Towards the Design and Synthesis of Conducting Polymer-Based Sensory Materials

by

Lewilynn V. Lopez de Leon

B.S., Chemistry (1988)

University of the Philippines

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Chemistry

at the

Massachusetts Institute of Technology

February 1997

Signature of Author ____________________
Department of Chemistry
January 31, 1997

Certified by ____________________
Professor Timothy M. Swager
Thesis Supervisor

Accepted by ____________________
Professor Dietmar Seyferth
Chairman, Departmental Committee on Graduate Students

TOWARDS THE DESIGN AND SYNTHESIS OF CONDUCTING POLYMER-BASED SENSORY MATERIALS

by

LEWILYNN V. LOPEZ DE LEON

Submitted to the Department of Chemistry
on February 3, 1997 in partial fulfillment of the
requirements for the Degree of Masters of Science
in Chemistry

ABSTRACT

Progress toward the synthesis of monomers with receptor functionalities is reported. Macrocyclic monomers consisting of calix[4]arene functionalized bithiophene/thiophene were targeted which can be polymerized to give redox-activated receptor-functionalized polythiophenes. Unfortunately, conversion to the redox-active calix[4]arene-diquinone containing macrocycle has yet to be successful. Progress is also described toward the synthesis of polyanilines functionalized in the ortho position with a lariat crown ether. Synthesis of *o*-(2-methyleneoxy-12-crown-4)-aniline was successful but electrochemical oxidation did not give the expected polymer product. To eliminate the probable steric problem in the aniline polymerization reaction, synthesis of a lariat crown ether-functionalized aniline dimer was attempted. The key aniline coupling reaction was performed on a model system, using a methoxy group in place of the lariat crown ether. Nucleophilic aromatic substitution and palladium catalyzed coupling conditions were successfully carried out to give the expected methoxy substituted aniline dimer. However, use of the same conditions was not successful in producing the target crown-substituted aniline dimer. Synthesis of boronic acid functionalized aniline was carried out and preliminary electrochemical investigations revealed the compound to be polymerizable in acidic aqueous solutions.

Thesis Supervisor: Timothy M. Swager

Title: Professor of Chemistry

TABLE OF CONTENTS

LIST OF FIGURES

Chapter 1

Chapter 2

Chapter 3

Appendix

ACKNOWLEDGMENTS

Thank you to...

Professor Tim Swager, for taking me in as a graduate student and giving me the opportunity to be a part of chemistry again.

The Swager Group members, especially

> Dan, for all his "fatherly" advice on chemistry and life.
>
> Khushrav, for helping me get started in lab and shaping my chemistry lab training, for all the computer aid and the Indian buffets.
>
> Bing & Sherry, for their help and support with a number of things.
>
> Scott, for being my best buddy in the lab.
>
> Rich, Dave and Sean, the proof-readers.

My friends, near or distant but nevertheless always there : Jakki, Caty, Eva, Pia, Bernardo, Orson, Anna, Bambi and Evelyn.

My sister, Nic-nic, for the inspiration she provides.

My mom.

Marc, for being Marc and for innumerable reasons, a page wouldn't be enough to list them all.

Chapter 1

Introduction to Conducting Polymer Sensors

The ever increasing need for more sophisticated, sensitive and reliable sensors has prompted broad research efforts toward the development of new materials for sensory functions. A promising class of materials is conducting polymers. Conducting polymers can possess the electrical, electronic, magnetic, and optical properties of a metal while retaining the mechanical properties, processability, etc. commonly associated with conventional polymers.[1] The advantage of polymeric molecular sensors, specifically conducting polymer sensors, over a low molar mass molecular sensor as demonstrated by our group, is their enhanced sensitivity. This amplification of a molecular recognition event in a polymeric receptor assembly can be realized when the measured property is determined by the collective system. Conductivity is the best example of a collective property in conjugated (conducting) polymers, while properties such as redox potential and optical absorption/emission characteristics, though not entirely determined by a large collective system, are also strongly influenced.[2] The collective properties of conducting polymers are mainly due to their transport properties, specifically charge transport and energy migration, which are facilitated by their all conjugated backbone structure. Alteration in the electronic structure of the system can provide a number of different possible transduction mechanisms, influenced by transport characteristics.

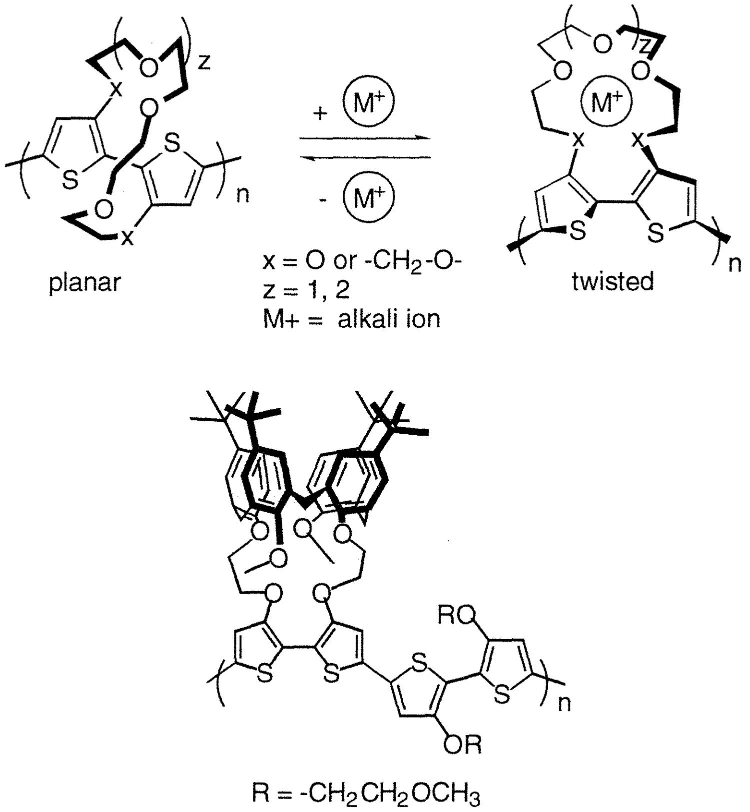
The use of conducting polymers as materials for biological and sensory devices has been widely studied and has recently found various applications. The versatile molecular recognition capabilities which may be imparted to conducting polymers, coupled with their ability to display easily monitored signals, provides the basis for powerful new sensing technologies.[3] The versatility stems directly from the availability of synthetic methodologies for the design of a diverse range of monomer types. Chemical or electrochemical polymerization of the monomers allows for the synthesis of conducting polymer-based sensors which can be mass-produced and miniaturized.[4] The recognition capability of the conducting polymer can be an inherent property of the resultant polymer or can be incorporated after the polymerization process.

Early work on conducting polymer based sensors involved redox or acid/base reactions between the conducting polymer and the analyte. However, these systems may be best characterized as indicators because of the irreversible nature of their interactions. The detection of gases such as HCl,[5] NH_3 and NO_2[6] was initially studied. Signals from these devices derive from changes in the resistance(chemoresistance) of the polymer film upon exposure to the gas of interest.[4]

Conducting polymer applications in biosensors have principally involved the integration of enzymes in conducting polymer films by either entrapment during the film's electrochemical formation or by the covalent attachment of the enzyme to the polymer.[7] Conducting polymers such as polypyrrole, polythiophene, polyaniline and polyindole have been used for the immobilization of enzymes at electrode surfaces.[8] Typical enzymes that have been immobilized in conducting polymer films are glucose-oxidase for glucose recognition[9] and diaphorase which catalyzes NADH oxidation in the presence of redox mediators.[10] The signals in these systems derive from the redox reaction of the enzyme with the appropriate substrate, which can either proceed *via* redox mediators or by direct electron transfer between the enzyme and the polymer.

Other work involving conducting polymer-based sensors includes organic chemical vapor detection by polypyrrole,[11-13] potentiometric anion sensors based on conducting polymer film electrodes,[14,15] and studies on response to humidity of conducting polyaniline.[16]

The major shortcoming of the above conducting polymer-based sensory materials is the dependence of the recognition event on chemical reactions, which more often than not, proceed irreversibly. Such an irreversible sensing mechanism would therefore require the material to be reset back to its original state[17] or simply function on a single time basis and be most properly termed an indicator. We have targeted the design of systems where the response is triggered by a reversible non-covalent interaction between the conducting polymer and the target analyte. Previous work in the Swager group includes the design of conducting polymers with molecular recognition components selective for alkali ions[18,19] and electron deficient organic molecules[2,17]. In particular, thiophene polymers have been chemically modified to incorporate recognition components, such as crown ethers and calix[4]arenes (Figure 1.1). These systems have the advantages of the reversible association between the conducting polymer-based receptors and the guest ions[18,19] as well as the sensitivity of polythiophene's conductivity to conformational changes and perturbations to its electronic environment.[20] In the presence of the guest ion, these conducting polymers display changes in UV absorption, conductivity and redox potential.



x = O or $-CH_2-O-$
z = 1, 2
M+ = alkali ion

$R = -CH_2CH_2OCH_3$

Figure 1.1. Polythiophenes containing simple crown ether functionality (top) and a calix[4]arene-substituted polythiophene (bottom) which displays high sensitivity to sodium ion.

In other previous work, polymers covalently linked to cyclophane receptors at regular intervals were designed such that interaction with paraquat guests triggered a response.[2] A system which displays a fluorescence chemosensory response, poly(phenylenethynylene) is shown in Figure 1.2. The response is a dramatic decrease in emission intensity after the guest-receptor interaction which can be attributed to the facile energy migration throughout the polymer.[2] Comparison with single receptor model systems indicated that the extended structure of the polymer produced amplification.

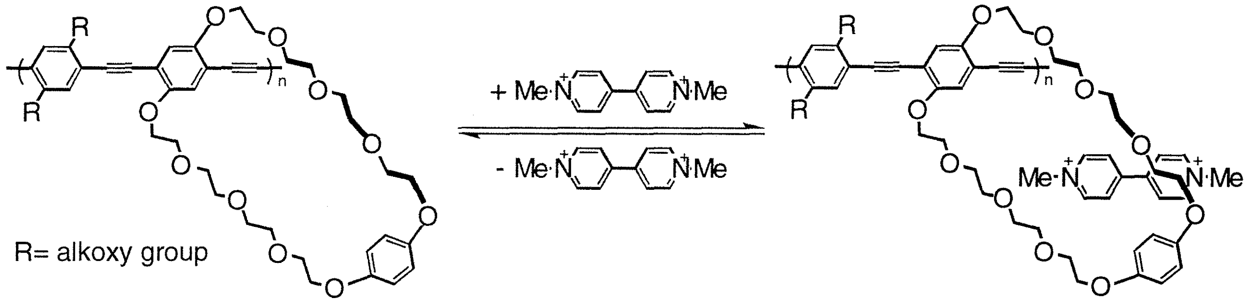


Figure 1.2. A poly(phenylenethynylene) which displays an amplified fluorescence chemosensory event by energy migration in the conjugated polymer. The reversible binding of paraquat as shown, results in quenching.

In these previous systems, the chemosensory signal has been an attenuation in a measured property. Due to the inherent advantages in sensors with low baseline (background) signals, we were interested in designing conducting polymers which would be electrical insulators in their resting state and would be transformed to a conductor when exposed to an analyte. Such a response could be produced by an analyte induced reversible doping reaction. The work in this thesis describes two approaches to these materials. Chapter 2 presents synthetic approaches to materials designed to exhibit ion-induced redox doping events. In Chapter 3, an alternative pseudo-protonic acid doping scheme is described.

Chapter 2

Synthetic Progress Towards a Redox Activated Conducting Polymer-Based Sensor

Introduction

Polythiophene is characterized an insulator or a large band gap semi-conductor in its neutral (undoped) state and becomes conducting when oxidized or reduced (doped). The charge carriers created with doping are transported through the polymer, resulting in an observed conductivity. The reduction and/or oxidation of the polymer is achieved either by chemical or electrochemical processes. We have been interested in incorporating a guest triggered redox-active component in the conducting polymer that will introduce the charge carrier into the polymer backbone, thereby eliminating the need for an "external" dopant. In particular, we targeted calix[4]arene-diquinone units, which have been proven to undergo reversible redox reactions.[21] Incorporating these groups into ion receptors which are affixed to the polythiophene chains (Figure 2.1) is expected to oxidize or reduce the conducting polymer in response to alkali metal ions and produce an increase in conductivity. This observed conductivity should be a function of the redox potential of the calix[4]arene-diquinone system which is sensitive to alkali ion concentration.

