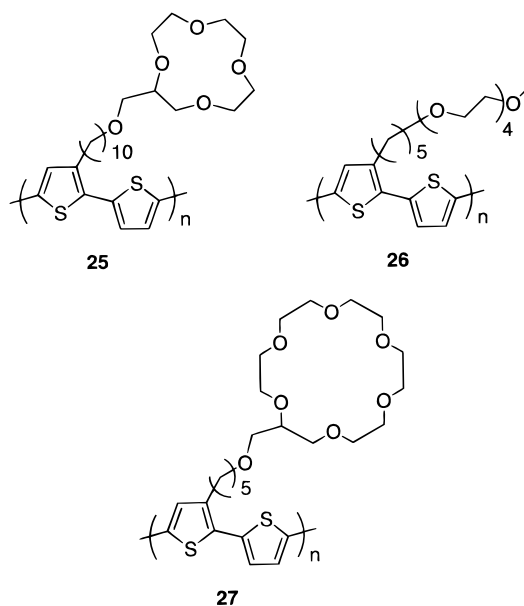
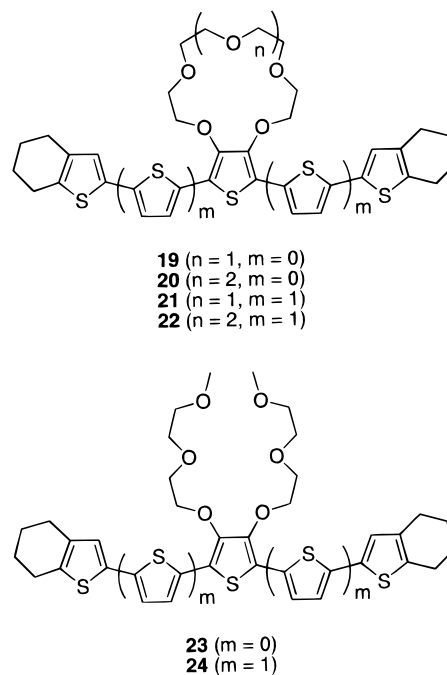
In 1995, Bäuerle's group³⁹ affixed crown ethers to the polythiophene backbone to affect direct π -conju-

gation of the crown oxygens, similar to compounds **10–12** developed by Swager and associates.^{33–37} A series of polymers derived from mono-, bi-, and terthiophene monomer units (**16–18**) were electropolymerized, and their cyclic voltammetric properties were examined in the presence of Li^+ , Na^+ , and K^+ .



Although binding constants were not given, the structural similarities of the macrocycles to benzo-15-crown-5 would suggest that Na^+ would display the highest binding constant. Polymer **16** showed the largest sensitivity to alkali metal ions. Addition of 1 equiv of Li^+ , Na^+ , or K^+ ion per crown ether resulted in a shift in the oxidation potential to higher potentials. When 2 equiv of ion per repeat unit was added during redox cycling, shifts of 211, 217, and 127 mV were observed for Li^+ , Na^+ , and K^+ respectively. For polymer **17**, the largest effect was seen with a 2-fold molar excess of Na^+ ($\Delta E = 57$ mV). For Li^+ and K^+ , the effect was similar, though the magnitude of the shift to higher potentials is about one-half that observed for Na^+ . The oxidation potential of polymer **18** was essentially unaffected by alkali metal ions during redox cycling, and only small shifts were noted. The researchers also described that the changes in oxidation potentials were larger than those observed by the same group for polythiophenes with pendant crown ethers (poly(**5**) and poly(**6**)), vide supra. For polymers **16** and **17**, the greatest effects were seen with Na^+ as expected due to the similar sizes of the Na^+ ion and 15-crown-5 ether cavity. Although no explanation was given for the lack of sensitivity of polymer **18** to the ions studied, it could be deduced that a high concentration of receptor sites is required (i.e., on every thiophene unit) in the backbone to give an adequate signal. As shown with systems **16–18** and **5** and **6**, the polymers with the highest concentration of receptor sites gave the best results. This is a design strategy that may be utilized in the synthesis of future conjugated polymer-based, chemosensory materials.

The Bäuerle group, using similar structures to **16–18**, have synthesized a series of oligothiophenes with fused 15-crown-5 and 18-crown-6 ether rings in the backbone (**19–22**) and with pendant 1,4,7-trioxaocetyl chains (**23, 24**).⁴⁰ Cyclic voltammetry was used to

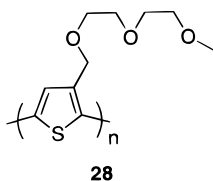


determine the effects of Li^+ , Na^+ , K^+ , NH_4^+ , and Ba^{2+} on the oxidation potentials of **19–24**. The analysis of the singly charged species showed well-defined correlations with the macrocycle size. Oligomers **20** and **22** with an 18-crown-6 moiety display the largest positive shift in $E_{1/2}$ with K^+ . These same oligomers were also observed to be more sensitive to NH_4^+ than those containing a smaller crown. The oligomers containing smaller crown ether macrocycles (**19, 21**) had larger responses to Li^+ and exhibited larger voltammetric responses to Na^+ , which also reflects a better size match. The pendant polyalkyl ether chain in oligomers **23** and **24** showed the largest response to Li^+ due to their ability to wrap around this smaller ion. An interesting observation from this study was that the presence of dication Ba^{2+} ion produced anodic shifts larger than the monovalent cations with all of the oligomers. Oligomers **20** and **23** exhibited the largest potential shift of 296 mV

with Ba^{2+} . To address the polymers response toward Ba^{2+} , competition experiments were conducted wherein the $E_{1/2}$ of the oligomers were determined in an equimolar mixture of Li^+ , Na^+ , and K^+ and then compared to an equimolar mixture of Li^+ , Na^+ , K^+ , and Ba^{2+} . In an equimolar mixture of Li^+ , Na^+ , and K^+ , the largest shifts of 174 mV for **21** and 154 mV for **19** were observed. When an equimolar amount of Ba^{2+} was added, shifts increased to 237 mV for **19** and 226 mV for **21**. These results showed that the shifts observed were on the order of shifts seen in Ba^{2+} -only experiments. It was therefore concluded that divalent Ba^{2+} was selectively recognized over the presence of the other cations.⁴⁰

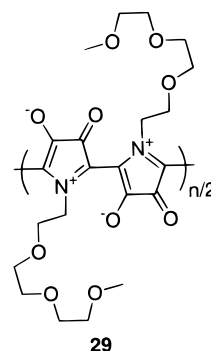
Recently, Bäuerle and co-workers reported further studies on polybithiophene-based systems functionalized with crown ethers or ethylene oxide chains. A series of polymers was assembled electrochemically, and their CV and UV-vis behavior in CH_3CN was examined as a function of metal ion present.⁴¹ Three of the polymers studied, **25**–**27**, exhibited changes in their CVs when exposed to 0.1 M solutions of alkali metal ions. In both cases, a shift in the first oxidation peak (exact values not reported) and a decrease in the electroactivity was observed with addition of metal ions. Relative electroactivities of the polymers were calculated by integrating the area under the redox curves when cycled in 0.1 M $\text{Bu}_4\text{NPF}_6/\text{CH}_3\text{CN}$ and compared after cycling in 0.1 M salt solutions of the alkali metal ions. For **25**, Li^+ had the greatest effect on the electrochemical behavior, inducing a 78% decrease in electroactivity followed by K^+ with a 34% decrease. No changes were observed in the presence of Na^+ . For **26**, the largest influence was seen with Na^+ which caused a 65% decrease in electroactivity of the polymer, while a 42% decrease was seen with both Li^+ and K^+ . For **27**, only K^+ induced a decrease (25%) in the electroactivity of the polymer. For **26**, UV-vis data showed no changes in the longest wavelength absorption in the presence of Na^+ , which had the largest affect on the CV behavior of the ions studied. No data were reported for **25** or **27**. On the basis of the CV and UV-vis results, the authors postulated that the behavior is due to hindered diffusion of anions into the polymer films. This is caused by the formation of an electrostatic potential barrier from complexation of the alkali metal ions by the pendant crown ether and ethylene oxide moieties.⁴¹ This explanation was previously posed by the authors in studies of the similar systems **3**–**6** and **16**–**18**.^{27,39}

McCullough's group reported extensively on the synthesis of functionalized regioregular head-to-tail polythiophenes carefully prepared by chemical polymerizations.^{42,43} In one investigation, they report the UV-vis absorption maximum of poly(3-(2,5,8-trioxanonyl)thiophene) (**28**) to blue shift 11 nm upon



addition of 0.1 M LiBF_4 in 1:1 $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$. This was attributed to Li^+ complexation by the pendant polyether side chains. In a later publication, it was also shown that **28** in its neutral state exhibited a drastic change in the absorption spectrum when treated with Pb^{2+} and Hg^{2+} in CHCl_3 .⁴⁴ These studies revealed a complete loss of the λ_{max} in the visible region, which was attributed to a complete removal of conjugation. The authors argued that such an effect could not result from coordination by the pendant polyalkyl ether chains and requires the direct coordination of Pb^{2+} or Hg^{2+} to the sulfur atoms of the polythiophene backbone. Control studies in the same solvent with Li^+ - or Zn^{2+} -based electrolytes showed no changes in the UV-vis spectrum. A separate group previously proposed that Pt^{2+} coordinates to the sulfur atoms of polythiophene based on XPS and cyclic voltammetry.⁴⁵ In this study, however, no changes in the neutral polythiophene absorption spectrum were observed upon exposure to Pt^{2+} .

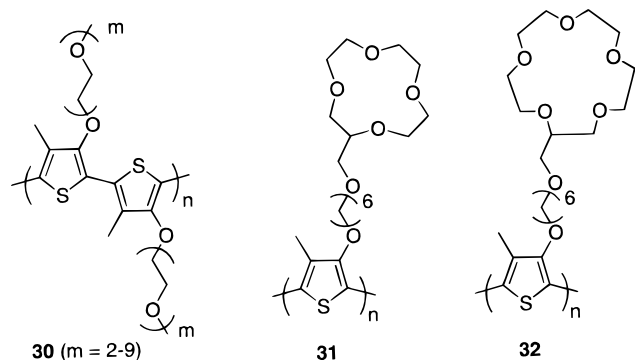
In 1995, Brockmann and Tour developed a zwitterionic polymer functionalized with alkyl ether chains (**29**).⁴⁶ A large number of electrolytes were



exposed to the zwitterionic system in MeOH, and ionochromic effects of cationic binding were examined.

The polymer, in turn, was shown to be completely iodide specific, as only iodide-containing salts induced a new absorption in the near-IR region. Specifically, an absorption band in the range of 816–876 nm was observed for LiI , NaI , and KI , whereas ClO_4^- , Cl^- , Br^- , and F^- salts of the same alkali metal ions produced no new absorptions. Iodochromism was ascribed to the nucleophilicity of I^- at the end groups of the polymers over other halogens in methanol and resulting planarization of the polymer backbone. Planarization of the zwitterionic backbone was also proposed to induce alignment of the polyalkyl ether chains in **29** for enhanced cation chelation.⁴⁶

Leclerc and co-workers published a series of papers on the iono- and thermochromism of regioregular poly[3-oligo(oxyethylene)-4-methylthiophene] (**30**) synthesized from the coupling of 3-bromo-4-methylthiophene and poly(ethyleneglycol) methyl ether.^{47–50} Recently, similar studies have been carried out with regioregular poly(3-alkoxy-4-methylthiophene)s with pendant 12-crown-4 (**31**) and 15-crown-5 (**32**) moieties.⁵¹ Polymer **30** contains polyalkyl ether side chains with a mixture of lengths ranging from 3 to 10 ethyleneoxide repeat units.⁴⁸ UV-vis and fluo-



rescence spectroscopy was used to determine the sensory properties of **30** in response to methanolic solutions of Li^+ , Na^+ , and K^+ . The largest effect was observed for K^+ . Upon increasing concentration of K^+ , the absorbance band of **30** at 426 nm increases while the band at 550 nm decreases. The same magnitude of the effect was obtained when KCl or KSCN was used. Experiments with Na^+ revealed a weaker effect, and no effect was observed with Li^+ .⁴⁸⁻⁵⁰ While the wavelength of the fluorescence band was unchanged with K^+ , the intensity increased with increasing K^+ concentration.⁴⁹ The authors attributed the selectivity of **30** for K^+ over Na^+ and Li^+ to the greater size of this ion. Hence, the pendant alkyl ether chains are required to distort from a chain-extended conformation to accommodate the larger cation. The increased steric demand twists the polythiophene backbone, leading to an increase in the 426 nm absorption.⁴⁹

Polymers **31** and **32** were chemically polymerized, and UV-vis spectroscopy was used to examine their response in solution to Li^+ , Na^+ , and K^+ . For **31**, the maximum absorption is found at 444 nm (acetone) with a weak absorption appearing at 544 nm; both were monitored with metal ion addition. The absorption at 444 nm was shown to decrease, while the absorption at 544 nm increases with increased concentration for all of the metal ions studied. The largest response was seen with Na^+ and the least with Li^+ . For **32**, a parallel change in the absorption maxima (ethyl acetate) was observed with the smallest response seen with Li^+ and the largest with K^+ . For **31** and **32**, the largest responses were expected to be with Li^+ and Na^+ , respectively, due to similar sizes of the ionic radii and the crown ether cavities. The minimal responses of **31** to Li^+ and **32** to Li^+ and Na^+ were postulated by the authors to be because of the small size of the ions and their ability to fit easily into the crown ether cavity which would induce only marginal side-chain organization. The largest responses of **31** to Na^+ and **32** to K^+ were attributed to the ability of the 12-crown-4 and 15-crown-5 units to form stable intra- and intermolecular 2:1 sandwich complexes. As a result, a large amount of side-chain ordering is required to compensate for the ion binding. This results in a planarization of the CP backbone, leading to increased conjugation lengths and the growth of absorptions at higher wavelengths.⁵¹

In 1997 Ion et al. communicated the development of a polypyrrole functionalized with a ferrocene-crown ether receptor.⁵² The monomer consists of a pyrrole moiety covalently tethered to a benzocrown

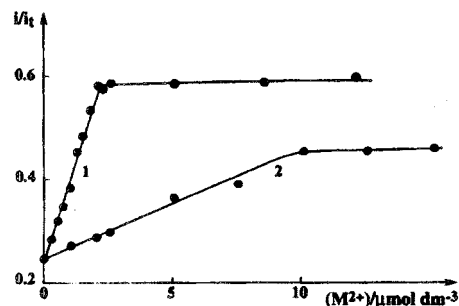
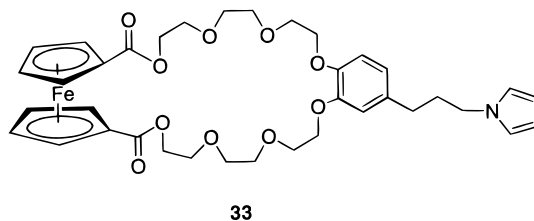


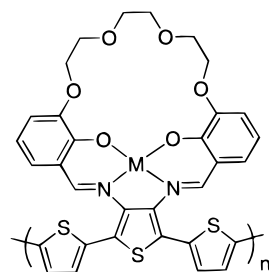
Figure 4. Response of a film of poly(**33**) on a Pt electrode to Ba^{2+} (plot 1) and Ca^{2+} (plot 2). (Reprinted with permission from ref 52. Copyright 1997 Wiley-VCH publishers.)

ring that incorporates an electroactive ferrocene group. In contrast to earlier studies of *N*-substituted polypyrrole benzo-crown ethers,²⁵ this species has a propyl spacer between the polymer and receptor, thereby giving a more stable structure. Electropolymerization of **33** in 0.1 M $\text{Bu}_4\text{NClO}_4/\text{CH}_3\text{CN}$ yielded a film on a Pt electrode with a ferrocene/ferricinium redox couple at $E_{1/2} = 0.56$ V (vs Ag/Ag^+) which was monitored to elucidate the chemosensory properties of poly(**33**) to Ba^{2+} and Ca^{2+} . The addition of progressive amounts of Ba^{2+} during redox cycling led to a decrease of the wave at 0.56 V and the formation of a new wave at 0.68 V. The growth of the new redox wave at $E_{1/2} = 0.68$ V eventually plateaus with increased amounts of Ba^{2+} , and the wave at 0.56 V of the uncomplexed polymer disappears completely with a large excess of Ba^{2+} . The large excess of Ba^{2+} was needed to access all of the binding sites within the film. Poly(**33**) exhibited a similar change in its CV with additions of Ca^{2+} . The wave at $E_{1/2} = 0.56$ V



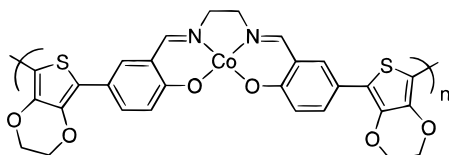
of the uncomplexed polymer decreased and a new redox couple at $E_{1/2} = 0.66$ V forms with increased concentration of Ca^{2+} . Competition experiments between the two divalent group 2 ions could not be carried out for poly(**33**) due to the nearly equal $E_{1/2}$ values for the Ba^{2+} and Ca^{2+} complexed polymer, although it can be deduced from the slopes of the curves found in Figure 4 that poly(**33**) is 10 times more sensitive to Ba^{2+} than Ca^{2+} . Poly(**33**) was also subjected to other ions such as Li^+ , Na^+ , K^+ , and Mg^{2+} , but no changes were observed.⁵²

Reddinger and Reynolds recently reported a novel example of an electroactive polythiophene-based material having the ability to simultaneously coordinate and respond to metal ions and nonionic molecules.⁵³ The system (**34**) is based on a poly-(terthiophene)-Schiff base monomer which has the potential to accommodate a number of transition metals. A polyalkyl ether chain bridging the phenyl rings creates an additional site for chelation of a second metal ion in **34**. Cyclic voltammetry was

**34** (M = Cu, Ni)

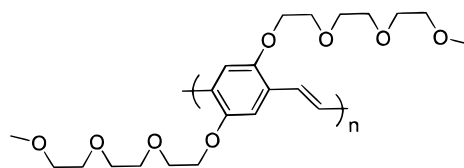
utilized to examine the sensory properties of **34** for Li^+ , Na^+ , Mg^{2+} , and Ba^{2+} and donor molecules such as pyridine or triphenylphosphine. Films of **34** were produced from electropolymerization of the terthiophene monomer in 0.1 M $\text{Bu}_4\text{NClO}_4/\text{CH}_2\text{Cl}_2$. During redox cycling of the film in CH_3CN containing 0.1 M Bu_4NClO_4 and adding 0.05 M cations of interest, changes in the $E_{1/2}$ potentials of **34** were observed. All of the cations studied induced positive shifts in the $E_{1/2}$ potentials with respect to the uncomplexed polymer in the order $\text{Li}^+ < \text{Na}^+ < \text{Mg}^{2+} < \text{Ba}^{2+}$ with Ba^{2+} showing the greatest shift of 145 mV and Li^+ the smallest ($\Delta E_{1/2} = 25$ mV). Li^+ and Na^+ also produced narrowed redox waves which the authors attributed to their enhanced mobility relative to the divalent cations.⁵³ Redox cycling of Mg^{2+} and Ba^{2+} was found to irreversibly shift the polymer's $E_{1/2}$. The response of the CV by the Lewis bases pyridine and triphenylphosphine were also examined on a film of **34** grown on a vitreous-carbon electrode. When a 5 nM solution of pyridine was added, the authors reported a >75% loss of electroactivity in the cathodic process and attributed this result to coordination of the metal center. Cycling in a pyridine-free solution resulted in only a 50% recovery of the electroactivity. Triphenylphosphine gave similar results to pyridine.⁵³

A similar Lewis base response has been found in a structurally related system composed of a Co(II)-Salen-3,4-ethylenedioxythiophene polymer backbone (**35**) by Kingsborough and Swager. Polymer **35** ex-

**35**

hibited a response upon exposure to Lewis bases pyridine and 2,6-lutidine.⁵⁴ Although the electroactivity was not reduced, in situ conductometric studies on interdigitated microelectrodes showed a 66% reduction of the conductivity of **35** when exposed to 40 mM pyridine. The original conductivity could not be restored in the presence of a fresh electrolyte solution. The response was attributed to the formation of five- and six-coordinate **35**-pyridine Lewis base adducts. The ability of **35** to maintain its electroactivity when coordinated was attributed to the authors design which matched the redox potential of the cobalt ion to the organic portion of the polymer.⁵⁴

Holzer et al. recently reported Li^+ shifts in the emission of a polyphenylenevinylene backbone with pendant polyalkyl ether side chains (**36**).⁵⁵ The

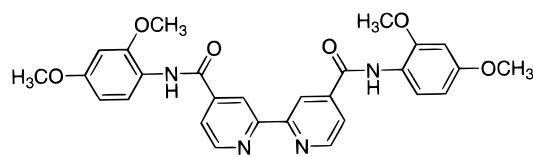
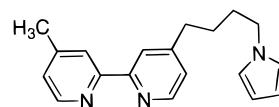
**36**

polymer was chemically polymerized and spun cast from THF on an indium tin oxide (ITO) coated glass slide. UV-vis measurements of pure **36** showed a λ_{max} of 510 nm that shifted to 498 nm upon Li^+ complexation.

B. Conjugated Polymers Functionalized with Pyridyl-Based Ligands

The ability of pyridyl-based ligands to coordinate a large array of metals makes them an attractive functionality to be incorporated into CP sensors. Ligands of this general class can be placed in direct π -communication with the polymeric and/or backbone tethered by extended alkyl chains. In both cases, coordination of metal ions may lead to conformational, optical, or electrochemical changes in the CP.

A significant amount of research has been devoted to the study of pendant tris(2,2'-bipyridine)ruthenium(II) ($\text{Ru}(\text{bpy})_3$)-based complexes due to their photophysical and electrochemical properties.⁵⁶ A series of reports by Moutet, Cosnier, and co-workers focused on $\text{Ru}(\text{bpy})_3$ -based complexes with pendant electropolymerizable pyrrole groups linked by an alkyl chain.^{57–61} More recently, in 1996, a related system, poly{[$\text{Ru}(\text{37})(\text{38})_2](\text{BF}_4)_2$ } (**39**), was developed whose redox system was sensitive to interactions with halide ions.⁶¹ The redox chemistry of the central

**37****38**

$\text{Ru}(\text{bpy})_3$ core is altered when halide ions are complexed by the amide portion of the complex, presumably via hydrogen bonding. In these complexes, **39** is immobilized on a Pt electrode and the CV response of a film of poly(**39**) is monitored upon addition of halide ions to the electrolyte solution. The CV of poly(**39**) in $\text{Bu}_4\text{NPF}_6/\text{CH}_3\text{CN}$ exhibits three reversible waves in the negative potential region attributed to successive one-electron oxidation/reductions of the bipyridine-based ligands ($E_{1/2} = -1.34, -1.88, -2.16$ V) and a broad wave at 0.95 V ascribed to oxidation

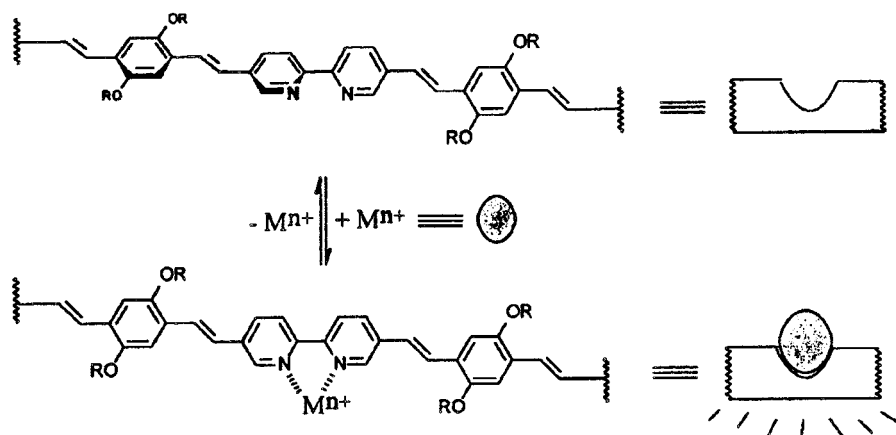
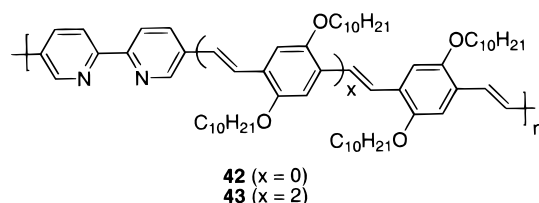


Figure 5. Illustration showing metal ion-induced conjugation enhancement of the polymer backbone and the corresponding responsive change. (Reprinted with permission from ref 62. Copyright 1997 American Chemical Society.)

of polypyrrole, dimethoxybenzamide, and the metal center. The observed responses are solely due to the Ru–tris(bipyridyl) complex; hence, the CP acts as a means to immobilize these complexes on the electrode and potentially to mediate redox transport between the centers. The wave at -1.34 V disappears with added F^- , and the remaining two waves in the negative potential region shift to more positive potentials at $E_{1/2} = -1.82$ and -2.04 V. A new irreversible anodic peak (I_{pa}) is observed at 0.05 V. Quasi-reversibility of the sensory response is displayed by the system as the wave at $E_{1/2} = -1.34$ V partially recovers when placed in a clean electrolyte solution of Bu_4NPF_6/CH_3CN . The related complex $[Ru(38)(bpy)_2](BF_4)_2$ (**40**) also showed the same CV changes when in the presence of a large amount (>10 equiv) of F^- . No explanation was given on the surprising cyclic voltammetric behavior of poly(**39**) and poly(**40**) in the presence of F^- as the authors stated that it is not clearly understood. Poly(**39**) showed the largest response to added Cl^- , and the -1.34 V wave displays a 40 mV maximum cathodic shift when Cl^- reaches a concentration of approximately 5 mmol/L. Changes in the CV are initially observed when the presence of Cl^- is as low as 0.1 mmol/L, and a completely reversible response was observed when the film was subsequently cycled in fresh Bu_4NPF_6/CH_3CN solution. A control experiment was conducted in parallel using $[Ru(38)_2(bpy)](PF_6)_2$ (**41**). The requirement of the amide groups in poly(**39**) for Cl^- recognition was corroborated since **36**, which is without amide groups, displayed no change in the electrochemical response in the presence of Cl^- . No potentiometric effects were observed for poly(**39**) when sensing Br^- or I^- , which is consistent with a hydrogen bonding mechanism.

Wang and Wasielewski investigated polymeric systems with a bipyridyl–phenylenevinylene backbone.⁶² Their approach is based on assembling polymers with “pseudo-conjugated, ligand-containing” backbones and making use of the 20° dihedral angle preferred between the pyridine groups of the backbone. Chelation of metal ions planarizes the bipyridyl recognition sites to increase the conjugation and reduce the local band gap (Figure 5). Hence, the alterations from chelation events and conformational changes can be monitored by UV–vis absorption and

fluorescence spectroscopy. Two polymeric systems were developed containing 2,2′-bipyridyl moieties separated by oligophenylenevinylene segments linked at the 5,5′-positions. Chemical polymerization led to molecular weights of $M_n = 6400$ for **42** and $22\,000$ for polymer **43**. The ionochromic responses to various

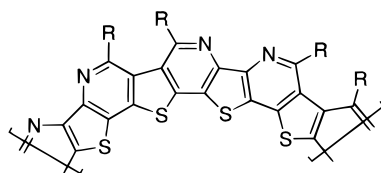


metal salts were measured in $CHCl_3$, and control experiments, with poly(phenylenevinylene) or 5,5′-dimethyl-2,2′-bipyridyl or a combination of both, supported the proposed mechanism. Polymeric solutions of **42** and **43**, which exhibit single broad absorption bands at 455 and 478 nm, respectively, were treated with 10^{-4} M solutions of 16 different di- and trivalent main group and transition metal ions and 6 trivalent lanthanide ions. In every instance, a red shift in the absorption λ_{max} was observed upon addition of a metal ion. For **42**, the largest red shifts were observed with Pd^{2+} ($\Delta\lambda_{max} = 109$ nm), Sn^{2+} ($\Delta\lambda_{max} = 103$ nm), and Sb^{3+} ($\Delta\lambda_{max} = 101$ nm) and the smallest shifts were recorded with the lanthanide ions Ce^{3+} ($\Delta\lambda_{max} = 42$ nm), Gd^{3+} ($\Delta\lambda_{max} = 43$ nm), and Eu^{3+} ($\Delta\lambda_{max} = 45$ nm). For **43**, the largest red shifts were seen with Sn^{2+} ($\Delta\lambda_{max} = 112$ nm), Pd^{2+} ($\Delta\lambda_{max} = 105$ nm), and Al^{3+} ($\Delta\lambda_{max} = 92$ nm) and the smallest shifts were revealed with Ag^+ ($\Delta\lambda_{max} = 38$ nm), La^{3+} ($\Delta\lambda_{max} = 38$ nm), and Ce^{3+} ($\Delta\lambda_{max} = 40$ nm). For both polymers the fluorescence was completely quenched by Cu^{2+} , Ni^{2+} , Co^{2+} , Pd^{2+} , Mn^{2+} , and Sn^{2+} . The group of Ag^+ , Al^{3+} , Cd^{2+} , Hg^{2+} , Zn^{2+} , and the lanthanide ions studied induced red shifts in the emission spectra while the lanthanides, Pb^{2+} , Fe^{3+} , Fe^{2+} , Cu^+ , and Sb^{3+} induced blue shifts.⁶² The multiple emission bands observed upon addition of lanthanide ions was attributed to energy transfer and emission from the f-block nature of the metals. As postulated by the authors, the red shifting of the absorption and emission bands is ascribed to electron density changes caused by the complexation of cat-

ionic mono-, di-, or trivalent metal ions and/or to conformational changes in the polymer's backbone as a result of the chelation. No trends in the magnitude of the red shifts in the polymers were observed that could discern between the different valence classes of metals. Hence, it was concluded that electron density effects, which should be most sensitive to charge, are not as important as the red shifts from planarization of the polymeric backbone. Blue shifts caused by the coordination of specific metals were attributed to a deconjugation effect on the backbone. It was postulated that reductions in conjugation resulted from monodentate coordination to pyridyl units.⁶² The polymers were also studied as spin cast films to examine the sensory responses in the solid state. In these studies, polymer **43** exhibited a 40 nm smaller λ_{max} shift to Pd^{2+} in the solid state as compared to the solution state. The Zn^{2+} response was also 18 nm smaller. These results were attributed to increased conformational restrictions in the solid state, which supports the hypothesis that conformational changes in the backbone plays the largest role in producing the observed effects.

The reversibility in the solution state was ascertained with Zn^{2+} and Pd^{2+} ions and solutions of polymers **42** and **43** in CHCl_3 . Addition of NH_3 completely removed Zn^{2+} from polymers **42** and **43** as determined by the changes in the absorbance and fluorescence spectra. Similarly, Pd^{2+} coordination was also shown to be reversible when CN^- , a stronger ligand, was used.

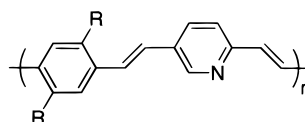
The same year, Zhang and Tour reported a ladder polymer system composed of fused thiophene and bipyridyl units which has an optical pH response.⁶³ UV-vis spectra for **44** in CH_2Cl_2 showed an intense absorption at 412 nm and a less intense absorption at 439 nm. Upon addition of trifluoroacetic acid to



44 ($R = p\text{-(C}_6\text{H}_4\text{)-C}_4\text{H}_9\text{-}n$)

the polymeric solution, a single absorption at 450 nm is observed. The authors concluded that protonation of the aryl nitrogen resulted in a proton-induced enhancement of the intramolecular charge transfer, which leads to the red shift.⁶³

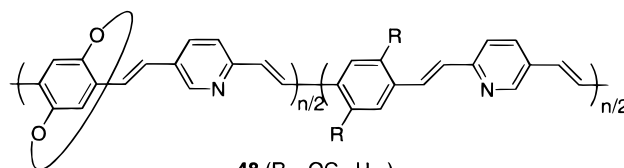
Also in 1997, Fu, Xu, and Swager assembled polymers with pyridyl units in the backbone that exhibit more substantial red shifts in the absorptions with protonation or alkylation.⁶⁴ Polymers **45–49** were polymerized employing Heck coupling reaction methods. The highly colored polymers show λ_{max} absorptions in the 408–466 nm range. Protonation of the pyridine units with aqueous HCl induces red shifts in the absorption for all polymers, with the largest shift seen for **45** ($\Delta\lambda_{\text{max}} = 71$) and the smallest for **47** ($\Delta\lambda_{\text{max}} = 26$). The relative magnitude of the optical shifts were ascribed to the donor–acceptor nature of the polymer. Protonation of the backbone



45 ($R = \text{OC}_{16}\text{H}_{33}$)

46 ($R = \text{C}_{12}\text{H}_{25}$)

47 ($R = \text{COOC}_{12}\text{H}_{25}$)

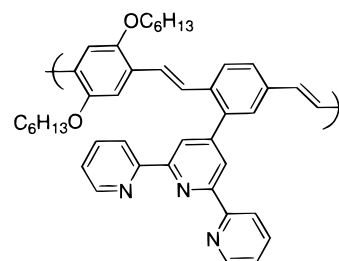


48 ($R = \text{OC}_{16}\text{H}_{33}$)

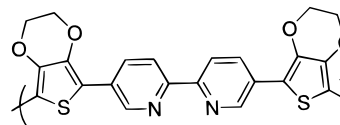
49 ($R = \text{C}_{12}\text{H}_{25}$)

enhances charge transfer from the electron-rich dialkoxyphenyl moieties to the electron-poor pyridine moieties, as also seen in the Wasielewski (**42**, **43**)⁶² and Zhang and Tour (**44**)⁶³ systems. This understanding was substantiated by the fact that polymers (**45**, **48**) containing electron-donating dialkoxy groups exhibited the largest red shifts.

A polyphenylenevinylene backbone functionalized with a terpyridine receptor on alternating phenyl groups was recently reported by Kimura et al. which is sensitive to a large variety of metal ions (**50**).⁶⁵ The



50



51

fluorescence and absorption characteristics of this system were affected by metal coordination. The UV-vis spectrum of **50** exhibits a single absorption at $\lambda_{\text{max}} = 450$ nm in $\text{CHCl}_3\text{--CH}_3\text{OH}$ that is attributed to the absorption of the phenylenevinylene backbone. The addition of progressive amounts of Fe^{2+} resulted in a decrease of the band at 450 nm and the formation of a new λ_{max} at 568 nm. The absorbance at 568 nm reached its maximum with the addition of 0.5 equiv of Fe^{2+} ions relative to the number of terpyridyl receptors, a feature attributed to the assembly of a bistridentate octahedral Fe^{2+} complex by the terpyridyl groups. The fluorescence in $\text{CH}_2\text{Cl}_2\text{--CH}_3\text{OH}$ could be completely quenched by the addition of Fe^{2+} , Fe^{3+} , Ni^{2+} , Cu^{2+} , Cr^{2+} , Mn^{2+} , and Co^{2+} ions. Metal ions Sn^{2+} , Pd^{2+} , Al^{3+} , and Ru^{2+} induced a blue shift in the absorption spectrum and the fluorescence was nearly completely quenched. The quenching is ascribed to an electron or energy transfer between the metal–terpyridyl complex and the polymer backbone.

Zn^{2+} induced a red shift in the emission spectrum from 524 to 563 nm and a partial decrease in fluorescence intensity. Similar to the studies of Wang and Wasielewski,⁶² the reversibility of Zn^{2+} –**50** coordination was studied by the addition of NH_3 to the solution, which nearly reestablished the original spectrum. For a solution of Fe^{2+} –**50**, the addition of NH_3 only resulted in a small return in intensity of the emission peak for uncoordinated **50**. This was ascribed to the stronger binding of Fe^{2+} to **50** in comparison to Zn^{2+} . In contrast, the authors found reversible behavior in thin films. Films of **50** deposited on a quartz plate and immersed in a solution of Fe^{2+} in CH_3OH exhibited complete quenching. Immersion of the resultant film in a NH_3 – CH_3OH solution for 1 min led to near complete recovery of fluorescence intensity. The contrast to that observed in solution was postulated to result from the fact that the Fe^{2+} –terpyridyl complexes on the surface of the film act as energy or electron traps that are easily decomposed by ligand exchange with NH_3 .⁶⁵ It is also more likely that the lack of polymer mobility in thin films prevents the formation of the more stable Fe^{2+} –(terpyridyl)₂ complexes.

Zotti and co-workers examined the UV–vis and CV response of an EDOT (3,4-(ethylenedioxy)thiophene)-bipy hybrid polymer (**51**) to H^+ , Li^+ , Na^+ , Fe^{2+} , Co^{2+} , Ni^{2+} , and Cu^{2+} analytes.⁶⁶ Films of **51** were assembled via electropolymerization in 0.1 M $\text{Bu}_4\text{NClO}_4/\text{CH}_3\text{CN}$ which exhibit an absorption maxima at 466 nm and an oxidative redox potential at 0.50 V (vs Ag/Ag^+) for the neutral polymer. Protonation of the pyridyl moieties by a 10^{-2} M $\text{HClO}_4/\text{CH}_3\text{CN}$ solution resulted in the largest red shifts of λ_{max} (60 nm) and the most positive oxidation potentials ($\Delta E = 0.20$ V). The response was attributed to donor–acceptor charge-transfer effects within the polymer, which is coincident to the systems reported by Wasielewski,⁶² Tour,⁶³ and Swager.⁶⁴ Similar effects (red shifts and increased oxidation potentials) were seen upon exposure to divalent metal ions Fe^{2+} ($\Delta\lambda_{\text{max}} = 60$ nm, $\Delta E = 0.20$ V) and Cu^{2+} ($\Delta\lambda_{\text{max}} = 60$ nm, $\Delta E = 0.15$ V) and to a lesser extent with Co^{2+} ($\Delta\lambda_{\text{max}} = 35$ nm, $\Delta E = 0.05$ V) and Ni^{2+} ($\Delta\lambda_{\text{max}} = 20$ nm, $\Delta E = 0.05$ V).⁶⁶ The variable responses from different metals is similar to that observed by Wasielewski⁶² and was attributed to an increase in conjugation length via planarization of the polymer backbone as a result of bidentate coordination of the pyridyl units.

C. Enantioselective Conjugated Polymers

Conjugated polymers with helical secondary structures have been assembled via chemical and electropolymerization in the presence of chiral and nonchiral electrolytes.^{67–80} CPs have also been functionalized with tethered chiral moieties exhibiting enantioselectivity toward chiral dopant ions. In 1988, Lemaire et al. synthesized thiophene units functionalized with pendant propyl (2*S*)-(+)-(**52**) and (2*R*)-(–)-2-phenylbutyl ether groups (**53**) and electropolymerized the monomers in 0.02 M $\text{Bu}_4\text{PF}_6/\text{PhNO}_2$.^{81–83} Films of poly(**52**) and poly(**53**) exhibited conductivities of approximately 1 S/cm. Specific rotations of $\alpha_D^{22} = +21^\circ 5'$ and $\alpha_D^{22} = -22^\circ 5'$ (2%, CHCl_3) were found

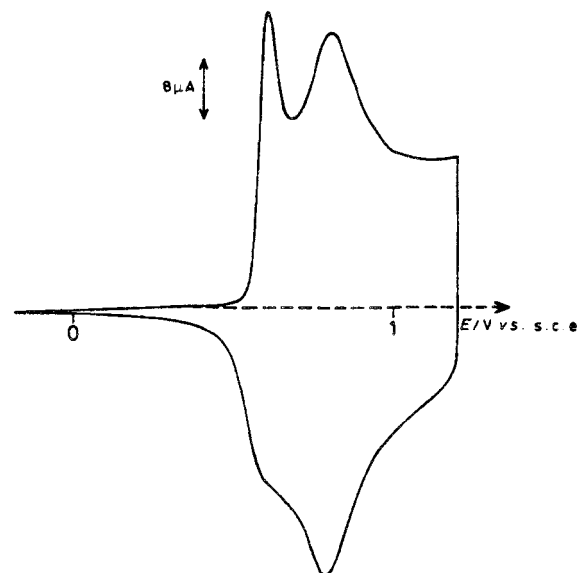


Figure 6. CV of chiral poly(**52**) in 0.1 M $\text{LiClO}_4/\text{CH}_3\text{CN}$. (Reprinted with permission from ref 81. Copyright 1988 The Royal Society of Chemistry.)