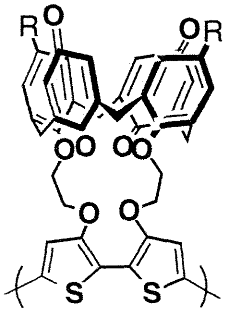
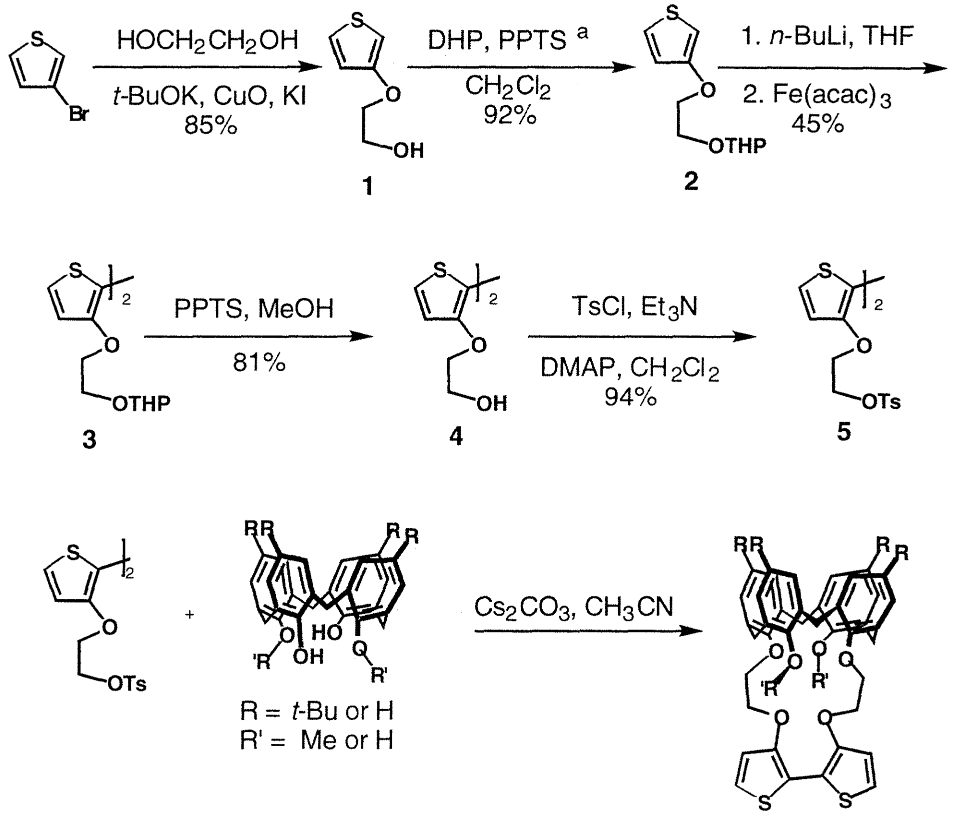


Figure 2.1. The target calix[4]arene-diquinone substituted polythiophene which is expected to give redox-activated response with alkali ion complexation.

Discussion of Results

Scheme 1 illustrates the approaches employed for the synthesis of the advanced intermediates (compounds **6** to **9**) needed for the preparation of the monomer which will be converted to the conducting polymer system depicted in Figure 2.1.

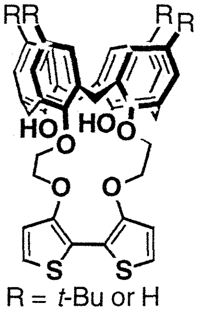
Scheme 1.



6: R = *t*- Bu R' = Me 77%
7: R =H R' =Me 30%
8: R = *t*- Bu R' = H } not isolated
9: R = H R' = H } in pure form

^{a} PPTS = pyridinium *p*-toluenesulfonate

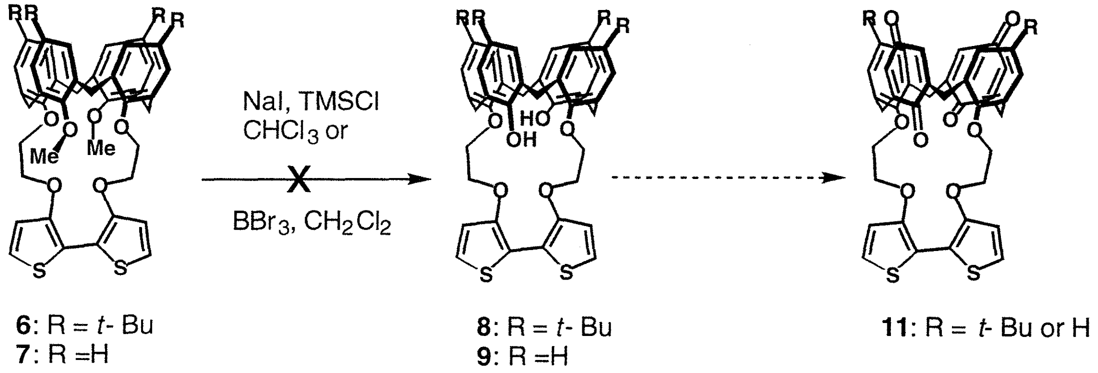
Compounds **1**-**6** were synthesized according to previous procedures[19] with the exception of the final macrocyclization which was improved to give a 77% yield of **6** by optimization with a syringe pump injection technique. Compounds **7** through **9** were also synthesized by similar high dilution procedures but the yields obtained are lower. For compound **7**, the lower yield (30%) could be attributed to the more flexible nature of calix[4]arene resulting from the absence of the *t*-butyl groups. This faster interconversion of calix[4]arene between its different conformations would complicate the macrocyclization reaction. For compounds **8** and **9**, the lower yield is most likely the result of the formation of side products which could potentially include the 1,2-disubstituted calix[4]arene, **10** as indicated by the complex ^{1}H-NMR spectra of impure **8** and **9**. Compounds **8** and **9**, both with two free hydroxyl groups, are difficult to purify and could not be isolated in pure form.



10

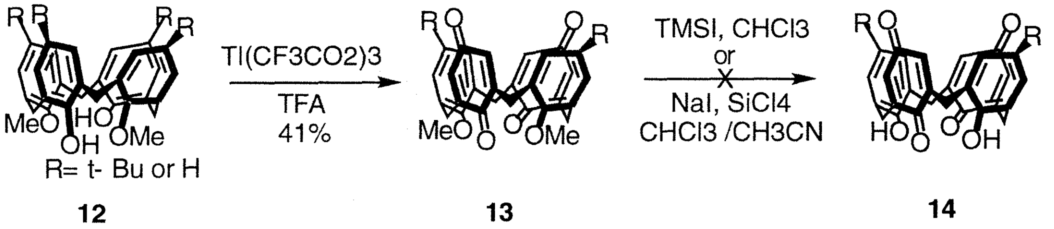
The next step toward the synthesis of the target monomer **11** was the oxidation of the calix[4]arene moiety to its diquinone form (Scheme 2). This transformation requires the addition of oxygen functionality on both the lower and upper rims of calix[4]arene. Compounds **8** and **9** should be easily transformed to **11**, but as mentioned earlier, they could not be isolated in pure form. Thus the removal of the two methoxy groups in compounds **6** and **7** was investigated as an alternative. Several attempts to demethylate **6** and **7** with typical reagents,[22] TMSI and BBr_3, produced only either starting material or unidentifiable side products, most likely resulting from the decomposition of starting material.

Scheme 2.

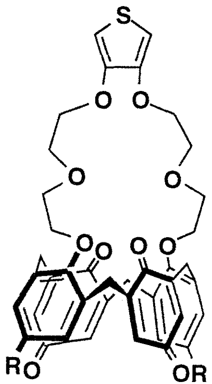


As an alternate route to the target monomer **11**, oxidation of calix[4]arene to the calix[4]arene diquinone **14** prior to the attachment of the bithiophene moiety was investigated (Scheme 3). The quinone-functionalized calix[4]arene, **13** was synthesized according to published procedures in 41% yield.[23] The methoxy groups in calix[4]arene **12** had been incorporated to prevent the conversion to the tetraquinone product which would occur under the thallium trifluoroacetate mediated oxidation reaction. However, **13** exhibited the same problem as compounds **6** and **7** in that removal of the two methoxy groups to give **14** proved to be an insurmountable obstacle. Compound **13**, with its highly reactive quinone functionality was degraded under the conditions required for the removal of the methoxy groups.

Scheme 3.



In an attempt to circumvent the difficulties encountered in the synthesis of the initial target monomer, we investigated modifications in the target structure. Scheme 4 outlines the steps taken to synthesize compound **19** which is a synthetic intermediate for our new target monomer **20**.



20

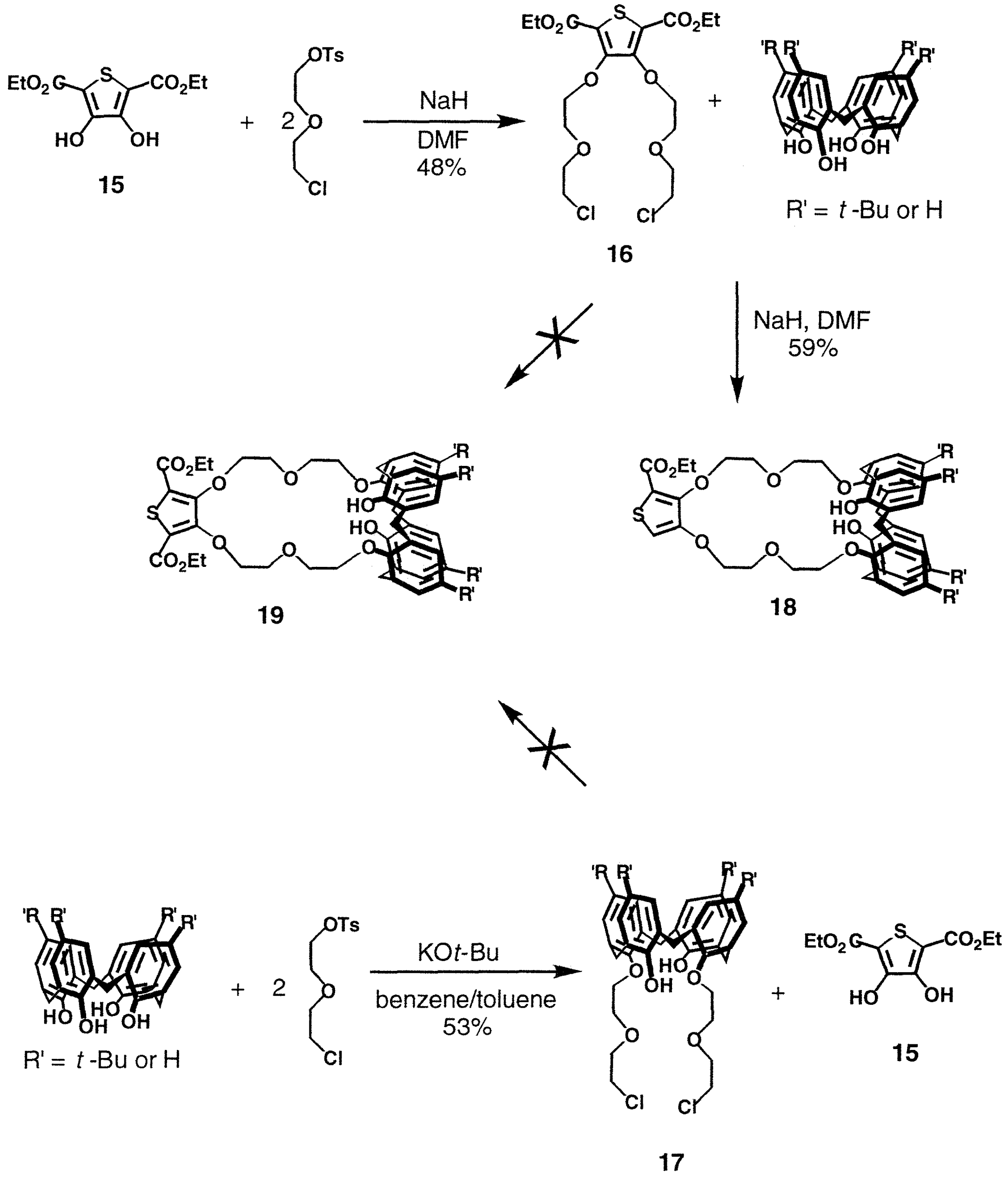
The key macrocyclization reaction in Scheme 4 was accomplished either by attaching the ethylene glycol linkers to the thiophene unit **15** to give **16** which is reacted with calix[4]arene, or by attaching the ethylene glycol linkers to calix[4]arene to give compound **17** and subsequently reacting it with the thiophene unit **15**. Diethyl (3,4-dihydroxy-2,5-thiophenedicarboxylate) **15**, synthesized using Hinsberg's reaction procedure,[24] was reacted sequentially with two equivalents of sodium hydride and then with two equivalents of 2-(2-chloroethoxy)ethyl *p*-toluenesulfonate in DMF at 85°C to give **16** in modest yields. Surprisingly, reaction with tetrahydroxycalix[4]arene, using sodium hydride in DMF did not give the expected product **19**, but the monodecarboxylated product, **18**.