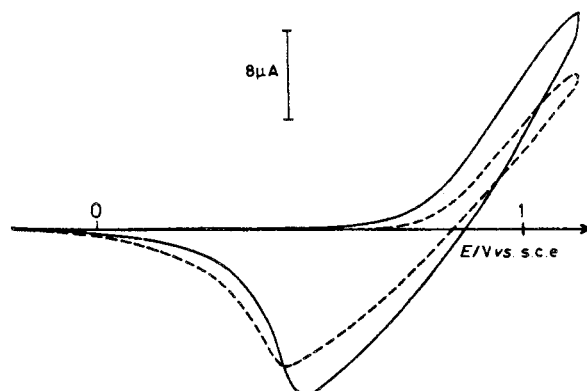
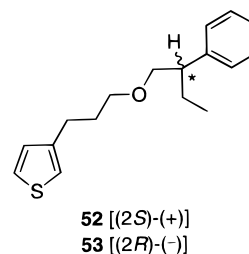


Figure 7. CV of chiral poly(**52**) using 0.1 M chiral anions as doping agents: (—) (+)-10-camphorsulfonic acid and (---) (–)-10-camphorsulfonic acid in CH_3CN . (Reprinted with permission from ref 81. Copyright 1988 The Royal Society of Chemistry.)

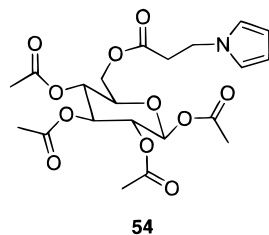
for monomers **52** and **53**, and electropolymerized films led to drastic increases in optical rotations in the polymeric state for poly(**52**) and poly(**53**) as a result of the polymer forming a helical structure. CVs



of poly(**52**) and poly(**53**) using LiClO_4 electrolyte in CH_3CN reveal two redox couples in both cases (Figure 6). A dramatic change in the CV was observed when using (±)-10-camphorsulfonic acid, an optically active anion as the electrolyte in CH_3CN (Figure 7). The most profound effect is partial passivation of the polymer film. A principle cause is likely the reduced ability of the new camphorsulfonic acid counterion

to diffuse into the film as is required to maintain neutrality. This explanation is consistent with the lack of electrochemical reversibility observed with this electrolyte, which would be associated with these kinetic barriers. Depending upon the optical sign of the camphorsulfonic acid, the electrochemical irreversibility could be improved (i.e., lower overpotentials required for oxidation and reduction). This would indicate a preference for specific diastereomeric interactions which facilitate the diffusion of the electrolyte into the polymer. It was also calculated when using a film of poly(**52**); the doping level was 50% higher than when using (+)-10-camphorsulfonic acid relative to (–)-10-camphorsulfonic acid. For poly(**53**), a 24% higher increase in doping level for (–)-relative to (+)-10-camphorsulfonic acid was observed. No explanation was given for the difference in doping levels for poly(**52**) and poly(**53**) toward their preferred chiral anion. For comparison, a control experiment with poly(3-methylthiophene) showed no differences in doping level over a given potential region when using either (+)- or (–)-10-camphorsulfonic acid. The explanation posed by the authors is that oxidation of poly(**52**) and poly(**53**) in the presence of (+)- or (–)-camphorsulfonic acid forms two different diastereoisomeric combinations which differ both kinetically and thermodynamically. The irreversible behavior of the electrochemistry precludes extracting thermodynamic information necessary to substantiate thermodynamic contribution. The difference in oxidation rate, the rate of incorporation of (+)- or (–)-10-camphorsulfonic acid into the polymer film, is generated by the stereoselective recognition of the chiral electrolyte during redox cycling.^{81–83}

In 1992, Saint-Aman and co-workers reported a pyrrole unit functionalized with a pendant optically active 1,2,3,4-tetra-*O*-acetyl- β -D-glucopyranose group (**54**).⁸⁴



Monomer **54** was electropolymerized in 0.1 M Bu₄NPF₆/CH₃CN on an ITO electrode, and the resulting polymer exhibited a quasi-reversible redox wave at $E_{1/2} = 0.60$ V. The optically active poly(**54**) film exhibited a value of $\alpha_D^{25} > 500^\circ$ resulting from helicity of the polymer. The enantioselective properties of poly(**54**) were determined by examining the CV behavior in the range from –0.4 to 0.6 V (vs SCE) in the presence of chiral doping agents (+)- or (–)-10-camphorsulfonic acid, as done for poly(**52**) and poly(**53**). In this range, poly(**54**) was electrochemically cycled and a significantly larger current was passed when using (–)-10-camphorsulfonic acid as an electrolyte (Figure 8). Also during electropolymerization, a higher amount of (–)-10-camphorsulfonic acid in comparison to (+)-10-camphorsulfonic acid was incorporated into the film using Bu₄NPF₆ as supporting

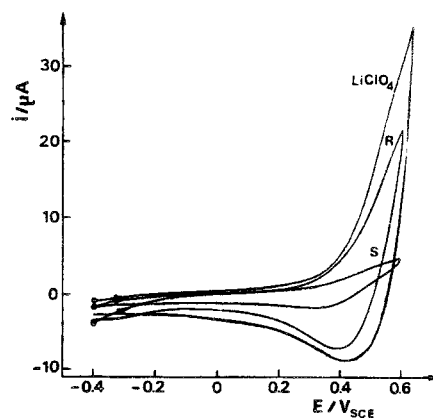


Figure 8. CVs of poly(**54**) using the chiral anion as doping agents: curve R denotes electrolyte (1*R*)-(–)-10-camphorsulfonic acid, curve S denotes (1*S*)-(+)-10-camphorsulfonic acid, and curve LiClO₄ denotes 0.1 M LiClO₄/H₂O. (Reprinted with permission from ref 84. Copyright 1992 Wiley-VCH Publishers.)

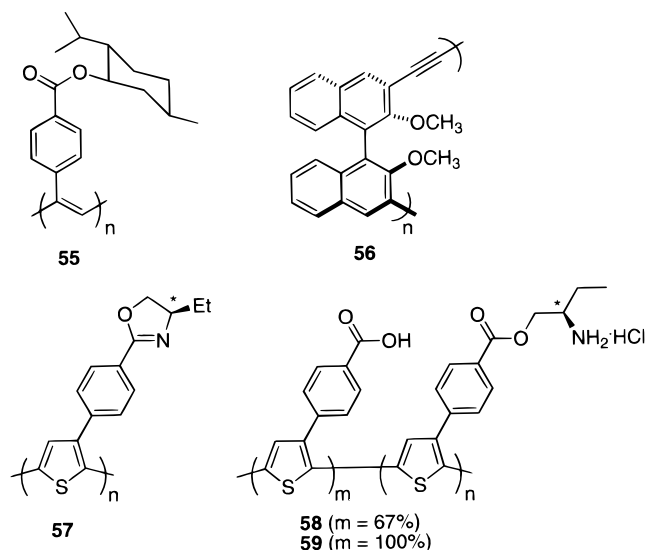
electrolyte in CH₃CN or H₂O. A parallel experiment was carried out in the electropolymerization of achiral 3-(pyrrol-1-yl)propionic acid, and no difference was found with levels of incorporation of (+)- or (–)-10-camphorsulfonic acid. It was found that during electropolymerization of poly(**54**), if (+)-10-camphorsulfonic acid or a racemic mixture of (±)-10-camphorsulfonic acid is added to the Bu₄NPF₆ electrolyte solution, polymerization is inhibited, while in the presence of (–)-10-camphorsulfonic acid the polymerization proceeds. This result is presumably due to the higher solubility of poly(**54**):(+)-10-camphorsulfonic acid arising from selective interactions, which may also explain the enantioselective properties found in the CV experiments.⁸⁴

In 1993, Aoki et al. reported a poly(phenylacetylene) functionalized with an optically active *p*-(1-(–)-menthoxycarbonyl) unit.⁸⁵ Polymer **55** was chemically synthesized and had much higher optical rotations of ($\alpha_D^{20} > -500^\circ$) than that displayed by the monomer ($\alpha_D^{20} = -68.8^\circ$) in CHCl₃. The polymer solution was cast into membrane form, and the enantioselectivity of **55** was determined by its permeability to (+)- or (–)-tryptophan. Applying a pressure of 1.8×10^{-12} m²/h over a period of 600–3000 h with a methanolic solution of (±)-tryptophan, the membrane showed an enantiomeric selectivity of 54–55% for (+)-tryptophan over (–)-tryptophan.⁸⁵

Fluorescence intensity changes in an oligomeric binaphthyl system upon exposure to chiral amines were observed by Wang and co-workers.⁸⁶ Sensitivity to D- and L- α -phenylethylamines and D- and L-phenylalanine methyl esters was shown by oligomeric system **56**. The authors observed relative changes in the quantum yield of **56** upon exposure to chiral amines. No shifts in the emission wavelength were observed. At an α -phenylethylamine concentration of $10\text{--}15(\times 10^{-5})$ M in CH₃CN, the ratio $[\phi/\phi_0]_L/[\phi/\phi_0]_D$ (ϕ_0 = fluorescence quantum yield of **56**; ϕ = fluorescence quantum yield of solution) was found to be 1.37. At a lower concentration range of $2\text{--}5(\times 10^{-5})$ M, a value of 1.07 was reported. Negligible changes in the fluorescence intensity in the presence of L- and D-phenylalanine methyl esters were observed with

values of 0.98, 0.96, and 1.10 for $[\phi/\phi_0]_L/[\phi/\phi_0]_D$ reported at concentrations of $2-4(\times 10^{-5})$, 5×10^{-5} , and $7-9(\times 10^{-5})$ M, respectively. The enantiomeric discrimination found for L- and D- α -phenylethylamines was postulated to be due to π - π interactions of the binaphthyl portion of **56** and the phenyl portion of the chiral amines and also from stereoselective recognition of the chiral amines by the helical oligomer.⁸⁷

Yashima and co-workers synthesized optically active, regioregular polythiophenes (**57-59**)⁸⁸ which exhibit a change in circular dichroism in the presence of metal ions and chiral amines. Polymer **57** was



assembled using McCullough and CuO-modified Stille cross-coupling methods.⁸⁸ An equimolar amount of partially soluble $\text{Cu}(\text{OTf})_2$ suspended in a CHCl_3 solution of **57** induced a split-type circular dichroism in the π - π^* region ($\lambda_{\text{max}} = 450$ nm). The intensity in the circular dichroism signal was also shown to increase with time. It was postulated that intermolecular coordination of Cu^{2+} to the nitrogen atoms of the oxazoline groups may lead to the assembly of a helical arrangement, which is manifested in the circular dichroism spectra. Similar circular dichroism responses were observed in the presence of Cu(I) and Fe(III) but with much less intensity.⁸⁸ UV-vis measurements of the same solution showed only negligible shifts in λ_{max} . Polymers **58** and **59** were synthesized from **57** in two steps via acid hydrolysis of the pendant oxazoline group followed by saponification of the resulting amino ester. In the presence of enantiomers *R*- and *S*-2-amino-1-butanol or *R*- and *S*-2-amino-1-propanol in DMSO, induced split-type mirror images in the circular dichroism were observed for **58**. Completely hydrolyzed polymer **59** could not be studied due to its insolubility.⁸⁸

D. Conjugated Polymers Functionalized with Novel Receptor Units and Architectures

The following section compiles a large number of CP-based systems composed of a diverse array of receptor and structural units. In 1988, Bidan et al. reported a 1,10-phenanthroline-based ligand with pendant alkyl chain tethered pyrrole groups (**60**).⁸⁹ Two ligands combine to chelate Cu^+ in a tetrahedral

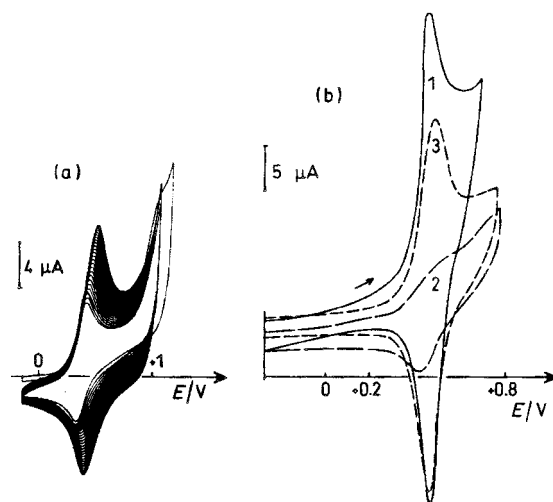
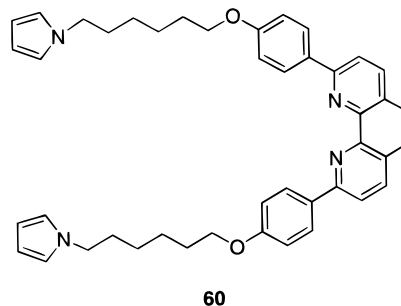


Figure 9. (a) Electrodeposition of $[\text{Cu}(\mathbf{60})_2]^+$ onto a Pt electrode in 0.1 M $\text{Et}_4\text{NClO}_4/\text{CH}_3\text{CN}$ (vs Ag/Ag^+). (b) Curve 1 is $\text{poly}([\text{Cu}(\mathbf{60})_2]^+)$ in 0.1 M $\text{Et}_4\text{NClO}_4/\text{CH}_3\text{CN}$. Curve 2 is the CV of a film of $\text{poly}([\text{Cu}(\mathbf{60})_2]^+)$ after immersion (30 min) in KCN solution. $\text{Poly}([\text{Cu}(\mathbf{60})_2]^+)$ is then immersed (30 min) in 0.2 M $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{BF}_4)/\text{CH}_3\text{CN}$ followed by rinsing and is denoted by curve 3. (Reprinted with permission from ref 89. Copyright 1988 The Royal Society of Chemistry.)

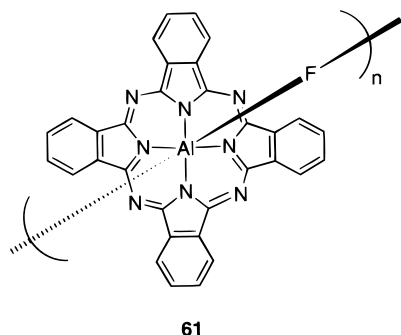
fashion, and the resulting complex ($[\text{Cu}(\mathbf{60})_2]^+$) was electropolymerized in 0.1 M $\text{Et}_4\text{NClO}_4/\text{CH}_3\text{CN}-\text{CH}_2\text{-Cl}_2$. The CV of $\text{poly}([\text{Cu}(\mathbf{60})_2]^+)$ exhibits a defined



reversible wave at 0.4 V, attributed to the $\text{Cu}^{2+}/\text{Cu}^+$ couple superimposed on a broad oxidation wave due to the polypyrrole. Cyclic voltammetry was used to monitor the coordinating ability of $\text{poly}([\text{Cu}(\mathbf{60})_2]^+)$. The film was demetalated by rinsing with a $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ solution of KCN, which resulted in a loss of electroactivity of the wave observed at 0.4 V. The film was subsequently washed in a solution of $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{BF}_4)$ which led to a reemergence of the $\text{Cu}^{2+}/\text{Cu}^+$ wave (Figure 9). In comparison, ligand **60** electropolymerized in the absence of the copper ion resulted in films that did not effectively bind metal ions. It was concluded that a template effect resulted from the polymerization of $[\text{Cu}(\mathbf{60})_2]^+$ followed by demetalation left cavities of a similar geometrical size and tetrahedral coordination in the film, which could be used for subsequent metal ion sensing.⁸⁹ Further studies of system **60** showed similar demetalation and remetalation with Zn^{2+} and Co^{2+} .⁹⁰

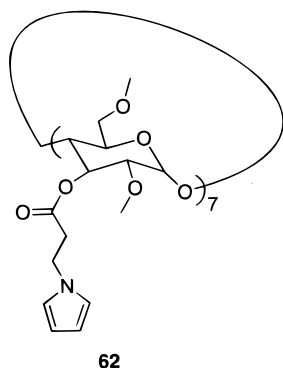
Metallophthalocyanine and metalloporphyrin polymers have been examined extensively as chemosensor materials.⁹¹⁻⁹⁴ Although monomeric phthalocyanines and porphyrins have been used for the same

applications, the polymeric forms are advantageous due to higher ordered chainlike structures, lower volatility, and more rigid morphology. A fluorine-bridged aluminum phthalocyanine (Alpc) polymer has been reported by Wright that has been shown to be sensitive toward NO₂ gas (**61**).⁹¹ Films of **61**



approximately 175 nm thick were deposited by sublimation on interdigitated Pt electrodes in order to examine the semiconductive behavior in the presence of NO₂. Studies on these devices revealed that the current (i.e., conductivity) increased from below the detection limit to approximately 2×10^{-4} A upon exposure to 300 ppb of NO₂ over a period of 10^4 s at 200 °C (applied potentials were not given). The slow response time was attributed to desorption of O₂ and H₂O before NO₂ could be adsorbed. Upon adsorption, the increase in conductivity was ascribed to the formation of charge-transfer interactions between Alpc units and the electron acceptor NO₂, which lowers the activation energy for charge carrier generation.⁹¹

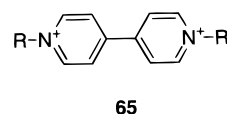
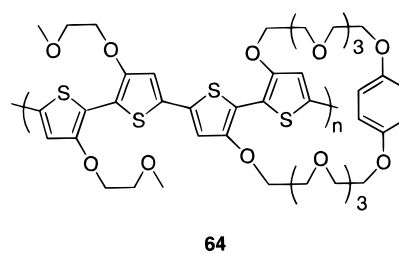
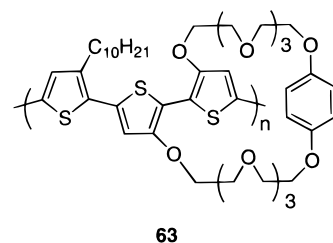
In 1993, Lepretre et al. showed that polymers derived from a cyclodextrin-functionalized pyrrole exhibited molecular recognition.⁹⁵ Cyclodextrins are cyclic glucopyranose oligomers which have the ability to form host-guest complexes. Monomer **62** was electropolymerized on Pt at a constant potential to give poly(**62**), which exhibited a single broad oxidation peak with $E_{1/2} = 0.3$ V (vs Ag/Ag⁺). In this study,



the authors used the polymerization of pyrrole as a method for the immobilization of the cyclodextrin hosts into a film. To remove unwanted electroactivity, the polypyrrole was oxidatively decomposed at a high potential (1.3 V). This prevented any overlap of the polymer redox waves with those of the molecules to be detected. The voltammetric response of guest molecules ferrocene and phenothiazine were examined in 0.1 M Bu₄NPF₆/CH₃CN and 0.1 M LiClO₄/

H₂O. The complexation levels of electroactive guest molecules in poly(**62**) were determined by calculating the amount of current passed in the anodic wave and comparing that to the number of cyclodextrin units in the film determined from the electroactivity of the initial polypyrrole film (about 7 pyrrole units per cyclodextrin macrocycle). Incorporation of ferrocene and phenothiazine was found to be nearly quantitative, and the electroactivity of the guests was proportional to the film thickness over a guest concentration of 10–50 mM. Competition experiments were carried out by addition of electroinactive (Bu₄N)₂NDS (NDS = 1,5-naphthalenedisulfonate) to solutions containing either ferrocene or phenothiazine. These studies show that NDS²⁻ does not compete with ferrocene binding, as no decrease in the surface-confined ferrocene wave was observed with added NDS²⁻. In contrast, NDS²⁻ could completely displace the phenothiazine units from the films. On the basis of these results, poly(**62**) films were found to display the following selectivity for ferrocene > NDS²⁻ > phenothiazine. This trend was found to be the same in both CH₃CN and H₂O.⁹⁵

Swager and co-workers demonstrated in 1994 that receptor-containing polythiophenes **63** and **64** gave chemoresistive and potentiometric responses to a cationic 4,4'-bipyridyl guest, **65**. This study,⁹⁶ fol-



lowed by subsequent investigations,⁹⁷ was the first report of molecular recognition-based reversible chemoresistive responses that thereby utilized the full potential of CPs as transducing agents. A cyclophane receptor was integrated in these polythiophenes which binds paraquat (**65**, R = CH₃) and related species that behave as strong π -electron acceptors. The authors carried out control studies on model polymers with the same electronic structure but lacking the cyclophane receptor and showed the receptorless materials to display negligible changes in conductivity. An X-ray crystal structure with a paraquat guest revealed that the system displays a rotaxane structure in which the guest pierces through

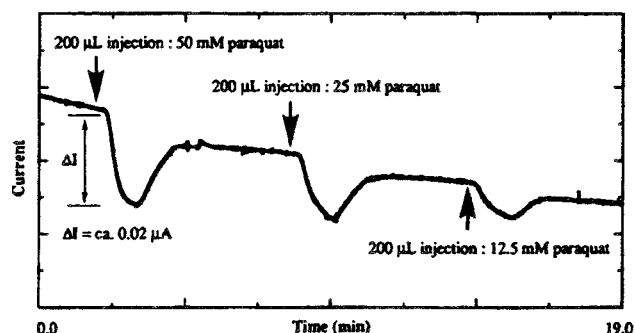
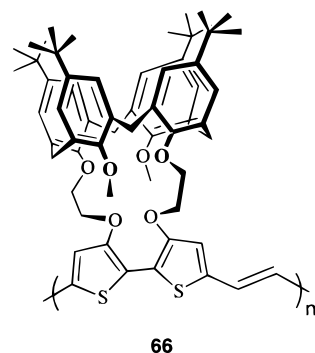


Figure 10. Chemoresistive response of a flow cell device fabricated from **64** electrochemically oxidized to -0.1 V (vs Ag wire). The plot shows the current flowing with a 50 mV offset potential between the electrodes versus time as 200 μ L of paraquat solutions of variable concentration were injected into the mobile phase (0.1 M LiClO₄/CH₃CN:H₂O (1:1), flow rate = 0.2 mL/min). (Reprinted with permission from ref 97. Copyright 1995 American Chemical Society.)