The facile removal of one of the ethyl carboxylates was consistently observed in different attempts of this reaction. However, this was not considered a major problem, as the eventual goal was to remove both ester groups from the thiophene unit.

Alternatively, tetrahydroxycalix[4]arene was reacted with 2 equiv. of 2-(2-chloroethoxy)ethyl-*p*-toluenesulfonate, in the presence of potassium *t*-butoxide in benzene/toluene to give a 53% yield of the disubstituted calix[4]arene product **17**. Reaction of

17 with **15** to give the desired macrocycle **19** proved unsuccessful. This could be explained by the lower reactivity of the dianion of **15** as compared to the dianion of calix[4]arene.

Scheme 4.



Efforts were then focused toward the decarboxylation of the remaining ester group on **18**. Hydrolysis of **18**, using tetrabutyl ammonium hydroxide in methanol or potassium hydroxide in THF/water mixture gave the carboxylate salt of **18**. Attempts to decarboxylate by heating in either acidic or basic conditions did not give the expected product. Decarboxylation attempts using Hunsdiecker's reaction conditions also did not give the expected product.

Future approaches towards redox dopable polythiophene should focus upon developing better protecting group schemes.

Experimental Section

General Methods. Air and moisture sensitive reactions were carried out in oven-dried glassware using standard Schlenk techniques under Ar or N_2 atmosphere. All chemicals used were of reagent grade. Anhydrous THF and toluene were used directly from Aldrich KiloLab metal cylinders. DMF was dried over activated alumina and stored over molecular sieves under N_2 atmosphere. 5,11,17,23-Tetra-*t*-butyl-25,26,27,28-tetrahydroxycalix[4]arene and 25,26,27,28-tetrahydroxycalix[4]arene were synthesized according to literature procedures.[25,26] 5,11,17,23-Tetra-*t*-butyl-25,27-dihydroxy-26,28-dimethoxycalix[4]arene and 25,27-dihydroxy-26,28-dimethoxycalix[4]arene were also synthesized according to literature procedures[26]. ^{1}H-NMR spectra were obtained on a Bruker AC-250 spectrometer. Chemical shifts are reported in ppm relative to residual protio solvent (chloroform: 7.24 ppm (^{1}H)). Mass Spectra using CI methods with $CHCl_3$ as the solvent were obtained at the University of Pennsylvania instrumentation center.

Bithiophene Macrocycle 6. A modification on the original procedure[19] was developed. A 2-neck round bottom flask was charged with NaH (113 mg, 4.7 mmol), 50 mL of THF and 10 mL of DMF and brought to reflux. In a syringe pump apparatus, a 30 mL plastic syringe was filled with 5,11,17,23-tetra-*t*-butyl-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (1.06 g, 1.7 mmol) in 20 of mL THF and 5 mL of DMF. A second 30 mL syringe was filled with compound **5**, 3,3'-bis(4-(*p*-toluenesulfonyl-1,4-dioxabutyl))-2,2'- bithiophene (930 mg, 1.57

mmol), in 10 mL of THF and 15 mL of DMF. The syringe pump addition was performed over a 24 hour period and the resulting solution was heated to 80^{o}C for four days. The solution was then cooled and the solvent removed under vacuum. The residue was dissolved in diethyl ether and washed three times with dilute aqueous $NHCl_4$ solution to remove DMF. The solution was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was chromatographed using 10% ethylacetate in hexane. It was further purified by washing with diethyl ether to give a white solid product in 77 % yield. ^{1}H-NMR (250 MHz): δ 0.79 (s), 0.93 (s), 1.00 (s), 1.17 - 1.32 (m), 3.0 (s), 3.14 (d), 3.27 (d), 3.32 (s), 3.54 (s), 3.75 (m), 3.86 (d), 4.11 - 4.12 (m), 4.26 - 4.43 (m), 4.66 (t), 6.46 (s), 6.85 (d), 6.94 -7.24 (m); [^{1}H integration: 0.79 - 1.32 (51% of H), 3.0 - 4.66 (31% of H), 6.46 - 7.24 (18% of H)].

Bithiophene Macrocycle 7. A 500 ml round bottom flask was charged with 25,27-dihydroxy-26,28-dimethoxycalix[4]arene (380 mg, 0.84 mmol) and 3,3'-bis(4-(*p*-toluenesulfonyl-1,4-dioxabutyl))-2,2'- bithiophene (500 mg, 0.84 mmol) dissolved in 200 mL of acetonitrile. Cs_2CO_3 (550 mg, 1.68 mmol) was added to the solution. The solution was refluxed for 24 h, then cooled and the solvent removed under vacuum. The residue was dissolved in methylene chloride and washed with water to remove excess and unreacted Cs_2CO_3. The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by column chromatography using 15 % ethylacetate in hexane. The white, glassy product was isolated in 30 % yield. ^{1}H-NMR (250 MHz): δ 3.22 (d, 4H), 3.61 (s, 6H), 4.36 (d, 4H), 4.47 (d, 4H), 4.57 (d, 4H), 6.14 - 6.29 (m, 4H), 6.92 - 6.99 (m, 4H), 7.15-7.27 (dd, 4H). MS m/z (M^+) calcd 702.2110, (M^+) obsd 702.

Bithiophene Macrocycle 8. This compound was prepared according to the procedure for **7**, using 5,11,17,23-tetra-*t*-butyl-25,27,26,28-tetrahydroxycalix[4]arene (270 mg, 0.42 mmol), 3,3'-bis(4-(*p*-toluenesulfonyl-1,4-dioxabutyl))-2,2'- bithiophene (250 mg, 0.42 mmol) and CsF (380 mg, 2.52 mmol) dissolved in 150 mL of acetonitrile. The crude product was purified by column chromatography using 10 % ethylacetate in hexane but only mixture of products were obtained. ^{1}H-NMR (250 MHz): 0.92 (s), 1.1 (s), 1.20 (s), 1.21 (s), 1.23 (s), 3.50 (br d), 3.86 (t), 4.20 - 4.5 (br m), 4.70 (t), 4.92 (t), 6.7 - 7.4 (m).

Bithiophene Macrocycle 9. This compound was prepared according to the procedure for 7, using 25,27,26,28-tetrahydroxycalix[4]arene (180 mg, 0.42 mmol), 3,3'-bis(4-(*p*-toluenesulfonyl-1,4-dioxabutyl))-2,2'- bithiophene (250 mg, 0.42 mmol) and CsF (130 mg, 0.84 mmol) dissolved in 100 mL of acetonitrile. The crude product was purified by column chromatography using 10 % ethylacetate in hexane but only mixture of products were obtained. ^{1}H-NMR (250 MHz): 3.34 (d), 3.43 (d), 4.12 - 4.74 (m), 6.56 -6.85 (m), 6.94 - 2.28 (m), 8.25 (s), 8.56 (s).

Diethyl(3,4-(2-(2-chloroethoxy)ethoxy))-2,5-thiophene dicarboxylate 16. To a 25 mL Schlenk flask was added diethyl (3,4-dihydroxy)-2,5-thiophene dicarboxylate (100 mg, 0.4 mmol) and 10 mL of DMF. The resulting solution was subjected to a freeze-pump-thaw cycle after which sodium hydride (20 mg, 0.8 mmol) was added. 2-(2-chloroethoxy)ethyl-*p*-toluenesulfonate (220 mg, 0.8 mmol) dissolved in about 5 mL of DMF was added to the solution. The solution was heated to 85^{o}C. Progress of the reaction was monitored by thin-layer chromatography. After 24 h, the clear yellow solution was cooled and the solvent was removed under high vacuum. The residue was dissolved in methylene chloride and washed with water to remove the residual sodium hydride and DMF. The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The viscous, oily crude product was chromatographed using a 5:3 hexane/ethylacetate solvent mixture to yield a yellow, low melting, waxy solid product in 48 % yield. ^{1}H-NMR (250 MHz): δ 1.37 (t, 6H), 3.61-3.63 (m, 4H), 3.78-3.88 (m, 8H), 4.30-4.40 (m, 8H). MS m/z (M^+) calcd 472.1627, obsd (M^+H) 473.

25,27-Dihydroxy-26,28-(2-(2-chloroethoxy)ethoxy)calix[4]arene <u>17</u>. Under an argon atmosphere, a 250 mL three neck flask containing 25,26,27,28-tetrahydroxycalix[4]arene (200mg, 0.31 mmol) in 50 mL of toluene was fitted with an addition funnel containing 2-(2-chloroethoxy)ethyl-*p*-toluenesulfonate (220 mg, 0.78 mmol) dissolved in 20 mL of benzene and a reflux condenser. Potassium-*t*-butoxide (35 mg, 0.31 mmol) in 20 mL of benzene was added to the solution *via* cannula and brought to reflux. The contents of the addition funnel were allowed to drip in the flask over a 90 minute period. The solution was left to reflux for 24 h, after which a second batch of potassium-*t* -butoxide (35 mg, 0.31 mmol) in 20 mL of benzene was added. The resulting solution was allowed to reflux for another 24 h. The solution was cooled and benzene/toluene solvent mixture was removed under vacuum. The residue was dissolved in methylene chloride and washed with dilute aqueous NH_4Cl solution. The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using 20% ethylacetate in hexane. The product was obtained in 53 % yield. ^{1}H-NMR (250 MHz): δ 0.95 (s), 1.29 (s), 3.30 (d, 4H), 3.74 (t, 4H), 3.95-4.02 (m, 8H), 4.07-4.17 (m, 8H), 4.33 (d, 4H), 6.78 (s), 7.05 (s), 7.19 (s, 2H), H). MS m/z (M^+) calcd. 860.4549, (M^+) obsd. 860.

Thiophene Macrocycle <u>18</u>. A 25 mL Schlenk flask was charged with 25,26,27,28-tetrahydroxycalix[4]arene (48 mg, 0.074 mmol), 10 mL of DMF and sodium hydride (14 mg, 0.58 mmol) and allowed to stir for an hour at room temperature. Diethyl (3,4(2-(2-chloroethoxy)ethoxy))-2,5-thiophene dicarboxylate (35 mg, 0.074 mmol) in 3 mL of DMF was then added *via* syringe over a fifteen minute period. The solution was heated to 100 ^oC. After 48 h, the solution was cooled and the solvent was removed under high vacuum. The residue was dissolved in methylene chloride, washed with water and concentrated *in vacuo*. The crude product was chromatographed with 30 % ethylacetate in hexane as the eluent. The product obtained was the mono-decarboxylated thiophene in 29 % yield. ^{1}H-NMR (250 MHz): δ 1.15 (s, 18H), 1.20 (s, 18H), 1.39 (t, 3H), 3.32 (t, 4H), 4.01-4.48 (m, 16H), 4.49

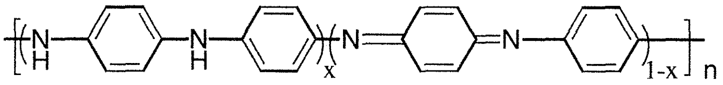
(m, 4H), 6.44 (s, 1H), 6.82 (s), 6.91-7.00 (m) [1H integration: 6.82-7.00 (8H)], 8.47 (s, 1H), 8.63 (s, 1H). MS m/z (M^+) calcd. 976.5159, (M^+) obsd. 976.