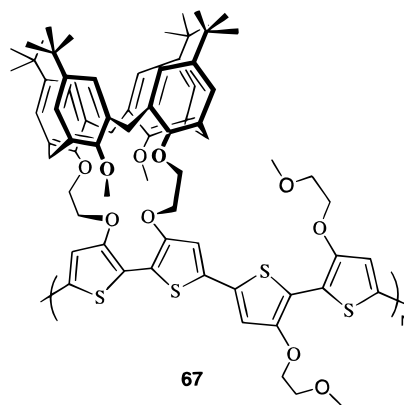
the center of the macrocycle. This structure produces strong π - π interactions between the electron-poor guests and the electron-rich thiophene-based receptor. The binding constant with paraquat was determined to be 1360 M⁻¹, a value considerably larger than isostructural nonthiophene analogues.⁹⁷

The conductivity of polythiophenes **63** and **64** are very sensitive to the binding of paraquat.^{96,97} The initial studies were performed with a stronger acceptor analyte where the 4,4'-bipyridyl group is alkylated with a *p*-fluorobenzyl group, **65** (R = CH₂C₆H₄F). Upon exposure to 45 mM of this guest, polymer **63** maintained reversible electroactivity with a 99 mV anodic shift and a 52% decrease in conductivity. Studies with paraquat showed much smaller potential shifts, and in the case of **63**, the shift was actually cathodic, presumably due to a planarization of the backbone. Nevertheless, in all cases exposure to paraquat resulted in a reduction in conductivity. The origin of the conductivity changes were ascribed to charge-transfer interactions between the polymer's π -electrons and the empty orbitals of the guest, as well as electrostatic repulsions between the charges of the guests and the cationic carriers in the polymer. These results are also consistent with the larger responses observed for the more electron-rich polymer, **64**. Studies with a flow cell were performed (Figure 10) that demonstrate the rapid reversibility of the system as well as the fact that the magnitude of the response scaled with the amount of paraquat injected.

Novel calix[4]arene-functionalized systems **66** and **67** were reported by Swager and co-workers in 1995 that exhibit chemoselective properties.^{98,99} Polymers **66** and **67** were chemically synthesized by a Stille-type cross-coupling method with $M_n = 47\,000$ for **66** and 22 000 for **67**. Binding constant measurements of the calix[4]arene-bithiophene moiety resulted in $K_a = 7.6 \times 10^7$ for Na⁺ and the binding constants approximately 100 times lower for K⁺ and Li⁺. Ionochromic responses of the polymers in THF toward Li⁺, Na⁺, and K⁺ (0.5 mM) were examined using UV-vis absorption and fluorescence emission spectroscopy. Solutions of **66** and **67** showed similar λ_{\max} values (498 and 500 nm, respectively), and both systems showed near perfect selectivity toward Na⁺,



66



67

with a 24 nm blue shift seen in **66** and 32 nm red shift for **67**. Neither polymer exhibited spectral shifts for Li⁺, while only **66** exhibited a response to K⁺ ($\Delta\lambda_{\max} = -8$ nm). The calixarene-containing monomer displayed complex conformational behavior, and it appears from this work as well as later studies that the electronic properties of the polymer strongly influence the conformation, *vide infra*. For **67**, the red shift was attributed to a planarization of the bithiophene units by the strong binding of Na⁺. Hence, for **67**, the equilibrium uncomplexed conformation of the bithiophene in the uncomplexed macrocycle is less planar. The blue shift observed for **66** with Na⁺ binding suggests a more planar equilibrium conformation in the absence of Na⁺. Fluorescence measurements for **67** showed a 6 nm λ_{\max} shift to lower energy and a sharper peak upon Na⁺ complexation. The peak narrowing was attributed, as is consistent with the UV-vis absorption, to an increase in the population of planarized bithiophene sites by Na⁺ complexation. The ionochromic responses of **66**–**68** are complicated by the electronic and steric factors controlling the polymers conformation and the conformational flexibility of the calix[4]arene core. These two factors provide a system that is difficult to fully understand. Cyclic voltammetric and resistivity responses of **67** were measured in 0.1 M Bu₄NPF₆/CH₃CN. The instability of **66** in its oxidized state prevented chemoresistive studies; however, **67** displays an anodic shift of > 100 mV in the oxidation potential in the presence of 0.5 mM Na⁺. This effect is expected based on electrostatic factors and the reduced ability of the Na⁺ complexed oxygens to donate electron density to the polymer's π -electron system. No voltammetric effect was seen with exposure to K⁺, and very little change was seen with Li⁺. Conductivity measurements of films of **67** on interdigitated micro-

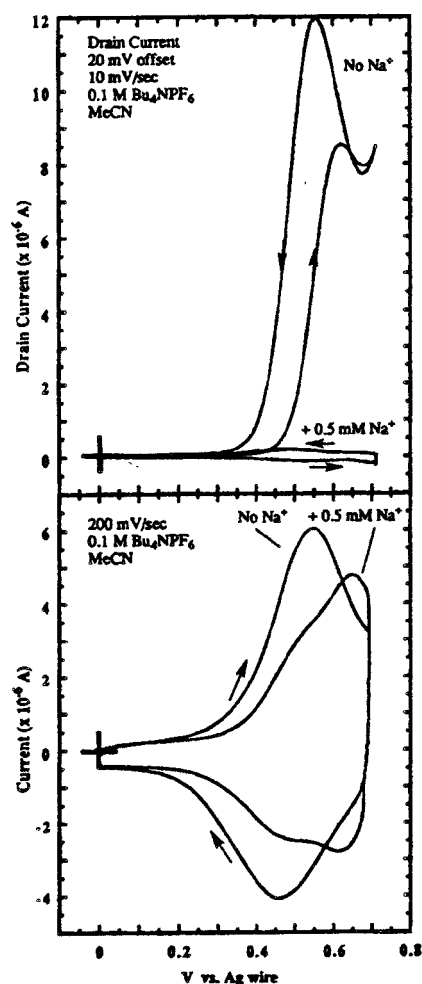


Figure 11. CV (bottom) and corresponding drain current (conductivity) studies (top) for **67** in the absence and presence of Na^+ . (Reprinted with permission from ref 97. Copyright 1995 American Chemical Society.)

electrodes showed a >99% decrease in peak conductivity upon exposure to Na^+ . Both the voltammetric and resistivity responses are in contrast with optical measurements that suggested a more planar conformation with Na^+ complexation. Hence, electrostatic repulsions with the carriers and reduced donation of the oxygen lone pairs are adequate to dramatically change the polymers conductivity. The system was reversible, although the Na^+ ions are only removed by maintaining the films in a highly oxidized state. The latter feature is a result of the fact that the receptor's binding constant is a function of the oxidation state of the polymer.

Additional studies of **67** illustrate the superior sensitivity of conductivity as a transduction signal relative to absorption and potentiometric changes. Although Li^+ and K^+ produced little to no change in the optical and voltammetric response of the polymers, ionoresistive measurements on **67** displayed significant conductivity decreases. This was ascribed to electrostatic repulsions between the bound alkali metal cations and the positively charged carriers in the p-doped polymer backbone. The authors concluded that the oxidation potential and UV-vis absorption data are controlled by the local environment in the polymer. On the other hand, conductivity

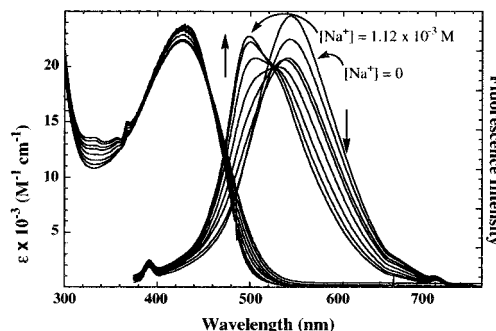
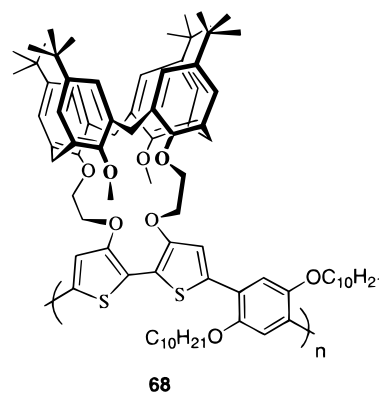


Figure 12. Absorption and emission spectra of **68** showing changes with increasing concentrations of Na^+ . (Reprinted with permission from ref 100. Copyright 1998 American Chemical Society.)

is a collective effect of the entire polymeric system and thereby amplifies small perturbations induced by weak analyte binding.^{1,98,99}

Swager's Lab in 1998 incorporated the same receptor into a poly(phenylene bithiophene) backbone (**68**).¹⁰⁰ Polymer **68** was chemically polymerized, and

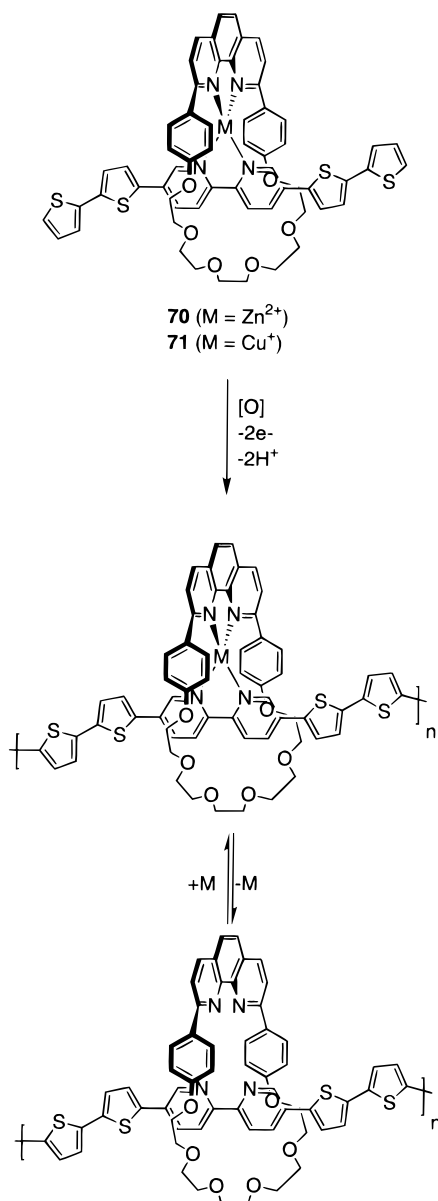


the sensitivity of **68** to Li^+ , Na^+ , K^+ , and Ca^{2+} was investigated by absorption and fluorescence spectroscopy. The calix[4]arene receptor, similar to what was reported for **66** and **67**, in **68** displayed a highly selective response to Na^+ . It was shown that the addition of Li^+ or K^+ to a solution of **68** in THF exhibited negligible changes in the absorption or emission spectra. However, when the concentration of Na^+ was incrementally increased to $1.12 \times 10^{-3} \text{ M}$, the progressive growth of a dramatic blue-shifted emission ($\Delta\lambda_{\text{max}} = -50 \text{ nm}$) at 548 nm was observed. In contrast, the absorption spectra exhibited only a slight increase over concentration ranges of Na^+ (Figure 12). The sensitivity of **68** to Ca^{2+} was investigated due to its similar size to Na^+ but showed no concentration-dependent response in the absorption or emission spectra. This was attributed to the greater enthalpy of solvation for Ca^{2+} and to the preference of Ca^{2+} to be eight coordinate versus the six-coordinate binding offered by the binding site.

On the basis of the lack of response in the absorption data, it was concluded by the authors that ion complexation does not alter the ground-state bithiophene conformation of **68**. In this case, the bithiophene groups favor a twisted ground-state conformation. This is in contrast to that found in systems **66** and **67**, where Na^+ complexation induces significant λ_{max} shifts. On the basis of the dramatic emission changes

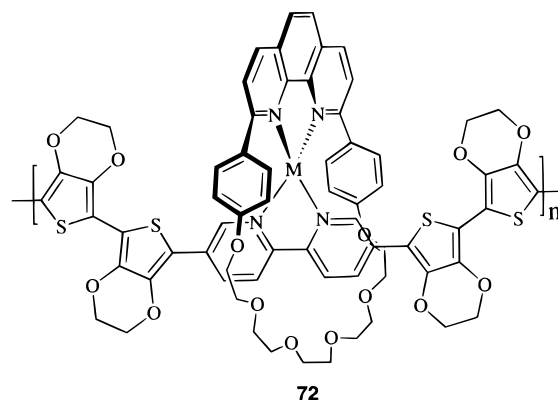
with Na^+ , the excited state of the uncomplexed receptor was proposed to relax to a planar conformation. This explanation is consistent with the large intrinsic Stokes shift, and the authors propose that with Na^+ complexation, the calixarene–bithiophene units are locked in the ground-state twisted conformation. The result is a smaller Stokes shift and a shorter emission wavelength. A monomeric model compound shows the same spectroscopic effects, although the response as a function of concentration was different from that of the polymer. This difference for the polymer was attributed to energy migration along the backbone which allowed the excitations to migrate to an uncomplexed site that can relax to a planar conformation and fluoresce at a longer wavelength.¹⁰⁰

In 1996, CP-based metallorotaxanes¹⁰¹ were developed by Zhu, Carroll, and Swager that were capable of responding to transition metal ions.¹⁰² A macrocyclic phenanthroline⁹⁸ was threaded with bis(4,4'-bithiophenebipyridine) (**69**) mediated by metal coordination to form metallorotaxane monomers **70** and **71**. A λ_{max} red shift of 60 nm in the absorption of the



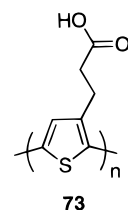
threading unit was observed upon Zn^{2+} coordination. Electropolymerization of the threading unit, **69**, was carried out on assembled metallorotaxane complexes in 0.1 M $\text{Bu}_4\text{NPF}_6/\text{CH}_2\text{Cl}_2$. Both poly(**70**) and poly(**71**) exhibit two ligand-centered redox waves at 0.96 and 1.23 V (vs Ag wire), while poly(**69**) shows two poorly resolved peaks. Conductivity experiments as a function of applied electrochemical potential on interdigitated microelectrodes for poly(**70**) and poly(**71**) are similar, with maxima at the half-wave potentials, while poly(**69**) exhibits only one peak. Poly(**70**) and poly(**71**) show reversible metal coordination that was not displayed by films composed of poly(**69**) alone. These results and other studies confirm that the phenanthroline macrocycle is physically entrapped around chains of the poly(**69**) and remains entrapped even when the metal ion is removed. When a film of Zn^{2+} -coordinated poly(**70**) on indium tin oxide (ITO) coated glass is rinsed in an aqueous ethylenediamine solution, the λ_{max} blue shifts from 501 (red film) to 467 nm (yellow film). Retreatment of the film with Zn^{2+} ions reestablishes the initial absorbance profile of the metal bound polymetallorotaxane. A related system has also been reported to have similar recognition properties.¹⁰³

Further investigations on metallorotaxanes were carried out on **72**, which had more electron-rich thiophene residues.¹⁰⁴ The lower oxidation potential



of the threading unit in this instance coincides with the half-wave potential of the Cu ion. This fact endowed the polymer with a high sensitivity to the presence of Cu^{2+} ion, and treatment of the metal-free polyrotaxane with Cu^{2+} resulted in a 10^6 to 10^7 order of magnitude increase in conductivity. Such large changes in conductivity are suggested to be the result of doping of the polymer. As such, this system represents an example of a molecular recognition-directed doping reaction.

In 1997, McCullough and associates reported a regioregular, water-soluble polythiophene system functionalized with propionic acid groups (**73**).^{105,106}



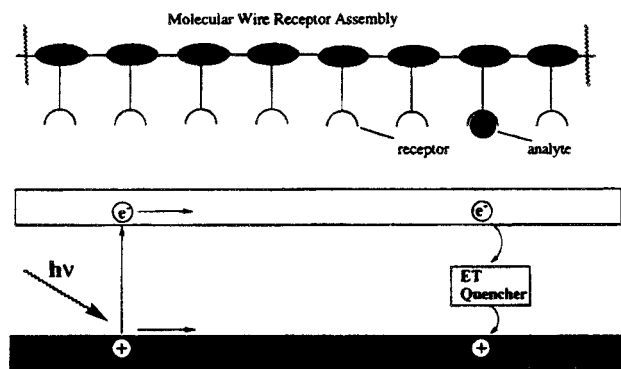
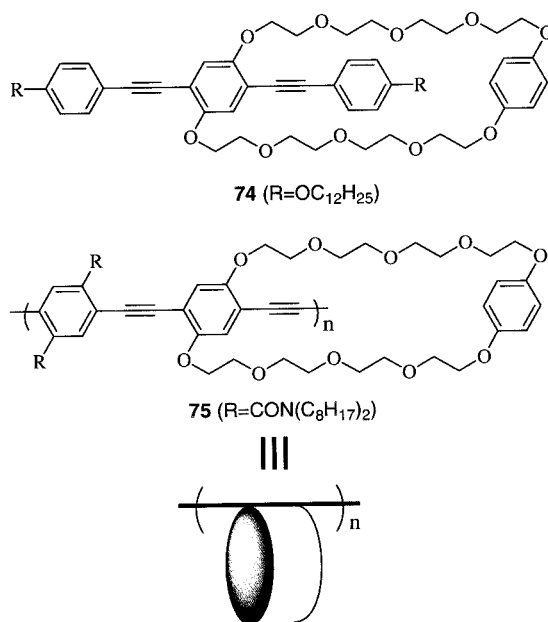


Figure 13. Band diagram illustrating the mechanism by which the molecular wire receptor assembly can produce an enhancement in a fluorescence chemosensory response. The horizontal dimension represents the position along the conjugated polymer shown schematically at the top. Excitons are created by absorption of a photon ($h\nu$) and then migrate along the polymer backbone. Analyte binding produces a trapping site whereby the excitation is effectively deactivated by electron-transfer quenching. (Reprinted with permission from ref 108. Copyright 1995 American Chemical Society.)