Chapter 3

Progress Toward Guest Induced Pseudo-Doped Polyaniline Sensors

Introduction

Polyanilines (I) are an important class of conducting polymers that can be synthesized from aniline derivatives by chemical or electrochemical polymerization. The resulting polymers are unique among other conducting polymers studied to date in that there are neutral forms of polyaniline, where (1-x)>0, in partially oxidized states.[27] In fact, polyanilines range in composition from three different oxidation states, the fully reduced form (x=1) also called leucoemeraldine, the fully oxidized form (x=0), also called pernigraline state, and the half-oxidized polymer (x=0.5), the so-called emeraldine state.[1]



I

Doping of the leucoemeraldine form can be done by the conventional chemical and electrochemical means involving oxidation of the polymer. However, it is also known that compositions in partially oxidized states (i.e. emeraldine) are capable of being doped by a non-redox protonation process. In such a case, the imine nitrogens are protonated, thereby introducing mobile charge carriers in the polymer backbone.[27] According to studies done by MacDiarmid, et. al. complete protonation of the imine nitrogens of the emeraldine with hydrochloric acid is accompanied by an increase in conductivity of approximately 10^{10}.[1]

This dramatic change in conductivity with protonic acid doping lends credence to the potential of polyanilines as sensory materials. It is our goal to design systems where the receptor-analyte interactions would mimic the protonation of the nitrogens inducing a large increase in conductivity. Since protonic doping involves introduction of positive charge carriers in polyaniline, the molecular recognition events employing positively charged ions as the analyte are natural candidates. The use of a crown ether as the molecular recognition component for polyaniline based sensors has the advantage in that the complexations of alkali ions with crown ethers are among the best understood host-guest interactions.

Figure 3.1 shows the structure of our target polyaniline-based ion sensor. It consists of a lariat crown substituent per aniline unit of the polymer and binding of metal ions should produce interactions with the imine nitrogens of the polymer.

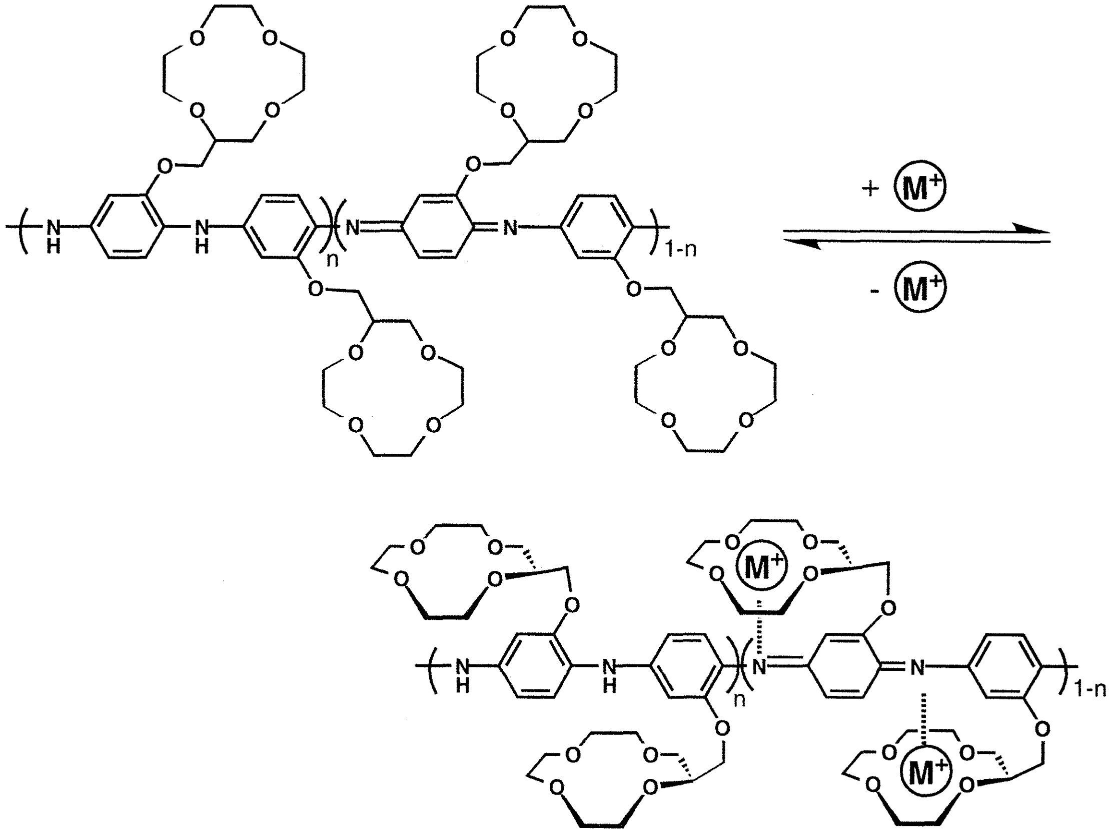


Figure 3.1. Schematic showing how metal ion binding with crown-ether functionalized polyaniline can function as a pseudo protonic doping event.

Another triggering interaction that we were interested in utilizing was that between boron and nitrogen. It has been reported that while boronic acid saccharide complexation occurs only at high pH conditions, wherein the assistance of a OH^- group is required to form the boronate anion, a neighboring amine group participation can lower the pH requirement for the boronic acid complexation.[28] Thus, if we can strategically append boronic acid functionality to the polyaniline backbone, the interaction of boron with the amine or imine nitrogens of the polymer will assist the complexation of boronic acid with vicinal diol containing compounds such as ethylene glycol, pinacol and glucose. In this case, the pseudo-protonic doping response of polyaniline would be extended beyond that of cations and into the area of organic molecules.

Figure 3.2 shows a structure with boronic acid functionality appended to the polyaniline system. The boronic acid groups are expected to bind vicinal diols with the assistance of the imine nitrogen atoms of the polymer.

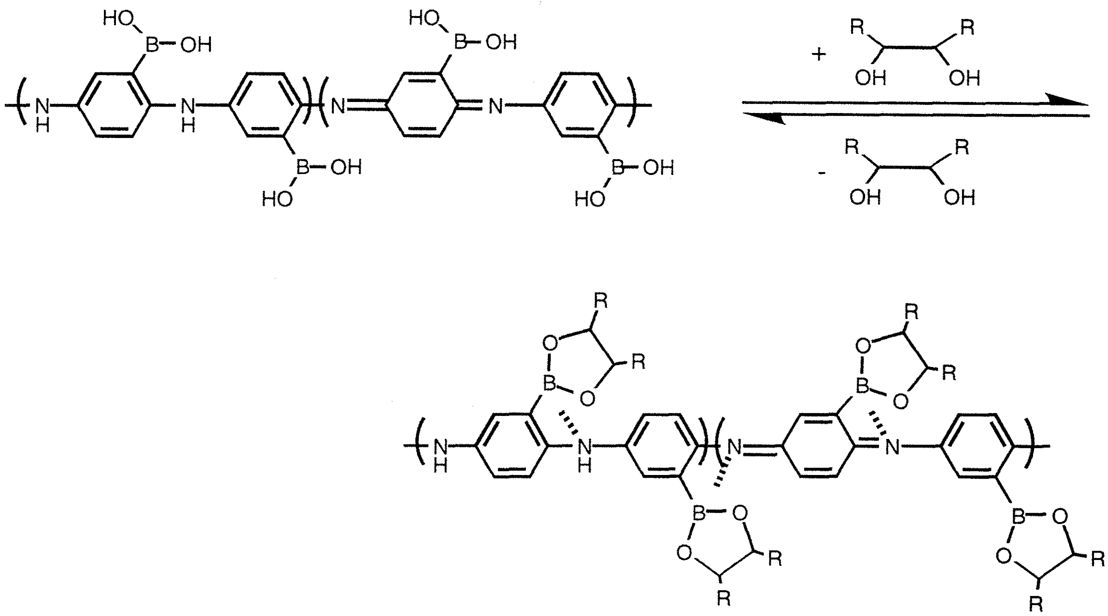
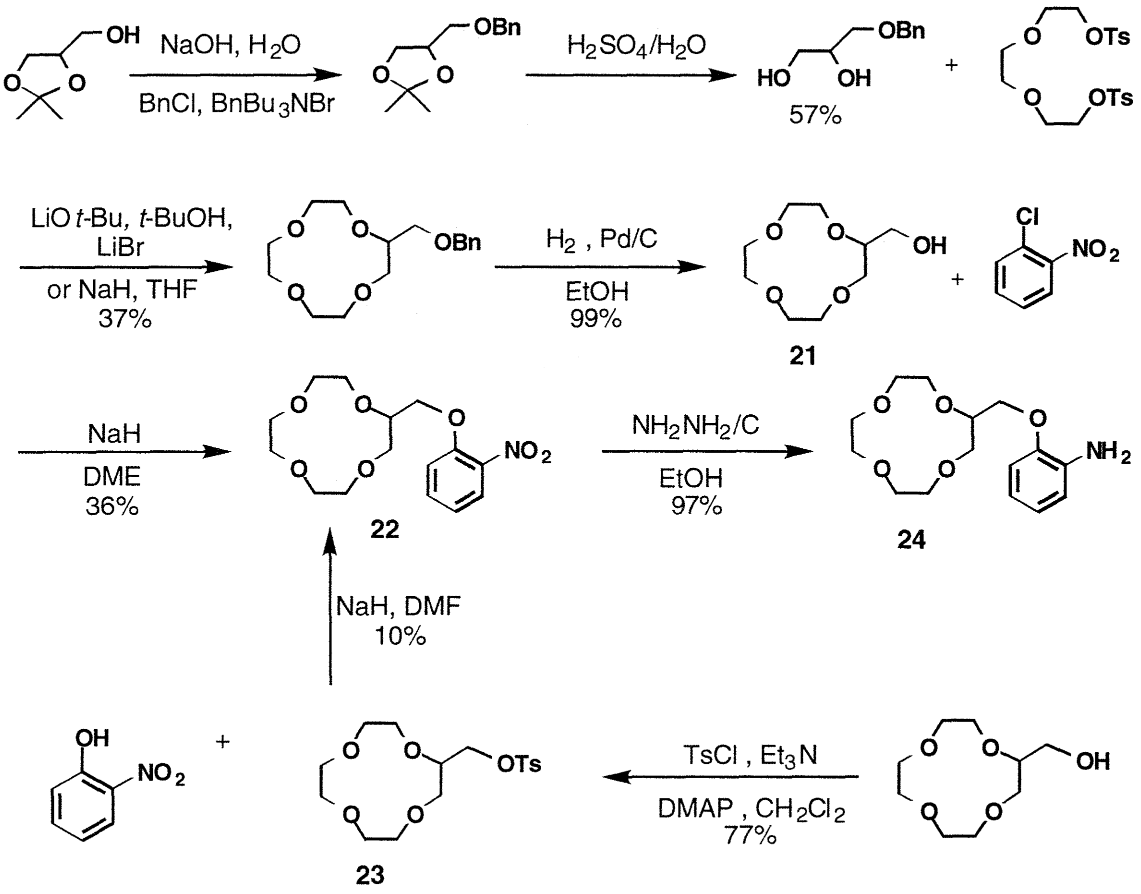


Figure 3.2. Schematic illustration of boronic acid functionalized polyaniline for the binding of vicinal diol-containing compounds which leads to a psuedo-protonic doping event.