The response of **73** to different size counterions in its deprotonated state was investigated in H_2O using UV-vis spectroscopy. Although **73** had limited solubility in H_2O , the addition of NR_4OH ($\text{R} = \text{H}, \text{Me}, \text{Et}, \text{Pr}, \text{Bu}$) induced solubilization via deprotonation and salt formation. The addition of 1 equiv of NH_4OH resulted in a 130 nm red shift (the largest of the bases studied) in the λ_{max} to 540 nm. Progressively smaller red shifts were observed with larger ammonium counterions. The counterion dependence of the absorption response and other studies led the authors to postulate the formation of an aggregated supramolecular assembly directed by hydrophobic polymer-polymer interactions, hydrogen bonding, and/or a salt pairing of the propionic pendant chains (i.e., rodlike phase).^{105,106} When the amount of NH_4OH added to the solution is increased to 5 equiv, the absorption at 540 nm grows along with the formation of a new absorption at 420 nm. At yet higher concentrations of NH_4OH , the peak at 540 nm decreases and eventually disappears as the absorption at 420 nm gains intensity. The absorptions of polymer **73** in the range of 420 nm are observed at all concentrations of NBu_4OH and NPr_4OH . With NBu_4OH , and at very high concentrations of NH_4OH , the authors proposed that the polymer was better solvated, thereby resulting in a lowering of interchain interactions (less aggregation) and the steric requirements of the counterion resulted in twisting of the polymer's conjugation. Thus, **73** is chemoselective since the shifts in λ_{max} correlate to different size bases.^{105,106}

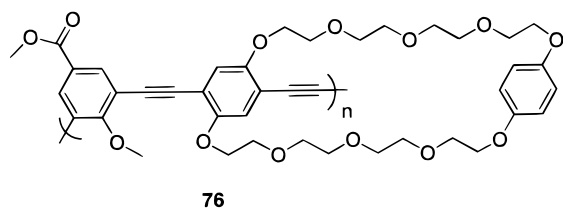
The utility of CPs for fluorescence-based sensing was first demonstrated by Zhou and Swager.^{107,108} A general finding of these studies is that the act of "wiring receptors in series" creates superior sensitivity over a small molecule indicator. The observed amplification is a result of the ability of the CP's delocalized electronic structure (i.e., energy bands) to facilitate efficient energy migration over large distances (Figure 13). To demonstrate this principle, studies were conducted in parallel on a small mol-

ecule indicator containing a fluorescent monomeric cyclophane receptor, **74**, and polymeric analogues of different molecular weights, **75**. The cyclophane



receptors were chosen to bind paraquat and related compounds that are very effective electron-transfer quenching agents. By conducting detailed photophysical studies, these investigators were able to determine that both the monomer and polymer displayed quenching resulting from the binding of the paraquat by the cyclophane to form a rotaxane complex. Comparisons in solution of the quenching demonstrated a greatly enhanced sensitivity of the polymer over the monomeric compound. The proposed origin of this effect is facile energy migration along the polymer backbone to the occupied receptor sites (Figure 13). In this scheme, the signal is amplified due to the fact that the polymer need only have a small fraction of receptor sites occupied to affect complete quenching. In contrast with a monomeric indicator, every receptor must be occupied for complete quenching. The authors demonstrated that the effect was molecular weight dependent and at low to intermediate degrees of polymerization, the signal amplification increased with molecular weight.¹⁰⁷ Once the molecular weight exceeded the average diffusion length of the excitation (ca. $M_n = 100\,000$), the effect was independent of molecular weight. Subsequent studies on thin films of **75** prepared by Langmuir-Blodgett deposition revealed a very high rate of energy transport between polymer layers ($k = 10^{11} \text{ s}^{-1}$) and an average exciton diffusion length that is greater than 100 Å.¹⁰⁹

Additional studies examined the role of molecular structure on the ability of the polymers to produce amplification.¹⁰⁸ Comparisons of a polythiophene **63** and a meta-conjugated substituted poly(phenyleneethynylene) **76** showed these systems to have diminished ability to amplify paraquat quenching. The lower performance of these systems was attributed to the reduced ability to undergo energy transport in **76** due to the lack of long-range conjugation and a decrease in fluorescence efficiency in **63**.



The signal amplification resulting from energy migration in CPs was applied in 1998 by Yang and Swager for the detection of explosives, specifically 2,4,6-trinitrotoluene (TNT) and 2,4-dinitrotoluene (DNT).^{13,14} The impetus behind developing such a system is the fact that there are roughly 120 million unexploded land mines worldwide and current methods of detection are limited.¹¹⁰ The challenge is to detect minute amounts of explosives leached from the land mines. These studies extended the methods reported by Zhou and Swager on isolated molecules in solution^{107,108} to thin film structures. The energy migration-based amplification is much greater in thin films, which display two- or three-dimensional structures, as compared to what is found in one-dimensional systems (i.e., isolated polymers in solution).¹⁰⁹ This effect is due to the fact that in one dimension a random walk of excitations necessarily revisits the same receptor sites multiple times. The amplification is increased by the excitation sampling the greatest number of potential analyte binding sites. Hence, a three-dimensional topology, wherein it is improbable that an exciton will visit the same site multiple times, is superior. To facilitate binding of TNT and DNT, as well as create a stable emissive thin film of a poly(phenyleneethynylene), Yang and Swager developed a series of porous polymers utilizing a rigid shape-persistent iptycene scaffold. The porous structure served to prevent direct interactions between the polymer backbones (chromophores), which generally lead to quenching, and to create a structure that behaves as a "sponge" for electron-poor π -electron-accepting analytes (Figure 14). Harnessing these

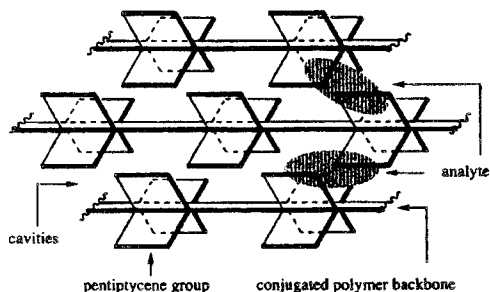
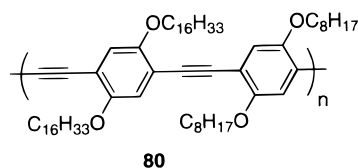
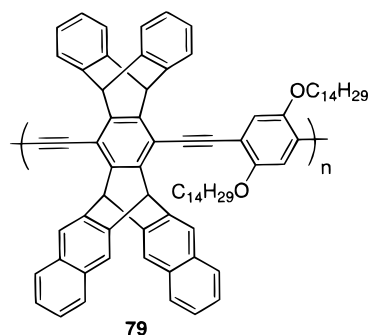
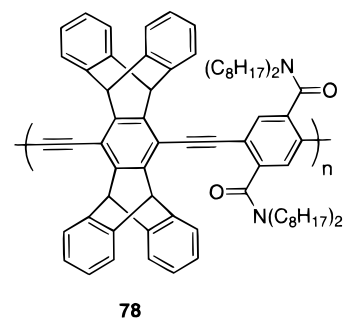
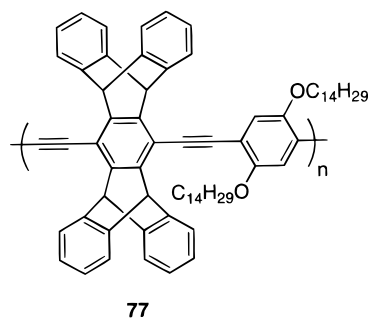


Figure 14. Conceptual drawing of rigid, shape-persistent iptycene-containing polymers and resulting porous structure. (Reprinted with permission from ref 14. Copyright 1998 American Chemical Society.)

design principles, polymers **77–79** were designed and compared to iptycene-less **80**.^{13,14} Polymers **77–80** were assembled using Pd-catalyzed cross-coupling chemistry.

Absorption and fluorescence emission spectra were measured as films were exposed to equilibrium vapor pressures of various analytes. For polymer **77**, it was observed that a series of nitro-containing, strongly



electron-accepting analytes similar in structure and including TNT and DNT significantly quenched fluorescence by an electron-transfer mechanism. Thin films of **77** displayed a sizable quenching within seconds of exposure to 10 ppb of TNT vapor, thereby demonstrating the extraordinary sensitivity imparted by energy migration.

Films of **77–79** displayed selectivities toward electron-poor analytes that were consistent with their electronic structure and size-exclusion characteristics. Systematic studies were done on a range of analytes, and in particular it was found that a series of quinones, despite having higher vapor pressures and greater electron affinities than their nitro-containing counterparts, did not effectively quench fluorescence of very thin films. Polymer **77** further revealed an interesting quenching dependence on film thickness that provided further insight into the diffusion mechanisms of the analytes. Thin films (25 Å) displayed a higher degree of quenching with nitro-

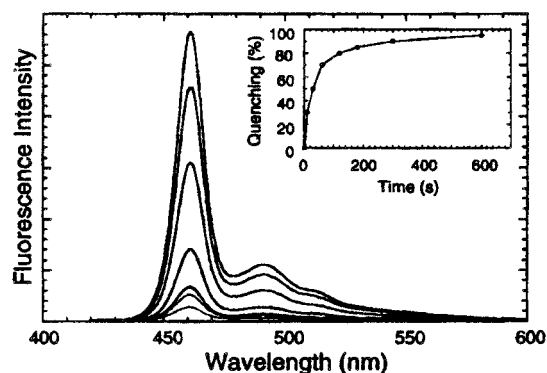


Figure 15. Time-dependent fluorescence intensity of **77** in a 25 Å film upon exposure to TNT vapor (room temperature) at 0, 10, 30, 60, 120, 180, 300, and 600 s (top to bottom), and the fluorescence quenching (%) as a function of time (inset). (Reprinted with permission from ref 14. Copyright 1998 American Chemical Society.)

containing analytes, while thicker films (200 Å) were more effectively quenched with quinone-based analytes. The 25 Å films of **77** can be quenched with polymer surface–analyte interactions, thereby making diffusion behavior relatively unimportant. Thicker films are quenched better with fast diffusing analytes. Additionally, when the binding constants were lower, thicker films were necessary to sequester the analytes effectively. Poor quenching by nitro analytes in thick films was attributed to slow analyte diffusion due to stronger electrostatic binding interactions with the polymer. The role of the nitro group was further understood when comparing the number of nitro groups in the analyte to the differences in fluorescence quenching for 25 vs 200 Å thick films (film thickness effect). It was shown that analytes with more nitro groups displayed larger film thickness effects, probably due to the stronger electrostatic interactions with the polymer. The increased quenching of thick films of **77** by the quinone-based analytes (80%) versus the nitro compounds (30%) was attributed to the smaller electrostatic interactions with the polymer and higher vapor pressures. Also, the high amount of quenching in a short amount of time (60 s) supports the design strategy of using iptycene groups to induce porosity into the films (Figure 15). The most electron-rich polymer, **80**, showed the smallest amount of quenching (20%) in thin films (30 Å) from exposure to TNT for 60 s. This was attributed to the low porosity of the film due to absence of cavity-forming iptycene groups. Despite having a similar polymer backbone to **77**, polymer **78** tended to show smaller quenching effects to the same analyte conditions. This was attributed to the electron-withdrawing nature of the amide groups, which lowers the electrostatic interactions with the electron-poor analytes. Polymer **79** was designed with extended iptycene units in order to increase porosity size in the bulk polymer. Polymers **78** and **79** exhibit similar fluorescence quenching characteristics in 25 Å films, while in 200 Å films, the quenching is less in **79**. Poorer diffusion as a result of smaller cavity size was attributed to increased overlap of the naphthalene units of the extended iptycene groups.¹⁴

Polyaniline was derivatized with boronic acid groups, which exhibits a response to saccharides.¹¹¹

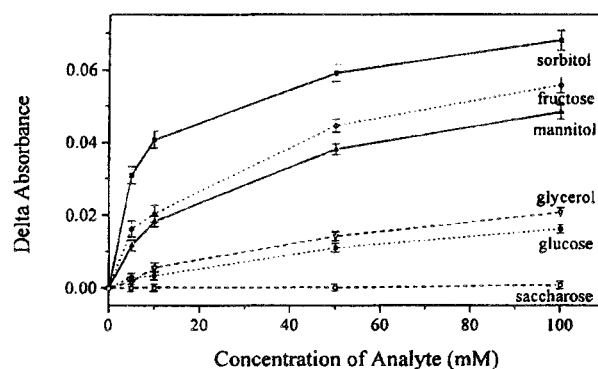
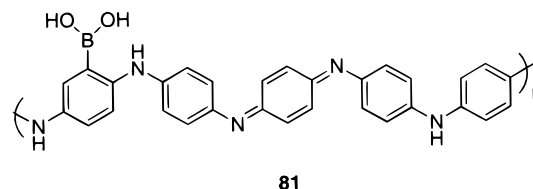


Figure 16. Changes in the absorption at 675 nm for **80** upon addition of increased concentrations of various saccharides (pH 7.2). (Reprinted with permission from ref 111. Copyright 1999 Wiley-VCH Publishers.)

The system developed by Pringsheim et al. is based on the binding reversibility of diols with boronic acids.¹¹² A random copolymer (**81**) was chemically polymerized onto the inner walls of cuvettes from an aqueous solution of aniline and 3-aminophenylboronic acid using $(\text{NH}_4)_2\text{S}_2\text{O}_8$ as oxidant. The sensory



properties of **81** were examined with the saccharides, saccharose, glucose, glycerol, mannitol, fructose, and sorbitol, using optical spectroscopy and compared with underivatized polyaniline. The λ_{max} at 675 nm (pH 7.2) for polymer **81** was monitored during additions of various concentrations of the saccharides. It was shown that sorbitol induced the largest change in absorbance for **81**, while saccharose was the only saccharide studied to not shift the absorbance (Figure 16). No absorbance changes were observed with polyaniline upon exposure to the same series of saccharides. The authors postulated that the absorbance changes seen in **81** may be attributed to a change in boron–nitrogen interactions and/or a decrease in hydroxy–nitrogen hydrogen bonding as a result of the saccharide binding. A third reason was also postulated to be changes in polaron delocalization due to the loss of the negative charge at the boronic acid anion at pH 7.2 from esterification of saccharide binding

III. Biological Sensors

Detecting small quantities of biomolecules is paramount in the diagnosis of diseases such as cancer and for real time monitoring of important blood analytes such as glucose.¹¹³ A major driving force for the integration of natural biomolecular recognition elements into sensors is their exquisite selectivity to specific analytes. Sensors containing natural biomolecular recognition elements are referred to as biosensors. A very popular class of biosensor is enzyme-linked immunosorbent assays (ELISAs). ELISAs can detect many biologically relevant analytes but are

limited by a number of drawbacks: they cannot easily be used in the field, they are time-consuming, and they require labeling of antibodies or proteins. These drawbacks have encouraged research into "reagent-less" sensors that require no additives except for the desired analyte to function. Development of reagent-less biosensors has focused on covalent linking of recognition domains to a solid substrate via a thin film. The recognition domain can be a ligand for the detection of a protein, a single strand of DNA or RNA for sequencing DNA, or a protein for a small molecule sensor.

Biosensors utilizing CPs, as a component in thin films, have been utilized for sensing both large and small biomolecules. Within these CP-based sensors, the transduction of a binding event has been achieved electrochemically, optically, acoustically, and gravimetrically. The topics covered in this section are CPs containing synthetic protein ligands, single-stranded DNA (ssDNA), and enzymes or antibodies. Design strategies employed to transduce binding events and the varied roles played by the CPs will be discussed.

A. Conjugated Polymers with Appended Protein Ligands, Nucleotides, or DNA

Detection of whole cells, individual proteins, or DNA requires that a transducer be attached to recognition elements such as ligands or single strands of DNA. A number of approaches have been published where CPs are used to detect protein–ligand interactions and single-stranded DNA (ssDNA). Electrochemical or optical transduction in most cases is based upon a conformational change in the CP backbone resulting from binding of a macromolecule or cell. The conformation of a CP directly affects the electronic states and thereby produces changes in UV–vis absorption, luminescence, redox potential, and conductivity.

Optical transduction of a macromolecular binding event was demonstrated by Charych et al.,¹¹⁴ with amphiphilic poly(diacetylene) Langmuir–Blodgett films (Figure 17). In one system, lipid diacetylenes containing saccharide headgroups designed to bind to the influenza virus were polymerized to produce a blue film. Upon incubation with the influenza virus the film changed from blue to red. The authors reported that the film upon exposure to the influenza virus provided a concentration-dependent color change. The polydiacetylene approach has been used to sense the interaction of different proteins^{115–117} and whole cells.^{118–125} A number of reviews have also been published that describe polydiacetylenic vesicles and multilayers in greater detail.^{126–128}

Recent investigations by Leblanc et al. provided insight into the mechanism of chromic shifts observed in the polydiacetylenic sensing systems.¹²⁹ Conjugated polydiacetylenes have two distinct absorption bands which correspond to the pure red (λ_{max} at 540 nm) and blue materials (λ_{max} at 640 nm). The change from the blue form to the red form can be affected by a number of factors including conformational changes induced by binding a protein to the surface of a polydiacetylene film. Several hypotheses for the color change have been put forth. The difference in

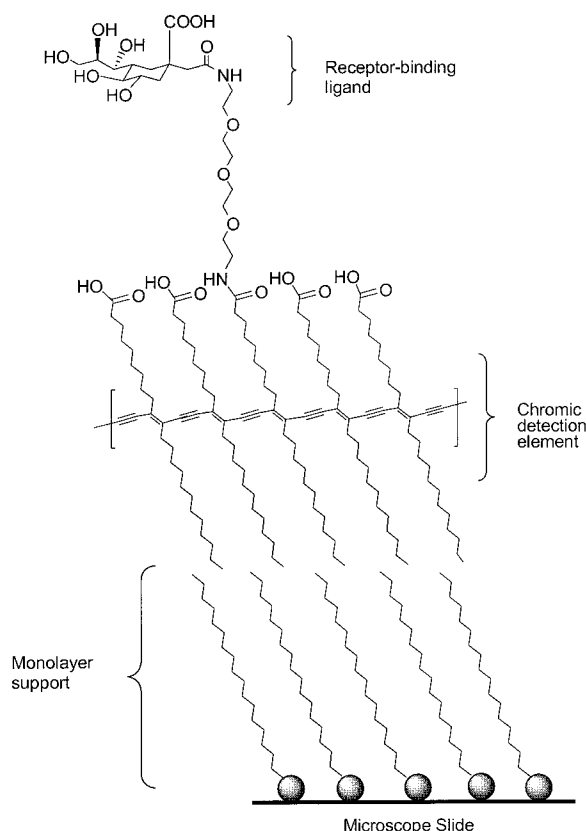


Figure 17. Schematic diagram of polymerized diacetylene bilayer assembly. The sialic acid appendage was used to bind influenza virus particles.