Discussion of Results

Crown-ether Functionalized Polyaniline Sensor. Two routes to monomer **24**, *o*-(2(methyleneoxy)-12-crown-4)-aniline are shown in Scheme 4. Starting from commercially available solketal and using known procedures,[29,30] **21**, 2-(hydroxymethyl)-12-crown-4, was isolated in 21% overall yield as a light brown oil. Conversion to *o*-(2-(methyleneoxy)-12-crown-4)-nitrobenzene, **22** was carried out either by the nucleophilic aromatic substitution of *o*-chloronitrobenzene by the sodium salt of **21** or by a Williamson ether reaction between **23**, (2-*p*-toluenesulfonylmethyleneoxy)-15-crown-5 and *o*-nitrophenol. Compound **23** was prepared from the reaction of **21** with tosyl chloride. The aniline-crown monomer, **24** was then obtained by reduction of **22**, using hydrazine monohydrate on activated carbon in ethanol.

Scheme 5.



Electrochemical oxidation of **24** using standard conditions[31] did not yield the desired polymer. Electrochemical oxidation of simple aniline derivatives proceeds by initial coupling of the aniline radical cations in a head-to-tail fashion to give the 4-amino-diphenylamine which is then further oxidized (at a lower potential) to eventually give the polymer product (Figure 3.3).[32] There is, however, a competing reaction where tail-to-tail coupling of the aniline radical gives a benzidine structure, which inhibits the polymerization process. We believe the latter is most likely occurring and there is the predominance of the competing tail-to-tail coupling, which gives a less sterically hindered product with the bulky crown ether group ortho to the amine. The benzidine product minimizes sterics between the crown ether groups and prevents the formation of polymeric products.

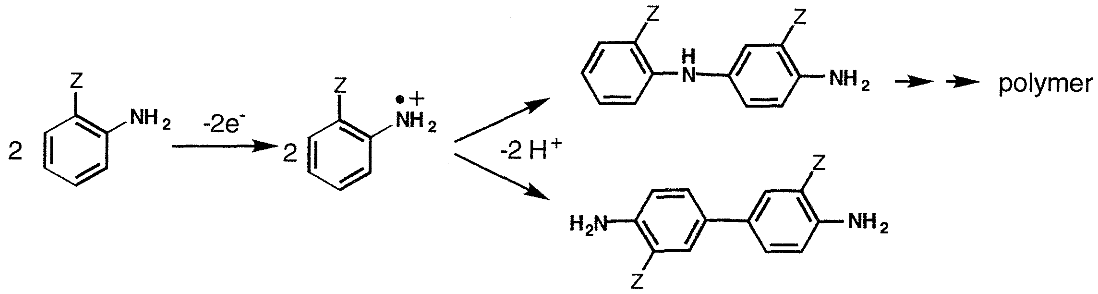
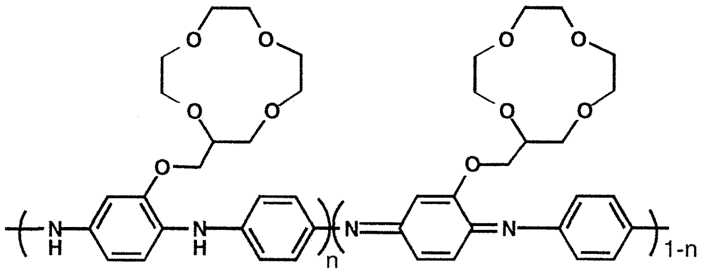


Figure 3.3. Two competing free-radical coupling reactions of *o*-substituted aniline. The head-to-tail coupling (top) produces polymer whereas the tail-to-tail coupling (bottom) does not.

Reducing the steric hindrance on the dimer unit should minimize the tail-to-tail coupling. Bearing this in mind, we designed a system with one crown ether substituent per two aniline units to give polymer **25**.

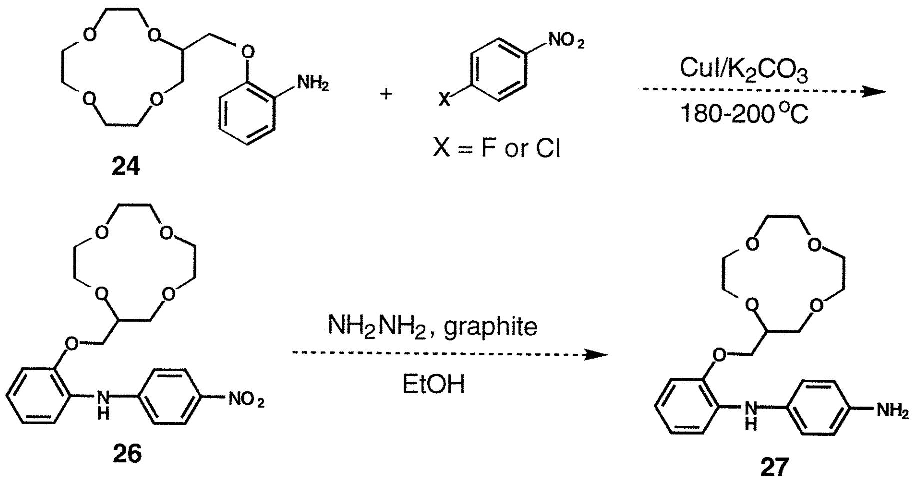


25

Scheme 6 shows the synthetic approach to the aniline dimer **27**, *N*-4-aminophenyl-2-(2-methyleneoxy-12-crown-4)aniline. Reaction of **24** with either fluoro or chloronitrobenzene by a nucleophilic aromatic substitution process would give compound **26**, *N*-4-nitrophenyl-2-

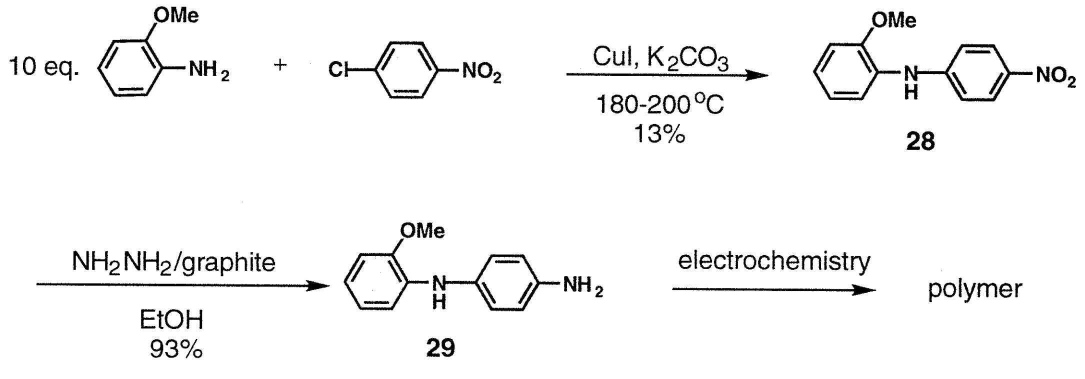
(2-methyleneoxy-12-crown-4)aniline. Reducing the nitro functionality of **26** to the amine should provide **27**, which can be electrochemically polymerized to give the desired polymer.

Scheme 6.



The synthetic methodology described in Scheme 6 was attempted on a model system, using 2-methoxyaniline in place of compound **24**. As shown in Scheme 7, 2-methoxyaniline was reacted with 4-chloronitrobenzene in 10:1 molar ratio at 180 - 200°C to give a 13 % yield of **28**, *N*-4-nitrophenyl-2-methoxyaniline. Conversion to amine **29**, *N*-4-aminophenyl-2-methoxyaniline, was accomplished using hydrazine monohydrate with activated carbon in ethanol. Cyclic voltammetry in aqueous acidic solution of **29** indicated the polymer formation on the platinum electrode surface (Figure 3.4).

Scheme 7.



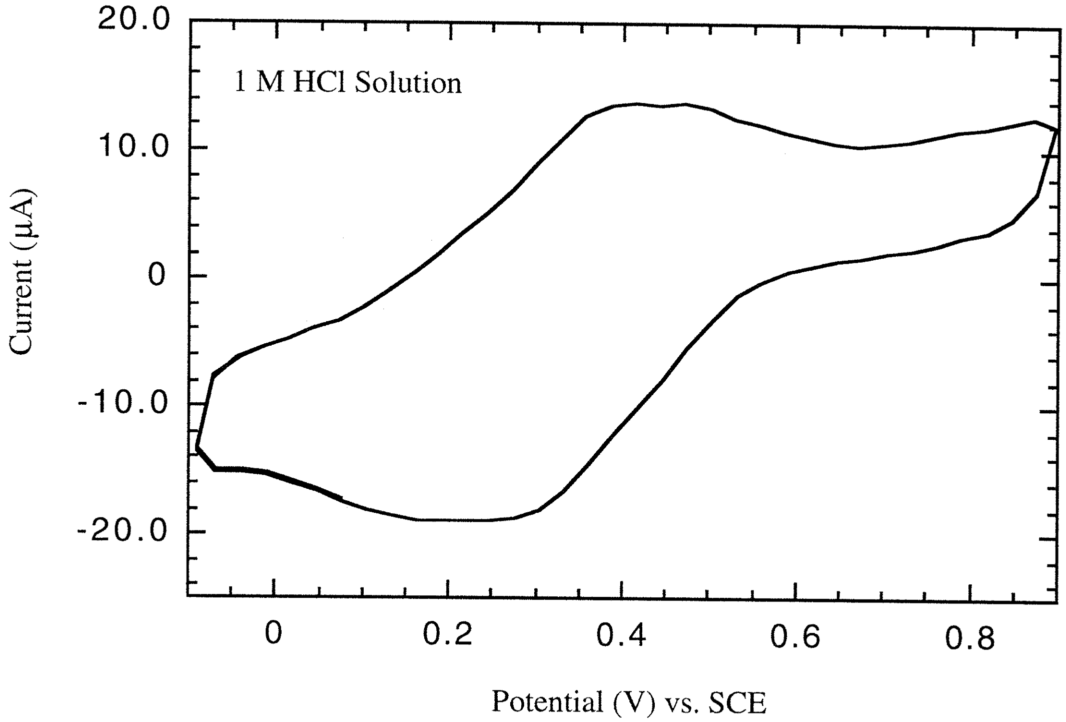
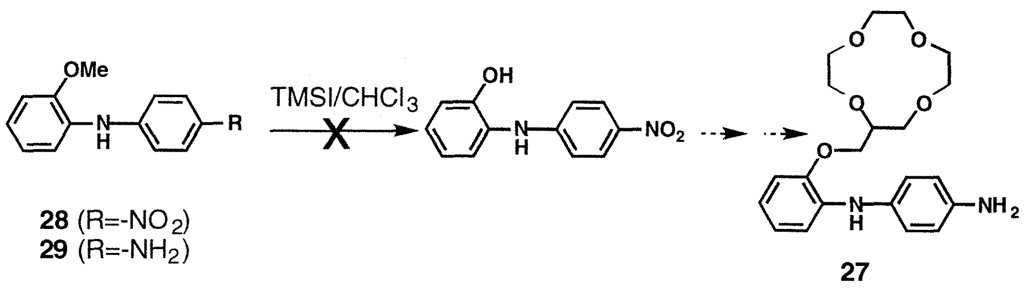


Figure 3.4. Cyclic voltammogram (scan rate of 80 mV/s) of methoxy-substituted amino diphenylamine **29** indicating polymer growth.

The use of excess aniline starting material, the low yield and the harsh reaction temperature conditions make the nucleophilic aromatic substitution reaction an impractical route to the synthesis of the crown-ether substituted aniline dimer. Nevertheless, we considered that removing the methyl group in compound **28** or **29** to give a hydroxy substituted diphenyl amine (Scheme 8) also provides a route to the desired dimer, **27** . Unfortunately the removal of methyl group by standard demethylation procedures was unsuccessful. The presence of the amine and the nitro groups most likely is the reason for this result.

Scheme 8.

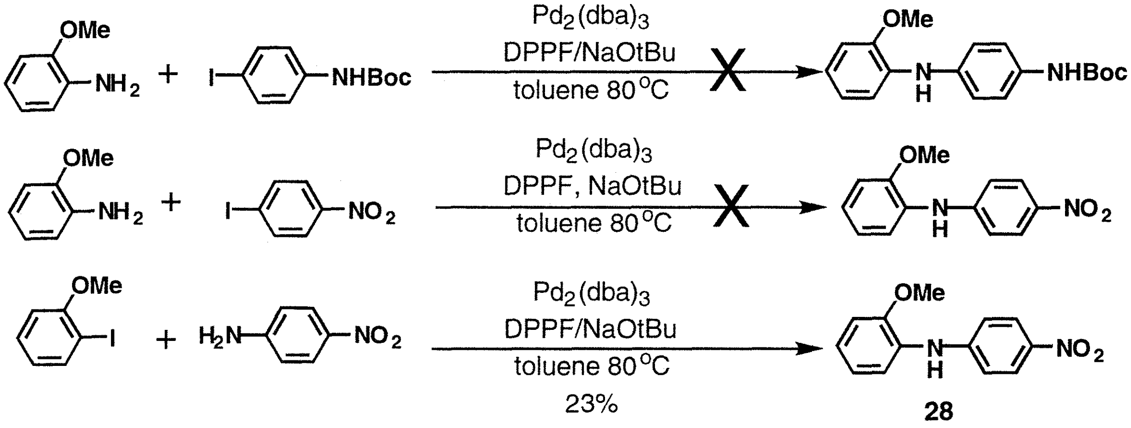


28 ($R=-NO_2$)
29 ($R=-NH_2$)

27

Other methods for synthesizing the aniline dimer under gentler reaction conditions were investigated. Buchwald has reported the coupling of primary amines with aromatic halides to give secondary amines using palladium catalysts.[33] Synthetic attempts using this methodology are shown in Scheme 9.

Scheme 9.

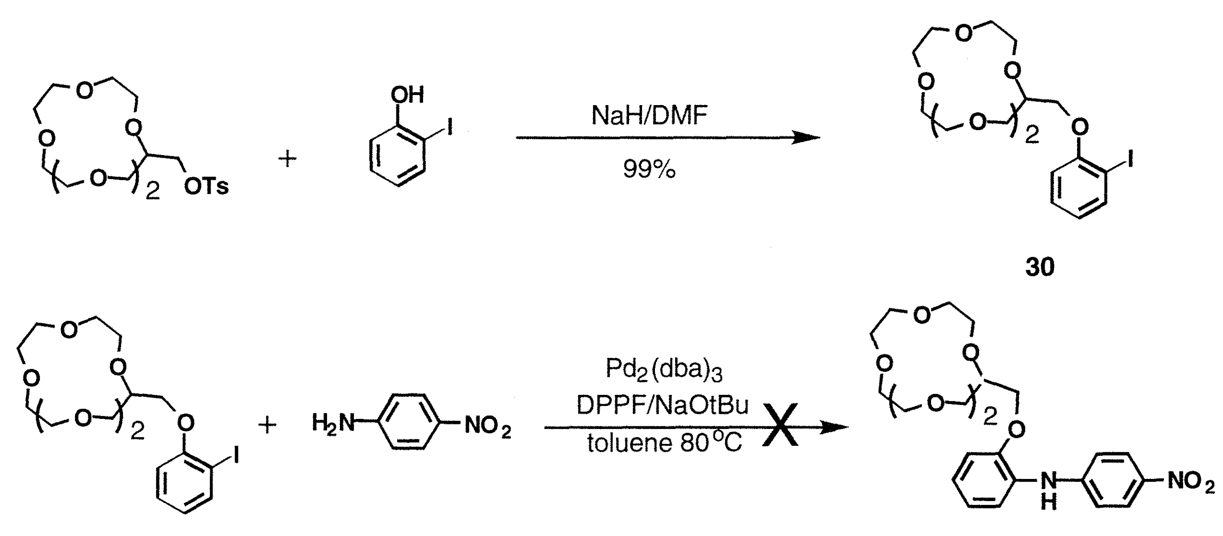


28

Reaction of 2-methoxyaniline with a Boc protected 4-iodoaniline using a palladium(0) catalyst, dppf (dppf=bis(diphenylphosphino)ferrocene) ligand and sodium *t*-butoxide in toluene at 80°C did not give the the expected product. This result is most likely due to the more acidic carbamate proton which prevents deprotonation of the amine, a step necessary for this coupling reaction. The same reaction conditions were applied to an alternative coupling reaction between *o*-methoxyaniline and *p*-iodonitrobenzene. This also did not give the expected product. At this point we suspected that the electron rich and highly reactive nature of the deprotonated *o*-methoxyaniline may cause it to be prone to oxidation. To eliminate this problem, an electron withdrawing substituent was placed on the aniline component of the coupling reaction. Using a 1:1 ratio of 2-iodoanisole and 4-nitroaniline under the same unoptimized reaction conditions, the expected product **28** was isolated in 23 % yield. This encouraging result with the model system led us to undertake a similar synthesis of **27** using the palladium mediated reaction.

Scheme 10 outlines our synthetic approach to **26** which should readily undergo reduction to give **27**. 2-(2-Methyleneoxy-15-crown-5)-iodobenzene, **30**, was synthesized from 2-iodophenol and the tosylate of (2-hydroxymethyl)-15-crown-5 using sodium hydride in DMF. Subjecting **30** and 4-nitroaniline to the palladium catalyzed coupling conditions did not produce the expected product. Several attempts with varying catalyst load, solvent system, and temperature regiems did not succeed in giving the desired product.

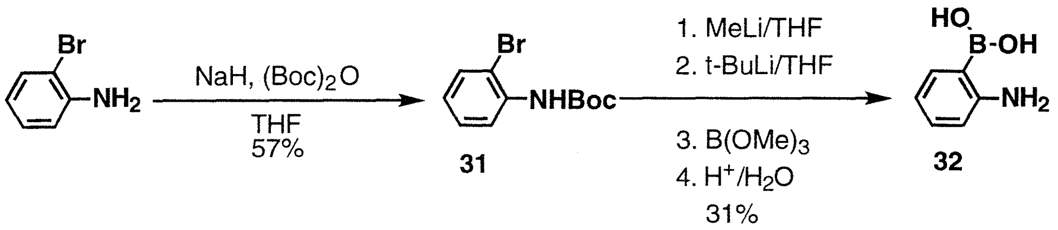
Scheme 10.



The role that the crown ether has in preventing the palladium's catalytic cycle is unclear. Additional routes to the synthesis of the lariat crown ether appended *N*-(4-aminophenyl)-anilines have yet to be explored.

Boronic Acid Appended Polyaniline. The synthesis of monomer 2-aminophenyl boronic acid, **32** is given in Scheme 11 from the reported procedure of Tour.[34] Boc protection of 2-bromoaniline using sodium hydride and Boc anhydride in THF was accomplished in 57 % yield giving **31**. Compound **31** was reacted with 1.1 equiv. of methyl lithium to deprotonate the carbamate proton and with 2.2 equiv. of *t*-butyl lithium for metal-halogen exchange. Addition of trimethyl borate generates the borate ester *in situ* , which was then hydrolyzed to give the boronic acid, **32**.

Scheme 11.



Preliminary electrochemical investigations of acidic aqueous solutions of **32** (0.1 M in 1 M HCl solution) indicate that a polymer is deposited with anodic cycling from 0 to 1.0 V. Figure 3.5 shows the cyclic voltammograms of the polymer of **32** and of the commercially available regioisomer of **32**, *m*-aminophenyl boronic acid, in fresh 1 M HCl solutions. The cyclic voltammograms of the boronic acid substituted polyaniline exhibited two oxidation peaks, in agreement with previous observations in unsubstituted polyaniline. The first anodic peak has been ascribed to the oxidation of the leucoemeraldine and the second peak to the oxidation of the radical cation of the polyamine accompanied by loss of protons.[27]

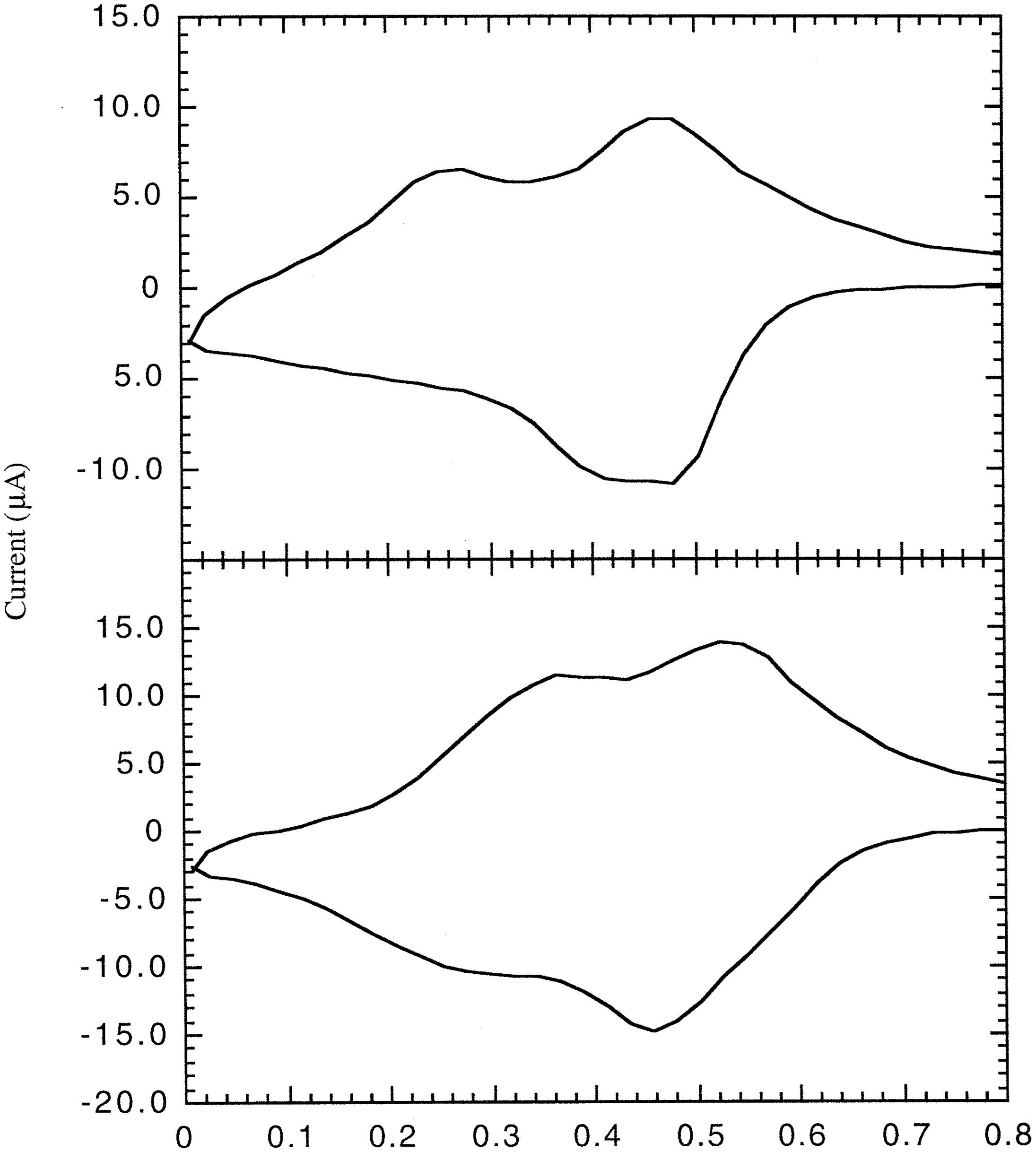


Figure 3.5. Cyclic voltammograms (scan rate 80 mV/s) of polymers of *m*-aminophenyl boronic acid (top) and *o*-aminophenyl boronic acid(bottom) in 1 M HCl aqueous solutions.

Theoretically, the polymer products of the two regioisomers should be indistinguishable, but the difference in their cyclic voltammogram profiles could be accounted for by the fact that for a pair of ortho and meta substituted isomers, the ortho substituted aniline gives a more regular polymer structure.[35] The presence of an ortho substituent prevents formation of ortho coupling that leads to probable structural defects. In the case of meta-substituted aniline, the ortho position is available for possible ortho coupling, leading to more complicated polymer structures.