the two forms could be due to the effective conjugation length where the blue form has been conjectured to have a longer conjugation length than the red form.¹³⁰ The reduction in the conjugation length has been proposed to result from conformational disorder of the side chains appended to the polymer backbone.¹³¹ While studying a diacetylene amphiphile containing a cyanuric acid headgroup, Leblanc observed behavior indicating that the side chains were ordered in both the blue and red forms of polydiacetylene. In these systems, the cyanuric acid headgroup can bind either to another cyanuric acid (CA) or to a barbituric acid (BA) forming highly ordered, linear hydrogen-bonded tapes at the air–water interface. Leblanc observed that the CA-functionalized poly(diacetylene) monolayers on a pure water subphase required much longer irradiation (254 nm) times to switch to the red form, which is unique compared to poly(diacetylenes) containing only carboxylic acid headgroups which undergo a transformation to the red form under modest periods of irradiation (254 nm). The CA-functionalized poly(diacetylene) monolayers on a subphase containing CA or BA did not switch to a red form at all; however, longer irradiation times resulted in a broadening of the 640 nm peak. To explain the differences that he observed, Leblanc postulated that the flexibility of the hydrogen-bonding state of the headgroups may be responsible for the differences observed. Leblanc suggested that irradiation to form polydiacetylenes initially results in polymers with long conjugation lengths. Upon further irradiation, the polymers begin to fold resulting in shorter conjugation lengths; this

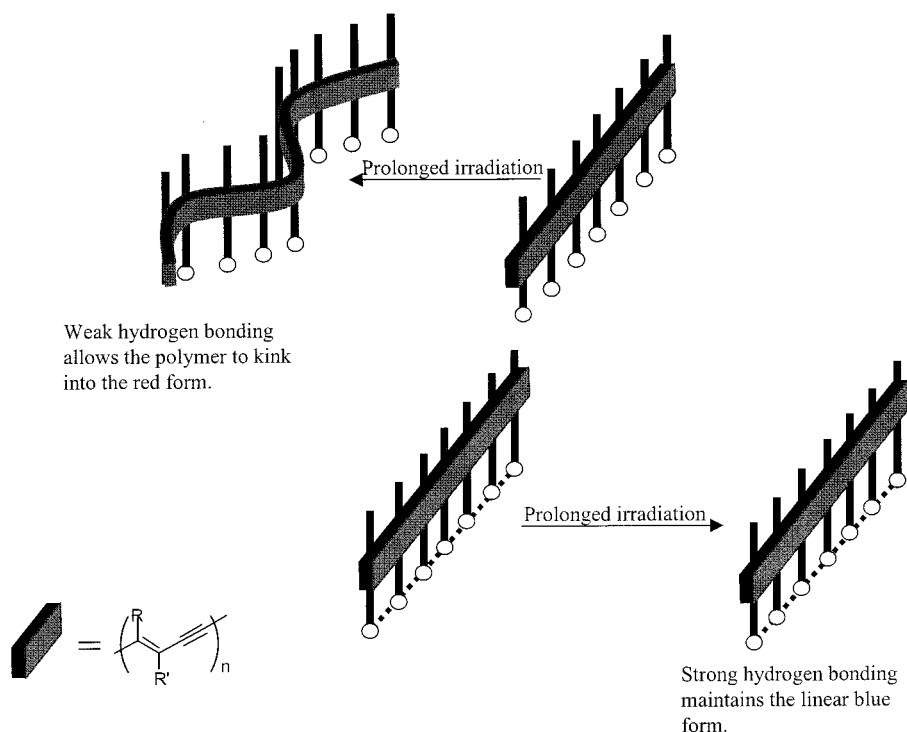
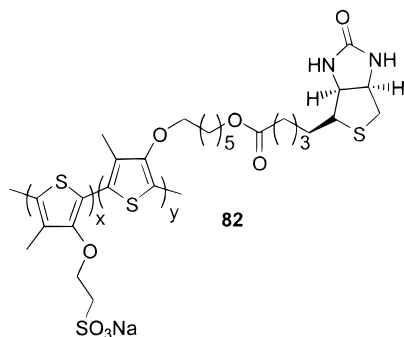


Figure 18. Leblanc's model of poly(diacetylene) folding. Leblanc proposes that prolonged irradiation kinks polymers that do not have strongly hydrogen-bonded headgroups. The kink provides a shorter conjugation length and gives rise to the red form of the polymer.

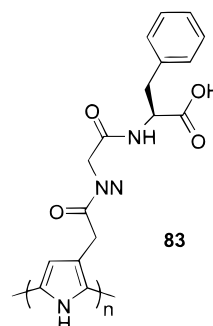
folding is hypothesized to cause the switch from the blue to the red form. To test this hypothesis, Leblanc synthesized polymers containing the CA-capped diacetylenic lipid along with a carboxylic acid-capped diacetylenic lipid in ratios of 10:1, 4:1, 1:1, 1:4, and 1:10. Irradiation of these polymers only provided the red form. Leblanc concluded that the incorporation of the carboxylic acid-capped lipids provided increased flexibility, and the flexibility allowed the polymers to fold even under short times of irradiation. The pure CA polymer over a CA- or BA-containing subphase is thought to form linear tapes, and these tapes provide a rigid linear polymer that cannot be perturbed into a nonlinear form as depicted in Figure 18. The more flexible polymers on the other hand can easily form kinks after prolonged irradiation. The kinks reduce the conjugation length resulting in the red form predominating.

Polymers other than polydiacetylenes have been used to detect proteins. For example, Faid and Leclerc demonstrated that biotin-functionalized polythiophene **82** can detect the binding of avidin using UV-vis absorbance measurements.^{132,133} In this work,



water-soluble polythiophenes functionalized with both sulfonates and alcohols were synthesized. The alcohols were esterified with biotin. On binding to avidin, the polythiophene underwent a chromic shift from violet to yellow. Prior to Leclerc's work, Tripathy et al. used biotinylated polythiophenes as a scaffold to construct molecular assemblies of proteins, and a similar approach to Leclerc's using a biotinylated polypyrrole has recently reported by Bidan et al.¹³⁴⁻¹³⁶

Garnier et al. utilized the electrochemical properties of polypyrrole functionalized with bioactive peptides (**83**) to sense another protein-ligand interaction.¹³⁷ In these studies, carboxypeptidase A binding



induces changes in the CV behavior of the peptide-functionalized polypyrrole. The authors observe an increase in the polymer's oxidation potential with increasing protein concentration. The change was attributed to a decrease in the rate of interfacial electron transfer between the polymer and the electrode upon protein binding. However, it is also possible that the polymer's conformation has changed upon protein binding causing the conjugation length

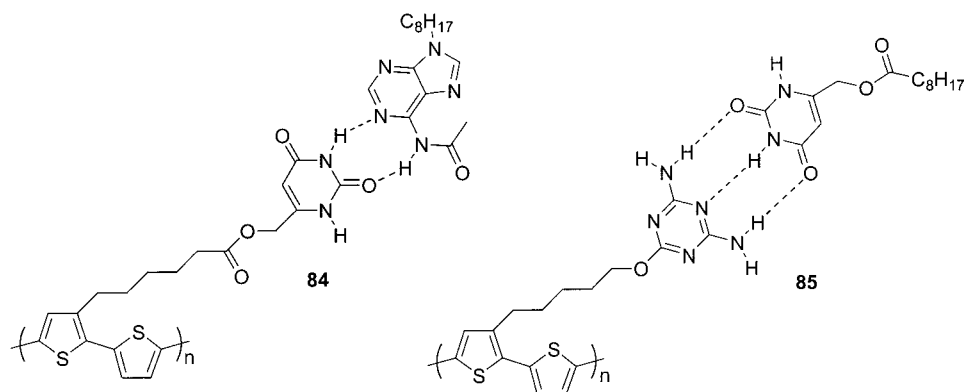


Figure 19. Representative examples of polymers capable of detecting the binding of purines (**84**) and pyrimidines (**85**).

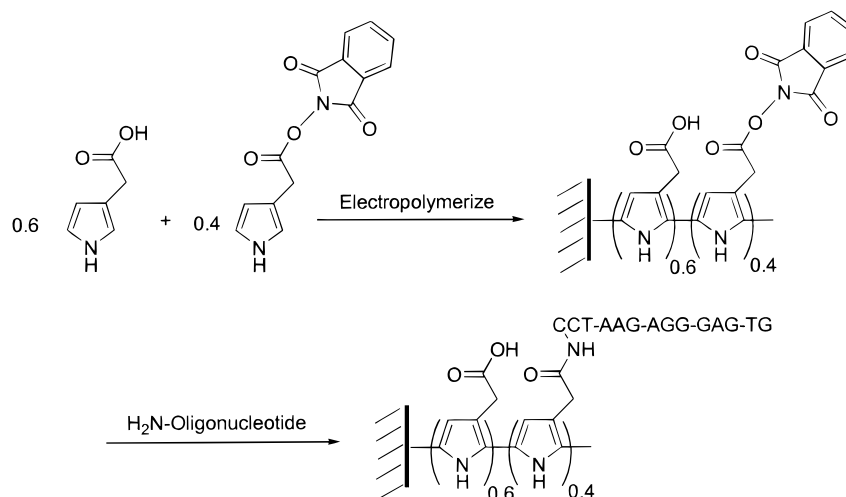


Figure 20. The oligonucleotide-functionalized polypyrrole precursor was electropolymerized at 0.9 V (vs SCE) onto a platinum electrode (0.7 cm^2) in acetonitrile. The resulting *N*-hydroxyphthalimide-functionalized polymer was reacted with an amino-substituted oligonucleotide in buffered DMF providing the desired polymer.

to decrease and thereby leading to an increase in the oxidation potential.

Emge and Bäuerle described a method to detect the binding of purine or pyrimidine bases by covalently attaching a pyrimidine or triazine to bi-, tri-, or polythiophenes (Figure 19).^{138,139} Here, the addition of small concentrations of a complementary purine or pyrimidine results in an increase in the oxidation potential, as well as a decrease in the electroactivity. The authors confirm hydrogen bonding between the polymer-bound base and added base by solution NMR titrations. The change in the polymer's redox behavior has been suggested to arise from entrapment of the bulky tetrabutylammonium ion electrolytes. The authors speculated that the complexation of the bulky bases by hydrogen bonding blocks the channels for ion transport and thereby traps the large electrolyte within the polymer film even after washing the purine or pyrimidine from the film. Expulsion of the bulky ions from the film by forming the highly positively charged polymer at 1.2 V (vs Fc/Fc^+) provided a substantial increase in the electroactivity but not a complete recovery. Despite the irreversibility, the system demonstrates that relatively weak binding analytes ($K_a = 150 \text{ L/mol}$) can influence the electroactivity of a CP.

The detection of sDNA has become very important for the field of genomics. Inexpensive, easy to use

sensory devices could allow clinicians to instantly detect markers for genetically based diseases. Most current DNA detection methods require functionalization of the DNA with fluorescent tags or radiolabels.¹⁴⁰ Ideally, an assay that does not require DNA functionalization prior to detection would have the greatest amount of fidelity. CP sensory methods have been reported for sDNA and protein–DNA detection.¹⁴¹ In the former effort, Teoule et al. attached an oligonucleotide strand to a pyrrole monomer via a modified pyrimidine.^{142–144} The pyrrole monomers were then electrochemically polymerized onto microelectrodes. Radiolabeled sDNA was then used to spatially monitor the hybridization to the polypyrrole-bound DNA. Garnier et al. extended this approach and showed that a polypyrrole with a 14-residue oligonucleotide functions as the transduction element (Figure 20).^{145,146} Hybridization of this polymer with a complementary strand increased the polymer's oxidation potential and decreased the current response in the CV. The authors suggested that the bulky, rigid DNA duplex formed via hybridization increases the energy required to planarize the polymer upon oxidation. The authors also observed that increasing the length of the DNA duplex resulted in higher oxidation potentials for the polymer, indicating that the sensitivity increases as the DNA strands increase in length.

Another approach to label-free detection of DNA has been accomplished using a polypyrrole film grown using an oligonucleotide as the counterion. Wang, et al. established that the oligonucleotide strands trapped within the polymer film were capable of hybridizing with a complementary strand. The hybridization causes a transient decrease in the CPs conductivity, whereas addition of a noncomplimentary strand results in a transient increase in the CPs conductivity. The authors suggest that the response observed could result from a variety of reasons including temporary deformation of the polypyrrole backbone upon hybridization. The initial report employed very simple poly(G) or poly(C) tracks of oligonucleotides. The authors report that they are currently investigating more complicated sequences and how well the films can differentiate between strands of close complementarity.¹⁴⁷ Recently, a review of electrochemical sensors for sensing DNA hybridization was published. The review places the CP work in context with other electrochemical methods used to detect sDNA–sDNA interactions.¹⁴⁸

B. Embedded or Attached Redox-Active Enzyme-Based Sensors

CPs were first reported to entrap enzymes almost 15 years ago by Aizawa and Yabuki in conference proceedings.¹⁴⁹ Peer reviewed publications submitted by Umana and Waller,¹⁵⁰ Foulds and Lowe,¹⁵¹ and Bartlett and Whitaker¹⁵² followed very shortly. In these first systems, polypyrrole was used to entrap glucose oxidase. Polypyrrole, which has been the most widely used monomer to entrap proteins, owes its popularity to its water solubility and the mild conditions used for electropolymerization.

The initial incentive was to use the conducting polymer to mediate electron flow to and from an electrode surface. Debate over the ability of a CP to mediate electron transfer has been ongoing since the beginning of the CP–enzyme field. In the case of polypyrrole–glucose oxidase, Belanger et al. demonstrated that polypyrrole's irreversible amperometric response results from polymer decomposition by hydrogen peroxide formed during the enzymatic degradation of glucose.¹⁵³ Belanger, and later Cooper et al., further demonstrated that incorporation of a hydrogen peroxide scavenger is sufficient to cease the response to glucose.^{153,154} In light of Belanger's research, many groups have been investigating CPs to effect electronic communication between the enzyme and electrode. Transduction of the enzyme's redox states or products can be accomplished by monitoring changes in the CP's electrochemistry or absorption spectra.

The three roles of CPs within enzyme-based sensors are (1) to physically trap the enzymes onto a substrate, (2) to function as electron mediators, shuttling electrons between the electrode surface and the enzyme, and (3) to transduce a binding event. These roles will be discussed in detail below. However, many reviews have previously been published on the subject of CP-based biosensors employing enzymes.^{155–187} As such, our coverage here will focus on key findings and the most recent literature.

1. CPs as Structural Elements

CPs are attractive polymers for enzyme entrapment because films can be produced rapidly with controlled thickness and porosity. CPs can also be selectively immobilized by electropolymerization over very small areas, thereby providing an easy route to functionalized microelectrodes.¹⁶⁹ In most cases, polymerization can be accomplished under conditions that do not destroy an enzyme's activity. The enzyme entrapment within a CP film can be accomplished noncovalently and covalently.¹⁸²

Noncovalent entrapment is easily carried out by electropolymerization of the CP monomers in the presence of the enzyme. Alternatively, soaking a CP film in an enzyme solution can also lead to entrapment.¹⁸⁸ These noncovalent entrapment methods require a relatively large enzyme concentration and rely on the charge complementarity between the CP and the enzyme. A polymer that carries a positive charge when being oxidatively polymerized will bind a negatively charged enzyme like glucose oxidase. The most popular monomer used for noncovalent entrapment has been polypyrrole, which when oxidatively polymerized carries a net positive charge.¹⁸⁹ We note that the counterion hypothesis has been rebuffed by Schuhmann who proposed that the entrapment of an enzyme "...is only due to a statistical enclosure of the enzymes present in the vicinity of the electrode surface".¹⁹⁰

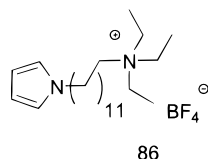
Enzymes that have been entrapped or attached to a CP include glucose oxidase,^{149–154,188–248} galactose oxidase,^{249,250} xanthine oxidase,^{251,252} nucleoside phosphorylase,²⁵¹ nucleotidase,²⁵¹ cholesterol oxidase,^{253,254} urease,^{255–261} glutamate oxidase,^{262,263} alcohol dehydrogenase,^{264,265} fructose dehydrogenase,²⁶⁶ glutamate dehydrogenase,²⁶⁷ lactate dehydrogenase,^{268–270} organophosphate hydrolase,²⁷¹ horseradish peroxidase,^{272–275} microbial peroxidase,²⁷⁵ lactoperoxidase,²⁷⁵ diaphorase,²⁷⁶ creatinase,²⁷⁷ creatininase,²⁷⁷ sarcosine oxidase,²⁷⁷ creatinine deiminase,²⁷⁸ penicillinase,²⁷⁹ polyphenol oxidase,²⁸⁰ and flavin reductase.²⁸¹ Most of these enzymes have been entrapped using polypyrrole, demonstrating that the conditions used to electrochemically polymerize this polymer are benign to the protein. Other polymers used to noncovalently entrap enzymes include polyaniline, polyindole, polythiophene, polyphenols, polyaryldiamines,²⁸² and poly(4-(2-aminoethyl)phenol).^{283,284}

Two articles compared the sensitivity of sensors utilizing various CPs for noncovalent entrapment.^{285,286} Trojanowicz et al. compared glucose oxidase, choline oxidase, and lactate oxidase entrapped in polypyrrole, poly(*N*-methylpyrrole), poly(*o*-phenylenediamine), and polyaniline. Dumont and Fortier studied glucose oxidase entrapped in polyaniline, polyindole, polypyrrole, poly(*o*-phenylenediamine), and polyaniline cross-linked with *p*-phenylenediamine. Both studies indicated that poly(*o*-phenylenediamine) (*o*-Ppd) provided the most stable and sensitive sensors. Dumont and Fortier observed that polypyrrole provided the most reproducible films and *o*-Ppd films provided the best enzyme retention when the films were exposed to organic solvents. Polyaniline and mixed polyaniline and poly(*p*-phenylenediamine) provide the

greatest permselectivity to acetaminophen, uric acid, cysteine, and ascorbate. Permselectivity is a measure of how discriminating a polymer is to a variety of substrates.²⁸⁷ The authors note that all of the films tested provided some level of permselectivity with respect to a bare electrode.

Zamboni et al. produced films with greater permselectivity by overoxidation of pyrrole to give neutral, nonconjugated polymers containing amide groups.^{288–291} The authors suggested that the carbonyl group of the amide electrostatically repels anionic molecules, which normally interfere with analyte sensing. The overoxidized polypyrrole also prevents fouling of the sensor by decreasing nonspecific protein binding. Nonspecifically bound proteins progressively decrease the sensor's response by blocking the pores, prohibiting analytes from accessing the enzyme.

Amphiphilic electroactive monomers have been used to successfully entrap enzymes into polymer films. These monomers can greatly reduce the amount of enzyme needed since the complex between the protein and the amphiphilic monomers can be isolated, thus enabling control of the amount of enzyme entrapped. This approach employing cationic amphiphilic pyrroles (**86**) was first developed by Cosnier and Innocent²⁹² and refined by Coche-Guerente et al.²⁹³ The amphiphilic pyrrole is first combined with

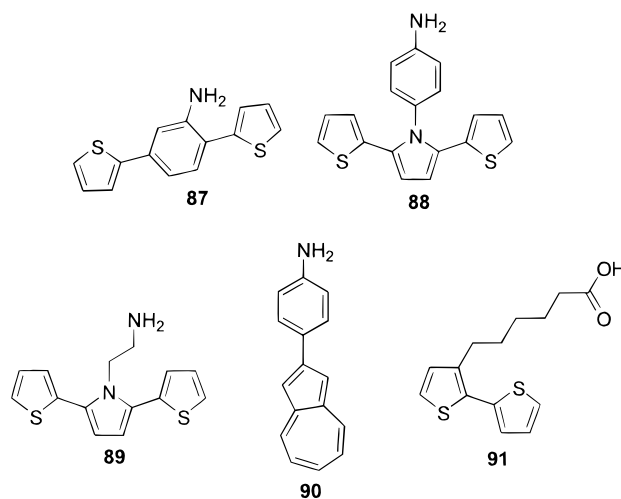


the enzyme in an aqueous suspension and is then spread over an electrode. Once dried under vacuum, the film is placed into a suitable aqueous electrolyte and electropolymerized forming an encapsulated enzyme matrix. The principle advantage of this approach is that it allows greater control over the enzyme loading and greater control of the overall composition of the polymer film. During polymerization, the loss of enzyme can be measured by analyzing the protein content of the electrolyte solution once electropolymerization is complete. Therefore, the true concentration of the protein can be rigorously determined. This entrapment approach has recently been reviewed.^{163,164}

Cosnier et al. reported the construction of composite urease or glucose oxidase, poly(pyrrole-pyridinium), Laponite clay films. The composites were constructed by first creating a gel of Laponite clay and cross-linked urease. The gel was then spread onto an interdigitated electrode precoated with electropolymerized polypyrrole. The negatively charged clay particles bind electrostatically to the positively charged pyridinium groups appended to the polypyrrole. The composite films were found to be less sensitive to urea when compared to enzymes entrapped inside a polypyrrole film without Laponite clay. However, the stability of the Laponite composites was orders of magnitude more stable to continuous use. The clay is thought to provide a hydrophilic component to the film, which helps to provide a more stable environment for the entrapped protein.^{294–296}

Cosnier et al. also utilized a biotinylated pyrrole to construct films adorned with biotin. The free biotin was then reacted with avidin, which provided a handle to react with biotinylated proteins enabling the construction of noncovalently assembled enzyme electrodes. Cosnier reports that the biotin approach provides enzyme attachment markedly higher than previous approaches developed in his laboratories.²⁹⁷

Two methods for the covalent attachment of enzymes to CP films have been reported. The first relies on grafting of the enzyme to a preformed polymer film by reaction with exposed functional groups such as carboxylic acids or amines. This method ensures excellent access between the analyte and the enzyme; however, the distance between the enzyme and the underlying electrode is large, which gives slow responses, and the enzyme concentration is limited by the electrode's surface area. By this method, Schuhmann et al. covalently attached glucose oxidase to a CP film from the polymerization of three amino-functionalized dithienylpyrroles (**87–89**).²²⁶ The cou-



pling of the enzyme to the exposed amines using a water-soluble carbodiimide yielded protein-functionalized films capable of detecting glucose. Schuhmann also used an amine-functionalized polyazulene (**90**) to further showcase this strategy.²¹⁷ Use of a carboxylic acid-functionalized polythiophene for post-polymerization attachment of glucose oxidase was also reported, and likewise Kossmehl et al. covalently attached lactate oxidase to the surface of polythiophene functionalized with carboxylic acids (**91**).²⁶⁹ Attaching the enzyme to the surface after polymerization allows for the polymer to be grown under conditions incompatible with the stability of the enzyme; therefore, this two-step method allows for use of optimum conditions for polymerization and for protein conjugation.¹⁷²

The second covalent approach attaches the enzyme to a monomer prior to polymerization. Subsequent polymerization of the protein-functionalized monomer with a nonfunctionalized comonomer provides films with controlled enzyme concentrations. Films utilizing protein-functionalized monomers are found to provide greater sensitivity, which is suggested to arise from the greater porosity of the film. Schuhmann covalently attached glucose oxidase to a pyrrole

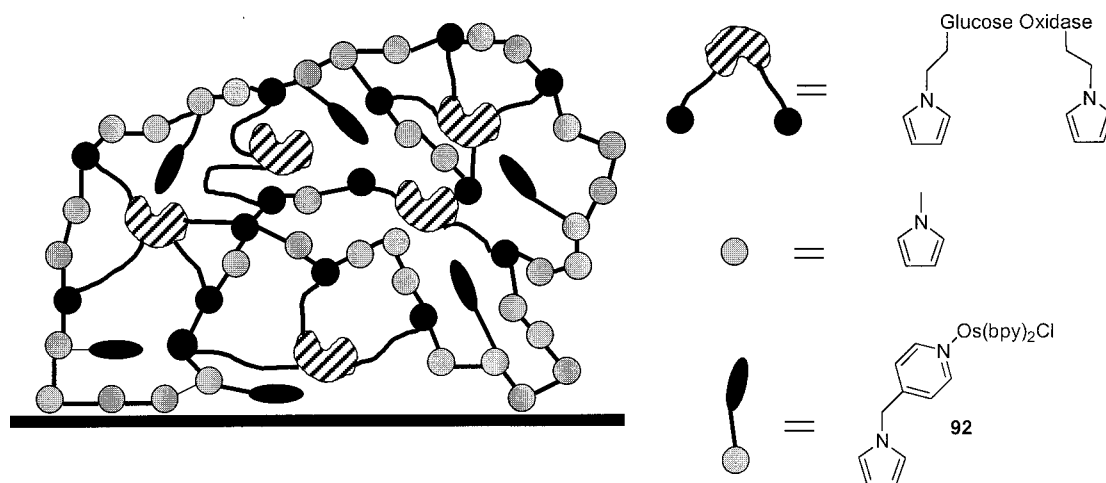


Figure 21. Terpolymerization of **92**, *N*-methylpyrrole, and pyrrole-modified glucose oxidase produces a composite electrode where the osmium-functionalized monomers shuttle electrons between the electrode and the enzyme.

monomer and proceeded to polymerize with *N*-methylpyrrole and an osmium-functionalized pyrrole comonomers (Figure 21) (**92**). The osmium-functionalized pyrrole served to shuttle electrons from the enzyme to the electrode surface.²¹¹ In another example, Schuhmann's group polymerized the same glucose oxidase-functionalized pyrrole monomer with bithiophene.²³² The resulting polymer had a higher redox potential relative to pyrrole resulting from the incorporation of the bithiophene units. The higher redox potential provides a polymer more stable to hydrogen peroxide, which is the product of the reaction of reduced glucose oxidase with oxygen.

In most cases where a CP acts as the sole scaffold to anchor an enzyme to an electrode surface, the polymer cannot mediate electron transfer between the electrode and the enzyme. Early on in this field, the CP was mistakenly thought to directly transport electrons between the electrode and the enzyme, but later investigation revealed that oxidation of hydrogen peroxide formed from the reaction of the reduced enzyme and oxygen is responsible for the response. A high working potential is required to oxidize hydrogen peroxide at an electrode surface, and most cases report potentials of 0.7 V (vs Ag/AgCl.) This feature is problematic since potentials above 0.6 V (vs Ag/AgCl) have been shown to oxidize endogenous molecules within blood serum, such as lactic acid and ascorbic acid. The interference from these molecules can greatly inhibit the sensing of glucose.

In an effort to reduce the working potential needed to oxidize hydrogen peroxide, a variety of mediators have been used. The most widely used mediators have been ferrocene and ferrocene derivatives.¹⁸² In some cases, the mediator has been noncovalently associated with the polymer film, and in other cases the mediator has been covalently associated.¹⁷² Covalent association is more attractive because the mediator can be washed out if it is noncovalently bound. However, covalent attachment requires that the tether between the mediator and the polymer be flexible and long enough for the mediator to interact with other mediators, the electrode, and the enzyme.¹⁷² A number of groups have utilized high, covalent loading of mediators within a film to ensure

that the charge can effectively move to the electrode. Schuhmann et al. utilized an osmium-functionalized polymer to mediate electrons, and Wang et al. employed ferrocene-modified aniline to shuttle electrons.^{298,299} Recently, incorporation of dispersed metal particles within the polymer matrix of an enzyme-entrapped CP electrode has been used to catalyze the oxidation of hydrogen peroxide. In this case, the CP may shuttle electrons from the metal particles to the electrode.^{237,238}

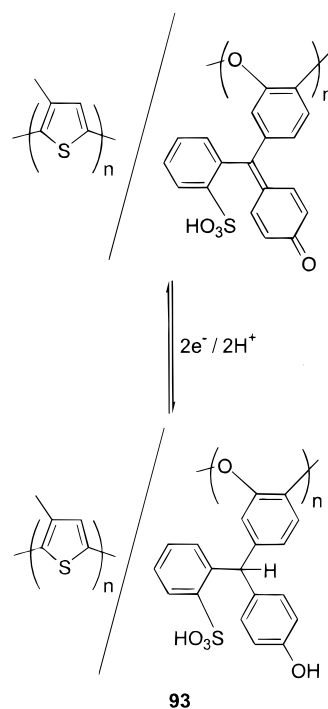
2. CPs as Mediators

Entrapment of an electroactive enzyme within a CP would at first glance appear to be an ideal environment for the polymer to act as an electron conduit between the enzyme and the electrode surface. However, in most cases, the communication does not occur. By design, electroactive enzymes generally bury their redox-active sites deep within the protein as a method of protecting the redox center from competing redox-active substrates. Some reports provide evidence that natural co-enzyme electron shuttles (like NADH)²³⁹ can only communicate between the polymer and the enzyme through a small molecule mediator. A number of groups suggested that certain enzyme entrapment methods can provide closer contact between the polymer and the protein.¹⁹³ However, it is only in these special cases that electron transfer has been proposed to travel to the enzyme through the conducting polymer. Many articles describing enzyme-based sensors entrapped with conducting polymers either ignore the mechanism of electron transfer or simply allude to the CP playing a role. However, most recent articles suggest that without an extrinsic mediator like ferrocene, charge transfer is accomplished by hydrogen peroxide.¹⁵³ In a 1995 review Schuhmann identified six examples where the CP acts as an electron mediator.¹⁷² A number of more recent examples have demonstrated the capability of CPs to act as mediators and provided new evidence that past models may be incorrect. For example, Nolte et al. published a series of papers detailing sensors created from depositing polypyrrole and glucose oxidase into the pores of a track-etched membrane,²¹⁹ which had been sputtered on one side

with platinum.^{204,205,210,219} Nolte suggested that the aforementioned sensor design used polypyrrole as a mediator between the enzyme-reduced FAD and the sputtered platinum. However, Kuwabata and Martin observed in the same system, but excluding both the polypyrrole and the glucose oxidase resulted in sensors with greater sensitivity to glucose.²²¹ Martin proposed that the sputtered platinum alone acts to oxidize the glucose directly and that the polypyrrole, track-etched membrane, and glucose oxidase merely occlude the platinum surface, thus decreasing the sensitivity. However, Martin did not investigate whether Nolte's films provided enhanced specificity for glucose over the unmodified platinum electrode. Khan and Wernet also reported the use of polypyrrole films with a layer of cross-linked glucose oxidase which were sputter coated with Pt.²²⁹ The films of Khan and Wernet are also less responsive than Martin's unfunctionalized sputtered platinum, indicating that the cross-linked glucose oxidase may actually passivate the surface. Unfortunately, Khan and Wernet did not comment on the film's performance when the glucose oxidase layer was omitted.

Horseradish peroxidase (HRP) entrapped in both polypyrrole and polyaniline can be used for hydrogen peroxide detection and appear to use the CP to shuttle electrons between the enzyme's iron center and the electrode. Tatsuma et al. reported that poly-(3-(3'-thienyl)propanesulfonic acid) (PTS) films containing HRP cast onto SnO₂ could be used to detect hydrogen peroxides and that the CP backbone was acting as an electron conduit between the electrode and the various oxidized states of HRP.²⁷² Tatsuma used a purified sample of PTS that had been expunged of any thiophene monomer or small oligomers. Care was taken to remove these impurities due to the fact that the authors had previously shown that these small molecules can act as electron mediators themselves, thereby clouding experiments designed to investigate the properties of the polymers alone.³⁰⁰ The authors also employed SnO₂ as the electrode substrate because it requires a substantial overpotential to oxidize or reduce hydrogen peroxide. In the presence of peroxide, the PTS-HRP film exhibited an increase in the cathodic current, indicating the electron transfer between the enzyme and the electrode was mediated by the polymer. The authors further demonstrated that microbial peroxidase and lactoperoxidase can also be used en lieu of HRP.^{273,274} The groups of Tatsuma (using polypyrrole) and Iwuoha (using polyaniline) both used HRP immobilized in their respective polymers to detect peroxides at similar levels of sensitivity in acetonitrile. Iwuoha et al. also used their system to monitor peroxides in a number of organic solvents and observed that the sensitivity of the sensor depends on the solvent media.²⁷⁵

Warriner et al. used a platinum electrode covered with poly(3-methylthiophene)/poly(phenol red) (**93**) with an overlay of gel containing entrapped lactate dehydrogenase to detect pyruvate via a direct reduction of NAD⁺ by the polymer film.²⁶⁸ Reduction of NAD⁺ is catalyzed by poly(phenol red), and the authors suggested that the poly(3-methylthiophene)



acts to shuttle electrons from the electrode to the quinones formed in the oxidation of the poly(phenol red). The ability to electrocatalytically reduce NAD⁺ at mild potentials (0.2–0.3 V vs Ag/AgCl) is a great leap forward in enzyme-based biosensing because it allows the use of dehydrogenase enzymes, most of which require NADH/NAD⁺. The dehydrogenase class of enzymes is much larger than oxidases, and the number of chemical structures that bind to dehydrogenases is considerably greater.²⁶⁸

3. CPs as Transducers

Utilization of CPs for transduction of an analyte–enzyme binding event is becoming more prevalent as the understanding of CP design principles becomes more sophisticated. The electroactivity and optical properties of many CPs are directly related to their protonation state, oxidation state, and conformation. Redox-active enzymes can produce products that can greatly influence local pH. Contractor et al. used changes in polyaniline's conductivity as a function of pH to sense glucose. In these investigations a layer of polyaniline was electropolymerized over two platinum electrodes and then overcoated with a polyaniline layer with entrapped glucose oxidase.²⁰² Upon reaction with glucose, the glucose oxidase produces gluconolactone and hydrogen peroxide, which alters the pH of the local environment. Wrighton et al.⁹ previously demonstrated the sensitivity of polyaniline's conductivity to pH in a similar device. Contractor ruled out polymer oxidation as the primary factor for the conductivity changes by monitoring the open-circuit potential of the bilayer film while increasing glucose concentration and by also conducting CV measurements with and without glucose present. Uchida et al. concurrently developed a similar method (Figure 22) to detect penicillin²⁷⁹ and later to detect glucose.²²⁰ Palmqvist and Berggren Kriz further utilized the same method to detect pH

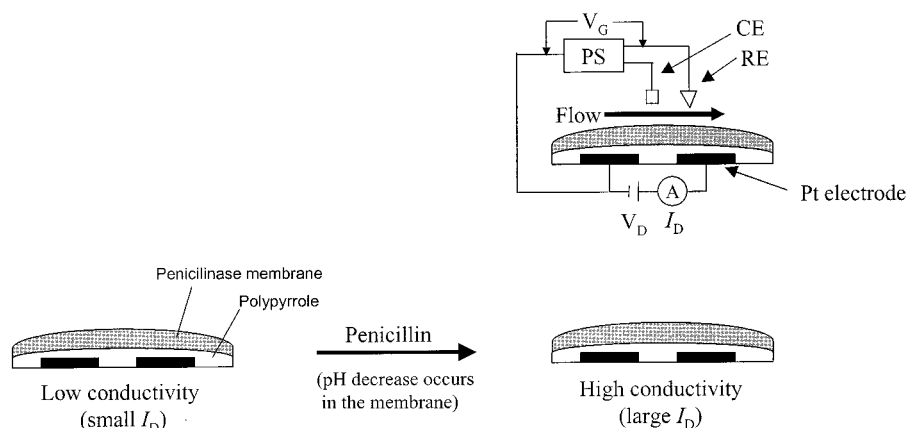


Figure 22. Uchida's penicillin sensor and the electrochemical configuration allowing in situ conductivity measurements: PS, potentiostat; CE (Pt) counter electrode; RE, reference electrode (SCE); V_G , gate voltage; V_D and I_D , drain voltage and current.

changes associated with yeast metabolism by covering the anode and cathode first with a film of polypyrrole and then a layer of yeast cells coated in agarose gel.³⁰¹ Upon feeding the cells glucose, a pH decrease can be detected by monitoring the change in the CPs conductivity, indicating that the yeast are metabolizing the glucose.

Bartlett and Birkin constructed layered devices similar to Contractor and Uchida where two carbon electrodes were coated with polyaniline followed by a layer of glucose oxidase entrapped in poly(1,2-diaminobenzene).¹⁸² Hianik et al. used bilayer membranes containing urease attached with biotin-avidin on polypyrrole to detect urea by observing the increase in the polymer's d.c. current flow as urea concentration increased. Presumably, this sensor takes advantage of the pH change that is induced by the increase in ammonium ion concentration, which is a product of urease action on urea.²⁵⁹

Employing the same method as Contractor and Uchida, Matsue et al. coated two adjacent electrodes with poly(pyrrole-*co*-*N*-methylpyrrole) containing diaphorase, a flavin enzyme that catalyzes the reduction of oxidized dyes by a NADH cofactor. In this case, diaphorase directly reduces the CP upon addition of NADH. The system described as a "switch" begins in its conductive state (oxidized form), and upon addition of NADH, the polymer is reduced to its insulating form. Matsue suggests that the system is a NADH switch, and they have yet to exploit the system's NADH sensing capabilities.²⁷⁶ Karyakin et al., using an electrode design similar to Contractor and Uchida, created polyaniline-based potentiometric sensors responding to pH,³⁰² glucose,²¹⁷ and organophosphates.²⁷¹

Entrapping polymeric anions into a CP can shift the redox potential to more negative values, because the counterions cannot be expelled. By placing the applied potential below the polymer's reduction potential in the absence of the polymeric anion, the CP will respond to cationic analytes, since the incorporation of cationic analytes allows reduction to occur. Cho and Huang exploited this phenomenon to detect the ammonium ion formed by the action of urease on urea.²⁶⁰ The authors deposited a Nafion film (an anionic polysulfonated polymer) onto a glassy carbon

electrode and electropolymerized polyaniline as the second layer. The polymers were then coated with a bovine serum albumin and urease layer, which was cross-linked with glutaraldehyde. The electrode was then exposed to urea solution and the amperometric signal increased as a function of urea concentration.

Polyaniline undergoes chromic changes upon oxidation or reduction. In the reduced leucoemeraldine form, polyaniline is colorless and when oxidized to the emeraldine salt it becomes green. Lima Filho et al. utilized the electrochromic changes of polyaniline to sense glucose. The authors placed a film of polyaniline with entrapped glucose oxidase on the inside window of a quartz cuvette. Upon addition of glucose the polymer presumably is oxidized by hydrogen peroxide and changes from a colorless leucoemeraldine form to blue-green in the emeraldine form and then finally to the violet pernigraniline form.²⁰³

C. Induced Fit Proteins Attached to Conjugated Polymers

Hexokinase is an abundant enzyme responsible for transferring a phosphate group from ATP to the 6 position of glucose. Upon binding glucose, hexokinase undergoes a conformational change. Cheng and Stevens used this conformational change to colorimetrically detect glucose.³⁰³ In this approach, hexokinase was attached to a lipid polydiacetylene film and glucose binding, as observed by UV-vis spectroscopy, caused the blue polydiacetylene film to partially switch to the red form. The authors proposed that the binding of glucose caused the hexokinase to change conformation, which in turn altered the diacetylene film from the blue form to 17% of the red form in 1 h.

D. Immunological-CP-Based Sensors

Antibodies are enzymes that are created by an organism to bind specific target molecules. The target molecules (antigens) are usually foreign to the organism and are expelled after being bound by the antibody. This housekeeping function of an antibody requires that the antibody bind its target strongly and specifically. The specificity and strength of an antibody-antigen interaction is very attractive from

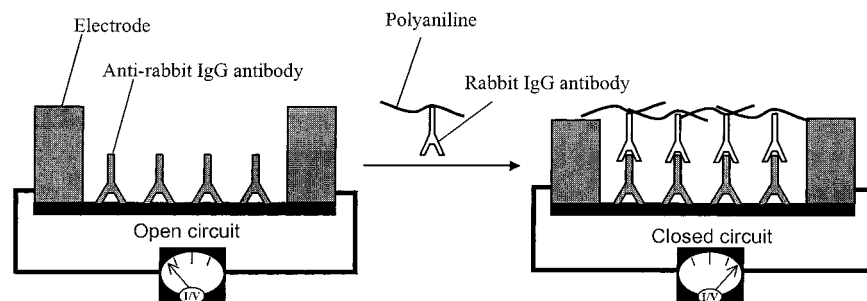


Figure 23. Sergeyeva's antibody-based transistor.