Experimental Section

General Methods. Air and moisture sensitive reactions were carried out in oven-dried glassware using standard Schlenk techniques under Ar or N_2 atmosphere. All chemicals used were of reagent grade and purchased from Aldrich unless otherwise noted. DPPF was purchased from Strem and used as received. Anhydrous THF, DME and toluene were used directly from Aldrich KiloLab metal cylinders. DMF was dried over activated alumina and stored over molecular sieves under N_2 atmosphere. ^{1}H-NMR spectra were obtained on a Bruker AC-250 spectrometer. Chemical shifts are reported in ppm relative to residual protio solvent (chloroform: 7.24 ppm (^{1}H)). Mass Spectra using CI methods with $CHCl_3$ as the solvent were obtained at the University of Pennsylvania instrumentation center. Electrochemical reactions were carried out using a Pine Model RDE 3 bipotentiostat under ambient conditions in acidic aqueous solutions with a SCE reference electrode.

***o*-(2-(Methyleneoxy)-12-crown-4)-nitrobenzene <u>22</u>**. A two-neck flask was charged with 2-(hydroxymethyl)-12-crown-4 (200 mg, 0.97 mmol), 20 mL of DME and sodium hydride (117 mg, 4.85 mmol). The solution was heated to reflux. 4-chloronitrobenzene (460 mg, 2.91 mmol) in DME was slowly added to the refluxing reaction mixture *via* an addition funnel over the period of one hour. The solution was then refluxed for 24 h, allowed to cool and washed with dilute aqueous NH_4Cl solution to quench and remove the unreacted sodium hydride. The solvent was removed under vacuum. The crude product was purified by column chromatography using 1:1 chloroform/ethylacetate as the eluent. The product was isolated in 36 % yield. ^{1}H-NMR (250 MHz): δ 3.64-3.93 (m, 15 H), 4.10 (d, 2H), 7.00-7.11 (m, 2H), 7.49 (t, 1H), 7.86 (d, 1H). MS m/z (M^+) calcd. 327.1318, (M^+NH_4) obsd. 345.

(2-*p*-Toluenesulfonylmethyleneoxy)-15-crown-5 **23a**. 2-(Hydroxymethyl)15-crown-5 (5.15 g, 20.6 mmol) was dissolved in 150 mL of methylene chloride in a 500 mL round bottom flask. The solution was cooled to 0°C in an ice-water bath while stirring. DMAP (1.26 g, 10 mmol) and diisopropylamine (4.3 mL, 25 mmol) were added to the stirring solution. *p*-Toluenesulfonyl chloride (4.32 g, 20.6 mmol) was added to the solution. The solution was allowed to warm to room temperature with constant stirring for 10 h. The solution was diluted with methylene chloride and washed with dilute aqueous HCl solution. The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was isolated in 77 % yield without a need for further purification. ^{1}H-NMR (250 MHz): δ 2.44 (s, 3H), 3.47-43.85 (m, 19H), 4.02 (dd, 1H), 4.16 (dd, 1H), 7.33 (d, 2H), 7.79 (d, 2H).

(2-*p*-Toluenesulfonylmethyleneoxy)-12-crown-4 **23b**. This compound was prepared according to the procedure for **23a**, using 2-(hydroxymethyl)-12-crown-4 , prepared according to a literature procedure.[29,30] Purification by column chromatography with 40% ethylacetate in hexane gave a 20 % yield. ^{1}H-NMR (250 MHz): δ 2.45 (s, 3H), 3.46-4.18 (m, 17H), 7.37 (d, 2H), 7.80 (d, 2H). MS m/z (M^+) calcd. 360.1243, obsd. (M^+H) 361.

***o*-(2-(Methyleneoxy)-12-crown-4)-aniline** **24**. A 25 mL Schlenk flask was charged with 2-(2-(methyleneoxy)-12-crown-4)-nitrobenzene, **20** (164 mg, 0.5 mmol), 5 mL of ethanol and activated graphite (15 mg). The heterogeneous mixture was purged with argon. Hydrazine monohydrate (0.15 mL, 3.0 mmol) was added to the mixture using a syringe. The mixture was allowed to reflux for 48 hours. The reaction mixture was filtered and the solvent was removed under vacuum. Purification was carried out by dissolving the crude product in chloroform and extracting it with 1 M HCl aqueous solution. The aqueous extract was washed with chloroform three times and subsequently neutralized with 1 M Cs_2CO_3 aqueous solution. The solution was then extracted with chloroform four times, dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The product was isolated in 97 % yield. ^{1}H-NMR (250 MHz): δ 3.62-3.91 (m, 15H), 4.02 (d, 2H), 6.70-6.81 (m, 4H). MS m/z (M^+) calcd. 297.1576, obsd. (M^+H) 298.

***N*-4-nitrophenyl-2-methoxyaniline <u>28</u>, Method 1.** Under an inert atmosphere of argon, 4-chloronitrobenzene (1.0 g, 6.35 mmol) was dissolved in 2-methoxyaniline (7.2 mL, 63.5mmol). To the reaction mixture were added CuI (0.12 g, 0.64 mmol) and K_2CO_3 (0.87 g,6.35 mmol). The reaction mixture was subjected to a freeze-pump-thaw cycle then was heated to 180°C for 20 h. The reaction was then dissolved in methylene chloride and washed with dilute ammonium chloride solution four times. Methylene chloride was removed under vacuum and the dark, purplish product was purified by column chromatography using 15 % ethylacetate in hexane. A bright yellow solid product was isolated in 13 % yield.

Method 2. Under an inert atmosphere of argon, a two-neck flask fitted with a condenser and a rubber septum was charged with 4-nitroaniline (0.5 g, 3.6 mmol), potassium *t*-butoxide (0.48 g, 4.3 mmol) and (dppf) Pd $(Cl)_2$ catalyst (0.15 g, 0.18 mmol). Cannula addition of 10 mL of anhydrous toluene was followed by syringe addition of 2-iodoanisole (0.47 mL, 3.6 mmol). The resulting dark orange solution was purged with argon for 30 minutes and then heated to 80°C. The reaction mixture was heated continuously for a total of 48 h. The reaction mixture was filtered through a buchner funnel. The filtrate was concentrated *in vacuo* . The crude product was chromatographed with 15% ethylacetate in hexane. The product was isolated in 23 % yield. ^{1}H-NMR (250 MHz): δ 3.90 (s, 3H), 6.51 (b, s, 1H), 6.98-7.10 (m, 4H), 7.40 (d, 2H), 8.14(d, 2H). MS m/z (M^+) calcd. 244.0848, obsd. (M^+H) 245.

***N*-4-aminophenyl-2-methoxyaniline** 29. A 25 mL Schlenk flask was charged with *N*-4-nitrophenyl-2-methoxyaniline, **25** (200 mg, 0.8 mmol), 15 mL of ethanol and activated graphite (80 mg). The heterogeneous mixture was purged with argon. Hydrazine monohydrate (0.21 g, 4.0 mmol) was added to the mixture *via* syringe. The mixture was allowed to reflux for 48 h. The reaction mixture was filtered and the solvent was removed under vacuum to yield a pure product in 93 % yield. ^{1}H-NMR (250 MHz): δ 3.55 (b, s 2H), 3.90 (s, 3H), 5.89 (b, s 1H), 6.66 (d, 2H), 7.02 (d, 2H), 6.70-6.99 (m, 4H). MS m/z (M^+) calcd. 214.1107, obsd. (M^+H) 215.

***o*-(2-Methyleneoxy-15-crown-5)-iodobenzene** 30 To a three-neck round bottom flask fitted with an addition funnel and a condenser, was added 2-iodophenol (0.3 g, 1.4 mmol), potassium carbonate (0.29 g, 2.1 mmol), potassium iodide (23 mg, 0.14 mmol) and approximately 30 mL acetone. The reaction mixture was brought to reflux, then **24a** (0.55 g, 1.4 mmol) dissolved in 20 mL of acetone was slowly added *via* the addition funnel. The reaction mixture was allowed to reflux for 16 h. The solvent was removed under vacuum and the residue dissolved in chloroform. The solution was washed with water three times, dried over Mg_2SO_4, filtered and concentrated *in vacuo.* to give pure **27** in 99 % yield. ^{1}H-NMR (250 MHz): 3.66-4.08 (m, 19 H), 4.11 (d, 2H), 6.70 (t, 1H), 6.82 (d, 1H), 7.25-7.31(m, 1H), 7.76 (dd, 1H).

BIBLIOGRAPHY

(1) MacDiarmid, A. G.; Epstein, A. J. *Makromol. Chem., Macromol. Symp.* **1991**, *51*, 11.

(2) Zhou, Q.; Swager, T. M. *J. Am. Chem. Soc.* **1995**, *117*, 12593.

(3) Teasdale, P. R.; Wallace, G. G. *Analyst* **1993**, *118*, 329.

(4) Partridge, A. C.; Harris, P.; Andrews, M. K. *Analyst* **1996**, *121*, 1349.

(5) Dogan, S.; Akbulut, T.; Yalcin, T.; Suzer, S.; Toppare, L. *Synth. Met.* **1993**, *60*, 27.

(6) *Proceedings of the International Meeting on Chemical Sensors, Fukuoka, Japan*; Seiyama, T.; Fueki, K.; Shirokawa, J.; Suzuki, S., Ed.; Elsevier: Tokyo, 1983; Vol. 17.

(7) Hiller, M.; Kranz, C.; Huber, J.; Bauerle, P.; Schuhmann, W. *Adv. Mater.* **1996**, *8*, 219.

(8) Schuhmann, W. *Mikrochim. Acta* **1995**, *121*, 1.

(9) Bartlett, P. N.; Birkin, P. R. *Synth. Met.* **1993**, *61*, 15.

(10) Matsue, T.; Nishizawa, M.; Sawaguchi, T.; Uchida, I. *J. Chem. Soc., Chem. Commun.* **1991**, 1029.

(11) Deng, Z.; Stone, D. C.; Thompson, M. *Analyst* **1996**, *121*, 671.

(12) Unde, S.; Ganu, J.; Radhakrishnan, S. *Advanced Materials for Optics and Electronics* **1996**, *6*, 151.

(13) Slater, J. M.; Watt, E. J.; Freeman, N. J.; May, I. P.; Weir, D. J. *Analyst* **1992**, *117*, 1265.

(14) Hutchins, R. S.; Bachas, L. G. *Anal. Chem.* **1995**, *67*, 1654.

(15) Galal, A.; Wang, Z.; Karagozler, A. E.; Zimmer, H.; Jr., H. B. M.; Bishop, P. *Anal. Chim. Acta* **1994**, *229*, 145.

(16) Timofeeva, O. N.; Lubentsov, B. Z.; Sudakova, Y. Z.; Cherayshov, D. N.; Khidekel, M. L. *Synth. Met.* **1991**, *140*, 111.

(17) Marsella, M. M.; Carroll, P. J.; Swager, T. M. *J. Am. Chem. Soc.* **1995**, *117*, 9832.

(18) Marsella, M. M.; Swager, T. M. *J. Am. Chem. Soc.* **1993**, *115*, 12214.

(19) Marsella, M. M.; Newland, R. J.; Carroll, P. J.; Swager, T. M. *J. Am. Chem. Soc.* **1995**, *117*, 9842.

(20) *Handbook of Conducting Polymers*; Skotheim, T. J., Ed.; Dekker: New York, 1986.

(21) Gomez-Kaifer, M.; Reddy, P. A.; Gutsche, C. D.; Echegoyen, L. *J. Am. Chem. Soc.* **1994**, *116*, 3580.

(22) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry;* 2nd ed.; John Wiley and Sons Inc.: New York, 1991.

(23) Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; Abu-El-Fadl, A.; Reinhoudt, D. N. *J.. Am. Chem. Soc.* **1990**, 6979.

(24) *Thiophene and its Derivatives*; Gronowitz, S., Ed.; John Wiley and Sons: New york, 1985; Vol. 44.

(25) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989**, *68*, 234.

(26) Van-Loon, J. D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R. *J. Org. Chem.* **1990**, *55*, 5639.

(27) Shacklette, L. W.; Wolf, J. F.; Gould, S.; Baughman, R. H. *J. Chem. Phys.* **1988**, *6*, 3955.

(28) James, T. D.; Linnane, P.; Shinkai, S. *Chem. Comm.* **1996**, 281.