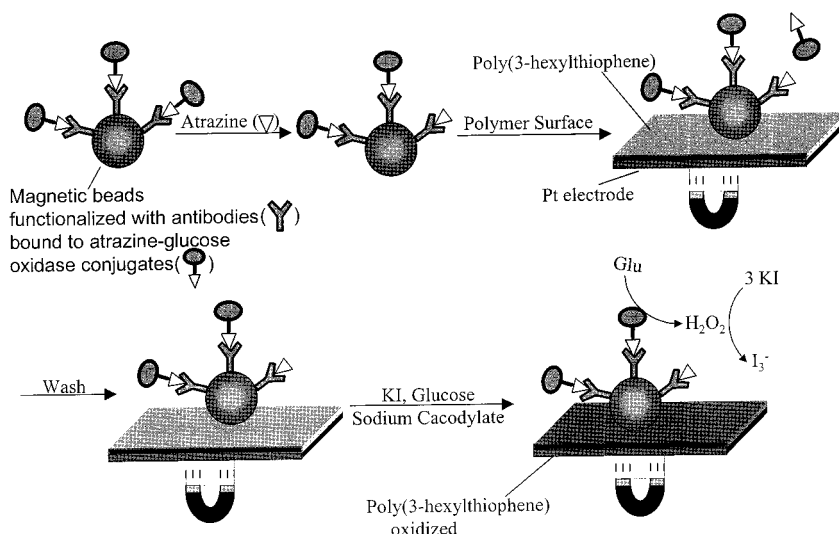


Figure 24. Schematic representation of Fare's atrazine detection assay.

a sensor point of view. Biosensors utilizing interactions with large association constants allow for the detection of very small quantities of analyte; however, the sensor reversibility becomes worse as the association constant increases. Along with the issue of reversibility, methods to transduce the binding event must be developed. As mentioned in section III. A, many groups have taken advantage of the mechanical changes that occur when a protein or DNA strand binds to a surface ligand or sDNA attached to the CP. In the case of a surface-entrapped antibody binding of an antigen, no large mechanical change is expected. As antibodies are highly preorganized for the binding of specific antigens, they undergo minimal conformational changes with binding. Hence, mechanisms that involve coupling of the antibody to conformational changes in the polymer are not effective.

A number of groups have reported the use of CPs to overcome the aforementioned problems associated with using antibodies for analyte detection. Different types of non-CP-containing antibody-based [ELISAs (enzyme-linked immunoassay), ECIAs (electrochemical immunoassay), etc.] assays exist, and these systems have previously been reviewed with respect to electrochemical transduction.^{304–306} Covalent attachment of polyaniline to a rabbit IgG antibody has been used by Sergeyeva to bind anti-rabbit IgG antibodies (Figure 23).^{307,308} The anti-rabbit IgG antibodies were affixed to an interdigitated electrode. The polyaniline attached to the complementary antibody served to bridge the space between the electrodes,

resulting in a signal. The method is quite effective, although it requires the labeling of the analyte one wishes to detect.

Englebienne and Weiland reported labeled antigens with water-soluble carboxylic acid-functionalized polythiophenes. Upon binding a corresponding antibody, the optical density of the polymer band at 380 nm was observed to increase with increasing concentration of antibody. The authors attributed the increase in polymer absorbance to a local pH change that occurs when the antigen and antibody bind. The assay was used to detect human C-reactive protein, human serum albumin, and theophylline-8-bovine serum albumin. The assay was performed in a homogeneous solution, which the authors indicated would be very useful for automating the experiments; however, the low sensitivity of UV-vis absorption measurements may limit the detection method to only substances that are found in high concentration.^{309, 310}

Fare et al. described a sensor design utilizing antibodies attached to a magnetic particle which during the course of the assay are magnetically attracted to a poly(3-hexylthiophene)-coated platinum surface for the detection of atrazine (Figure 24). Anti-atrazine antibodies attached to a magnetic particle are initially bound to an atrazine analogue covalently conjugated to glucose oxidase. These antibodies are incubated with the analyte atrazine for 8 min in a buffered solution. During the incubation period the atrazine in solution displaces some of the atrazine conjugated to glucose oxidase. After the

incubation period, a magnet is used to capture the antibodies onto the polymer surface. The freed atrazine–glucose oxidase conjugates, and any unbound atrazine is then washed away. The concentration of atrazine–glucose oxidase conjugates left are assayed by addition of glucose, which by action of the remaining glucose oxidase produces hydrogen peroxide to oxidize iodine to triiodide. The triiodide then oxidizes the polyaniline, and the change in capacitance current is measured.³¹¹ The amount of atrazine–glucose oxidase remaining is inversely proportional to the atrazine concentration.

The previously mentioned antibody–sensors require analyte functionalization or excess reagents and require up to 10 min to perform. Improved designs should require no additional reagents, allow for instant signal response, and be reversible. Neither of the aforementioned antibody–sensors addressed issues of reversibility, which is crucial to create a sensor as opposed to a dosimeter. Wallace et al. reported in a series of papers a simple sensing system relying on antibodies entrapped in a CP matrix.³¹² Antigen binding is measured using pulsed potential waveforms. The pulsed potential waveform modulates the binding of the antigen within the antibody allowing for the necessary reversibility. As the antigen concentration is increased, an amperometric response is observed. The method has been applied to detection of human serum albumin,^{313,314} Thaumatin,³¹⁵ Rhesus (D) blood group antigen,³¹⁶ halogenated organic compounds,^{317,318} and phenols.³¹⁹

IV. Conjugated Polymers with Entrapped Materials To Aid in Specificity

Polymerizing CPs in the presence of different counteranions provides CPs with varying potentiometric and amperometric responses to various charged analytes. The size and lipophilicity of the anion greatly influences the rate of anion expulsion when cationic CP is reduced to an insulating state. If the anion doped into the film is sufficiently lipophilic the anion, which serves as the polymers counterion, will remain in the film when the polymer is reduced. To maintain electrochemical neutrality, cations from the surrounding medium diffuse into the film. The size and charge of the cation can influence the rate of diffusion, which can be measured potentiometrically and can be used to differentiate between analytes. Conversely, the size and shape of the anion being expelled can provide a templated cavity, which selectively absorbs a particular analyte.

Anion exchange was used by Wallace et al. to detect amino acids^{320,321} and haloacetic acids.³²² The exchange of anions was associated with changes in the voltammetry and amperimetry. Wallace found that polypyrrole's sensitivity was dependent on the counteranion used during the polymerization and the nature of the pulsed potential waveform used to oxidize and reduce the polymer (vide supra).

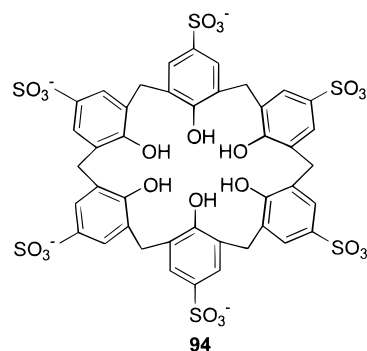
A polypyrrole film incorporating a dodecyl sulfate counteranion has been used to detect alkali metal cations,^{323,324} divalent metal cations, and vitamins B₁ and B₆.³²⁵ The presence of a lipophilic cation, which cannot be easily expelled, causes cations to diffuse

into the film upon reduction and expulsion of the cations upon oxidation. The rate of the diffusion and expulsion can be observed via shifts of the peak currents (I_{pa} and I_{pc}).

Catalysis of reactions at a CP surface has been used to detect ascorbic acid,^{326–328} various sugars, and amino acids.^{329,330} Ascorbic acid oxidation occurred at polypyrrole films doped with dodecylbenzenesulfonate ion (DBS). Using differential-pulse voltammetry, Lyons et al. were able to demonstrate that the polypyrrole–DBS film could distinguish between ascorbic acid oxidation and dopamine. An unmodified platinum electrode was not able to distinguish between the two analytes. The cyclic voltammogram showed only one peak, unlike the polypyrrole–DBS electrode, which showed two peaks. The authors provided no explanation for the selectivity observed using the polypyrrole–DBS modified electrode. Faguy et al. also used polypyrrole polymerized within montmorillonite clay to detect ascorbic acid.³³¹

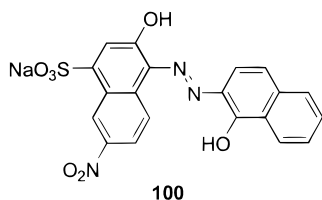
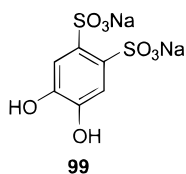
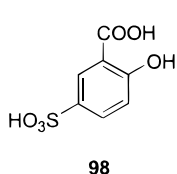
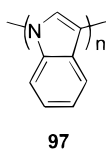
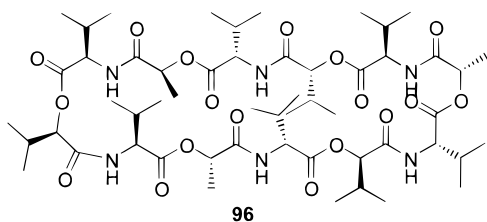
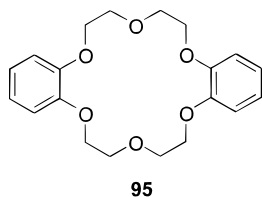
Films capable of oxidizing sugars and amino acids were constructed of polyaniline with copper dispersed within the film. Casella et al. synthesized the copper-containing films by exposing polyaniline films deposited onto glassy carbon to a solution of CuCl₂ in acid.³²⁹ The Cu²⁺ was then reductively deposited (–0.3V vs SCE) providing a polyaniline film with dispersed copper(0) particles throughout the film. Exposure of the polyaniline–Cu film to a variety of sugars and amino acids resulted in concentration-dependent anodic waves observed in the CVs between 0.3 and 0.8 V (vs SCE), indicating that the various analytes were being oxidized at the electrode. The electrode appears to have no structural selectivity, only selectivity based on an analytes oxidation potential.

Entrapping macrocyclic ionophores and recognition domains directly into CPs or into nonconjugated polymer layers above CPs have been exploited to detect a variety of analytes. Uranyl ions have been detected using a calix[6]arene (**94**) directly deposited into polypyrrole films.^{332,333} The authors used cyclic



voltammetry to monitor for the presence of uranyl ions, by measuring the reduction peak of the uranyl ion. The polypyrrole/calix[6]arene provided a sharper uranyl ion reduction peak relative to a bare electrode.

Entrapment of macrocycles such as dibenzo-18-crown-6 (**95**)^{334,335} and valinomycin (**96**)³³⁶ into CPs has been used for sensing potassium ions by observing redox changes in the polymer film as a function of K⁺ concentration. Pandey and Prakash electropo-

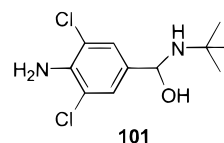


lymerized indole (the authors suggested, based on previous experiments,³³⁷ that the polymerization occurs at the 1 and 3 positions of indole through the ring nitrogen) onto a platinum electrode and then coated the polyindole (**97**) layer with a PVC/dibenzo-18-crown-6 membrane. The film showed a positive potentiometric shift, which was linear over five decades of K^+ concentration. The electrode is more responsive to K^+ than Na^+ or NH_4^+ . The authors noted that the PVC/dibenzo-18-crown-6 membrane can function as a K^+ sensor when directly bound to a platinum electrode, but the signal is noisier and appears to drift much more than the electrode containing the polyindole film. Previously, using a similar method, Lewenstam et al. entrapped ionophores such as sulfosalicylic acid (**98**), Tiron (**99**), and Eiochrome Black T (**100**) into polypyrrole to detect Cu^{2+} , Ca^{2+} , and Mg^{2+} .^{338,339}

Contractor also employed crown ethers to detect alkali ions.³⁴⁰ Deposition of a 18-crown-6 on a interdigitated electrode precoated with an electropolymerized layer of polyaniline provided a system capable of a modest 1.4 relative increase in conductivity with the presence K^+ . No response is observed with addition of K^+ to a bare polyaniline film. However, when the crown ethers are present, the addition of K^+ results in an increase in conductivity. The authors suggested that the increase in conductivity results

from a conformation change in the polyaniline's backbone, which results from the crown ether's complexation with potassium. The films are not very selective and will respond to monovalent as well as divalent cations. The authors corroborate their hypothesis, that the change in conductivity results from ion binding through a change in polymer conformation state, using a 1:1 crown ether:polyaniline mixture spread on a Langmuir trough. Addition of K^+ causes the area of the film to increase proportionally to the increase observed in conductivity.

Detection of clenbuterol (**101**), a β_2 -adrenoceptor agonist widely used as a performance enhancing drug, has been achieved by using a two-layer electrode. Sun and Aboul-Enein electropolymerized poly-



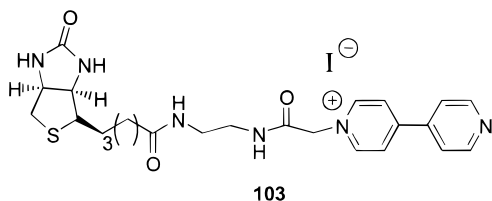
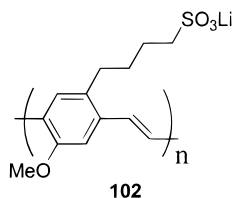
aniline onto a glassy carbon electrode as the first layer and then dip-coated a mixture of PVC, diisononyl phthalate (as a cross-linker), and a small amount of the clenbuterol-tetraphenylborate salt.³⁴¹ Once the dip-coated second layer is dry, the electrode's potential shifts strongly in the presence of clenbuterol (60 mV/concentrated decade of clenbuterol). The authors do not propose a mechanism accounting for the electrodes response. The clenbuterol-tetraphenylborate salt appears to be forming imprinted domains within the PVC membrane. Oxidation of the polyaniline will result in the formation of a positively charged polymer, which will displace positively charged (protonated) clenbuterol and the tetraphenylborate will then act as the polymers counterion. The expulsion/uptake of clenbuterol as the polyaniline cycles from positive to neutral appears to be very dependent on the solution concentration of clenbuterol. The mean electrode potential becomes less negative as the concentration of clenbuterol goes down. At a clenbuterol concentration of 1 M, the mean potential is -469 mV (vs SCE), and at a concentration of 10 μ M, the mean potential increases to -187 mV (vs SCE). The authors noted that the selectivity of the electrode is high and that the electrode functions well in biological fluids.

V. Unmodified CPs as Sensors

Unmodified CPs can respond readily to changes in their local environment. Unmodified CPs have been used to sense a great variety of analytes such as organic vapors,³⁴²⁻³⁴⁵ oxygen,³⁴⁶ nitrogen oxide gases,³⁴⁷ amines,³⁴⁸ hydrazines,³⁴⁹ pH,³⁵⁰ humidity,³⁵¹ various ions,³⁵² and cytochrome *c*.³⁵³ The reader interested in unmodified CPs as sensors should refer to recent reviews^{354,355} and books.³⁵⁶ Unmodified CPs tend to show very little specificity and are not useful as "stand alone" sensors but are very useful for arrays.¹⁵

Recent studies utilizing 2-methoxy-5-propyloxy sulfonate phenylene vinylene³⁵⁷ (unmodified in the sense that the polymer is not designed to interact with its substrate with any specificity) have expanded upon

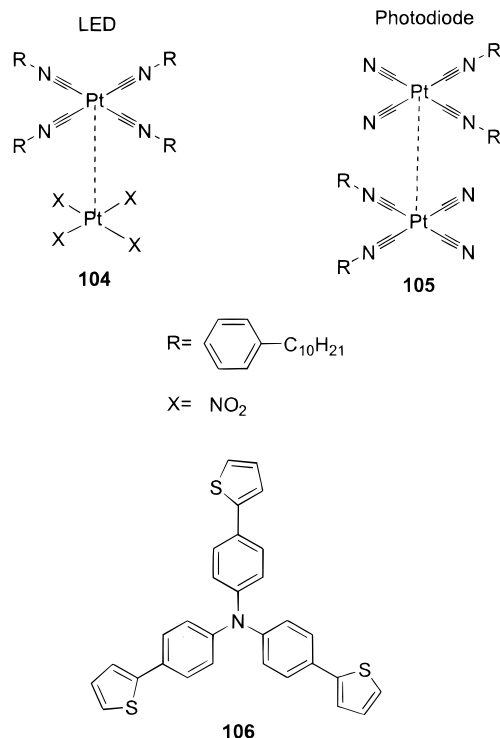
the method of Swager et al. by using energy migration as a mechanism to produce signal amplification in fluorescence chemosensors.¹⁰⁷ The authors claim “a greater than million-fold amplification” based on the differences in Stern–Volmer quenching constants of the polymer, **102** ($M_n = 10^5$), as compared to stilbene. This study made use of the same quenching



reaction, namely, quenching by methyl viologen (paraquat), that Swager used to first illustrate this effect.¹⁰⁷ However, unlike the earlier studies using synthetic receptors with a known binding constant,^{107,108} the authors were not able to deconvolute the effect of the binding constant on the quenching reaction. As a result, the 10^6 fold enhancement also contains the effective binding constant for the electrostatic interactions of the dicationic quencher to the polyanionic polymer. Studies with micelles show that the binding constant of methyl viologen to an anionic surface is in excess of 10^2 . This binding constant is expected to be much larger for a rigid anionic polymer, such as **102**, which can effectively encapsulate the cationic analyte in a coiled conformation. As a result, it is unclear if these recent studies report higher amplification factors than those reported previously for poly(phenylene ethynylene)s.^{107,108}

The efficient quenching processes for **102** were extended to demonstrate potential biosensory functions by the use of a biotin–methyl viologen hybrid **103**. This conjugate binds the polymer and effectively quenches the fluorescence. Upon exposure to the receptor protein, avidin, the biotin is bound to the protein ($K_a \approx 10^{15}$) and the methyl viologen is removed from the polymer, thereby restoring its fluorescence. The authors suggest that this innovative method may constitute a general mechanism for the design of new sensor scheme for biological analytes.³⁵⁷

CPs have been utilized to create LEDs, FETs, photodiodes, and other electronic devices. Miller et al. built on these efforts by constructing LED³⁵⁸ and photodiode vapor sensors.³⁵⁹ These sensors are two-layer devices where one layer is composed of a linear array of mixed-stack platinum complexes previously synthesized in the Miller group (**104** and **105**), which are responsive to organic vapors. The devices are constructed by electropolymerizing tris(4-(2-thienyl)phenyl)amine monomers (**106**) onto an ITO electrode, spin coating the mixed-stack platinum complexes onto the polymer film, and then deposition of a layer



of aluminum. In the case of the LED, the aluminum electrode was vapor deposited leaving a porous layer of metal. The photodiode was constructed with the aluminum electrode deposited as fingers 0.1 mm apart.

Prior to vapor exposure, the LED device emits with a photon/electron efficiency of 0.01% at $\lambda_{\max} = 540$ nm. Exposure of the LED to acetone-saturated argon vapor caused the λ_{\max} to red shift 35 to 575 nm. Miller was also able to create a vapor-responsive photodiode by employing a reverse bias to a device very similar to his LED. Before exposure to acetone, the photodiode has a peak photocurrent between 400 and 500 nm. The broad photocurrent sharpens and red shifts upon exposure to acetone vapor, placing the λ_{\max} at 560 nm. The quantum efficiency of the acetone exposed device was 0.03% at 0 V and 16.5% at 20 V reverse bias. Miller's results demonstrate the power of CP based materials; however, these sensors have not been shown to be specific and thus will primarily be useful for the construction of array sensors.

VI. Conclusion

In light of the sensory systems presented herein, it is clear that CPs represent one of the most useful chemical platforms for the design of chemical sensors. While the physics and chemistry of these materials has matured considerably over the last two decades, we are only at the genesis of controlled CP supramolecular structures. Ironically, most research in supramolecular science is driven by molecular recognition. Often missing from these recognition schemes is a viable transduction mechanism; we believe CPs will effectively fill in this transduction void.

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