(29) Dishong, D. M.; Diamond, C. J.; Cinoman, M. I.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 586.

(30) Miyazaki, T.; Yanagida, S.; Itoh, A.; Okahara, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2005.

(31) Diaz, A. F.; Logan, J. A. *J. Electroanal. Chem. Interfacial Electrochem.* **1980**, *111*, 111.

(32) Hand, R. L.; Nelson, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 850.

(33) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

(34) Lamba, J. J. S.; Tour, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 11723.

(35) Dao, L. H.; Leclerc, M.; Guay, J.; Chevalier, J. W. *Synth. Met.* **1989**, *29*, E377.

APPENDIX

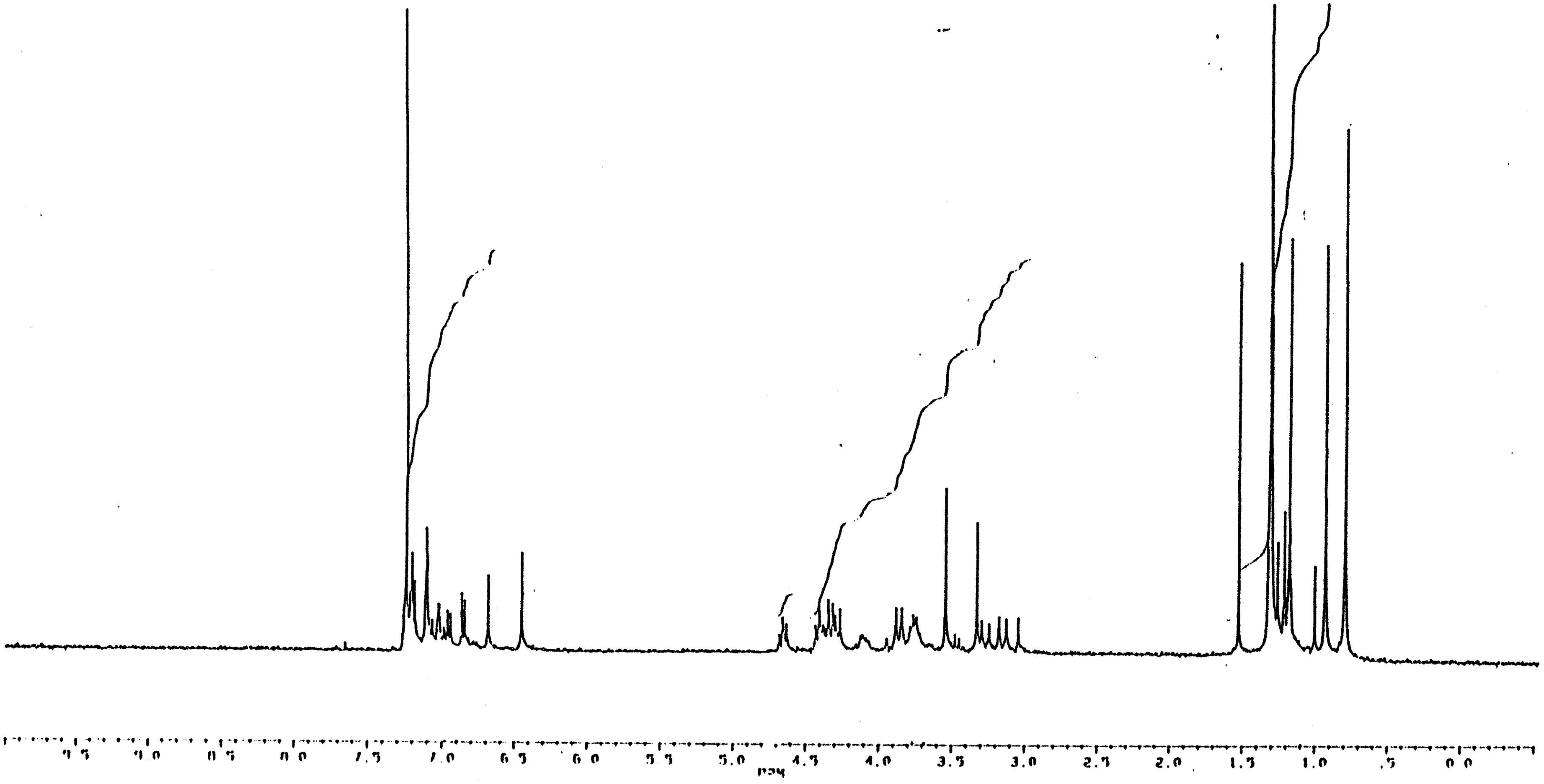


Figure A1. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 6.

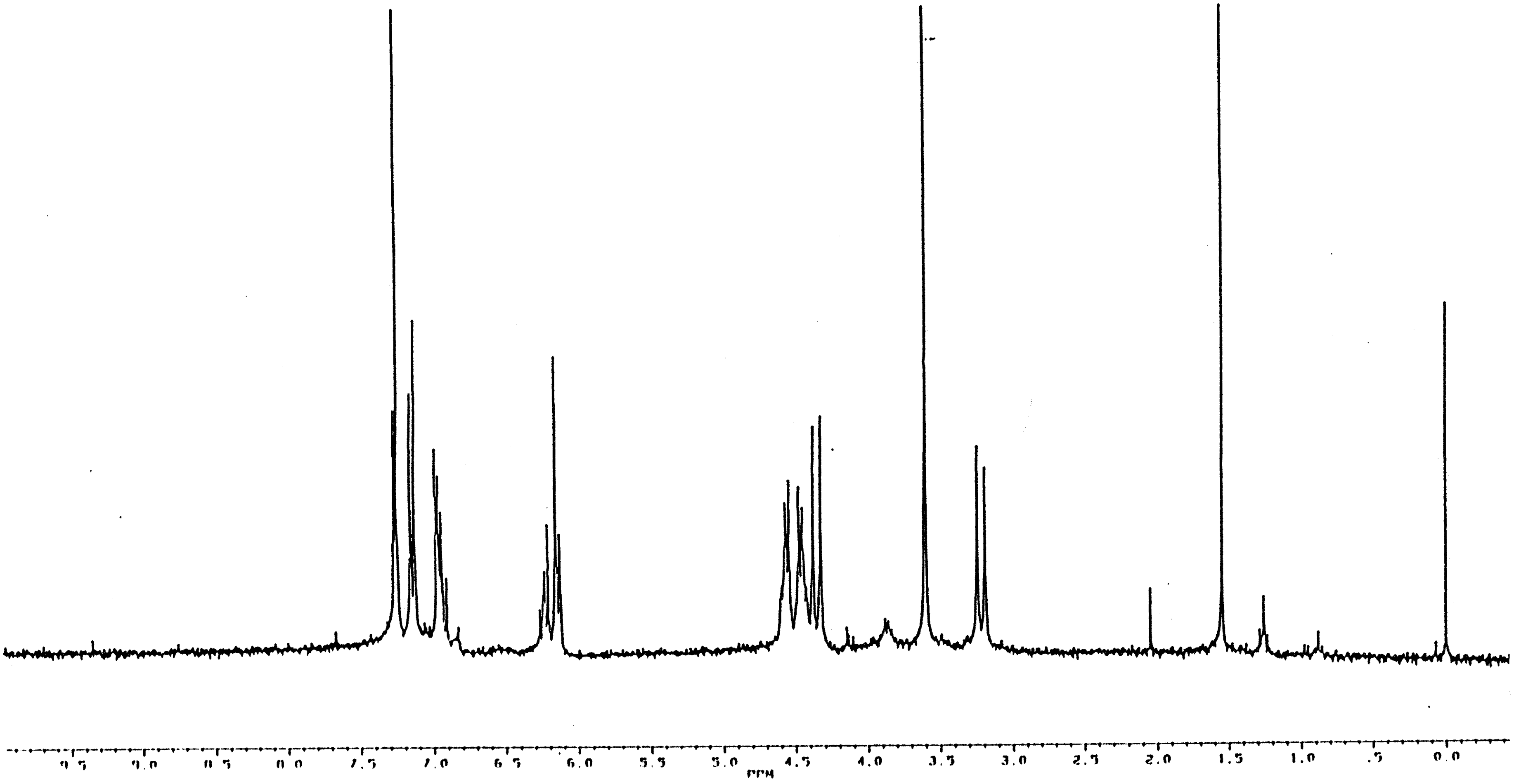


Figure A2. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 7.

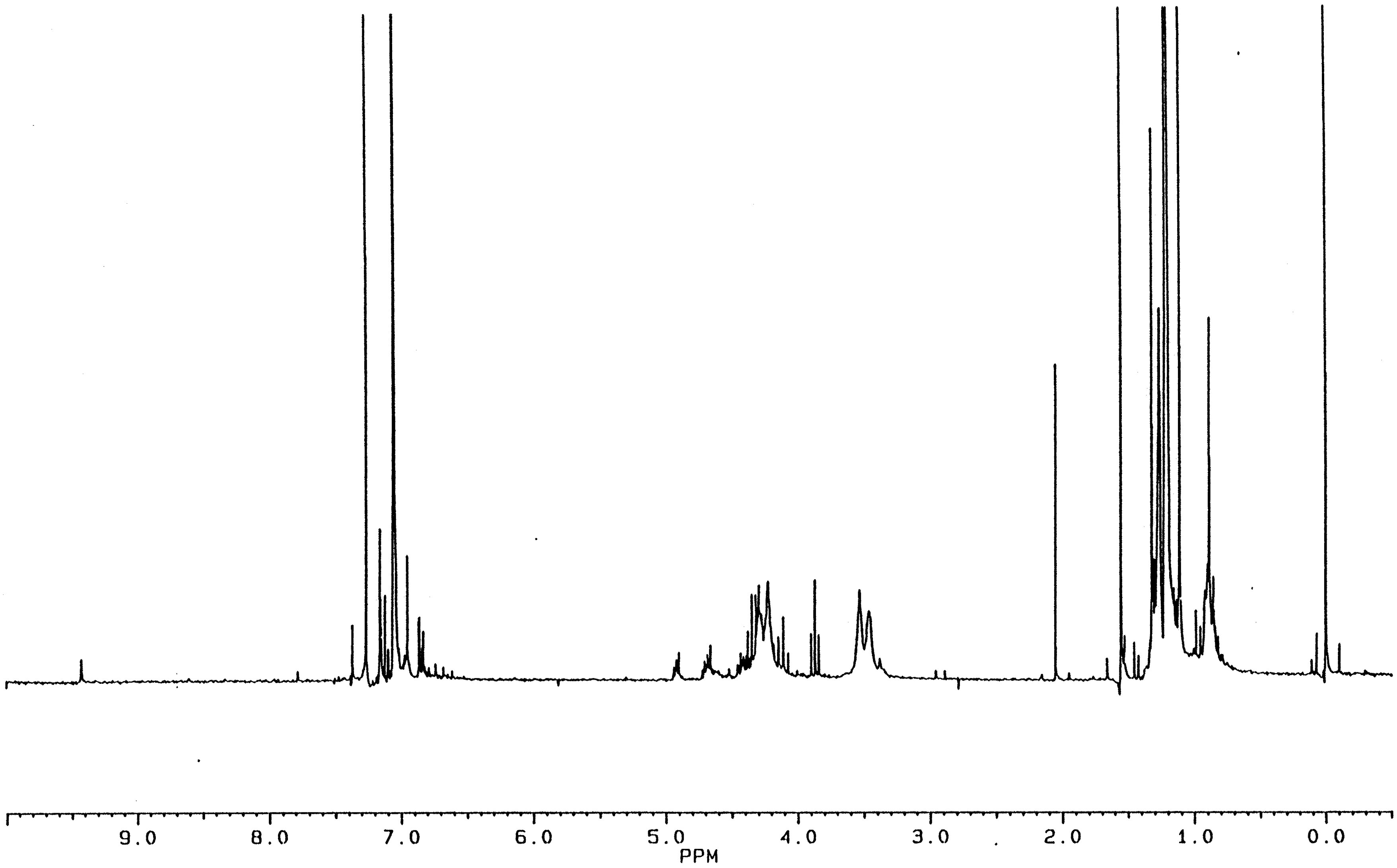


Figure A3. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 8.

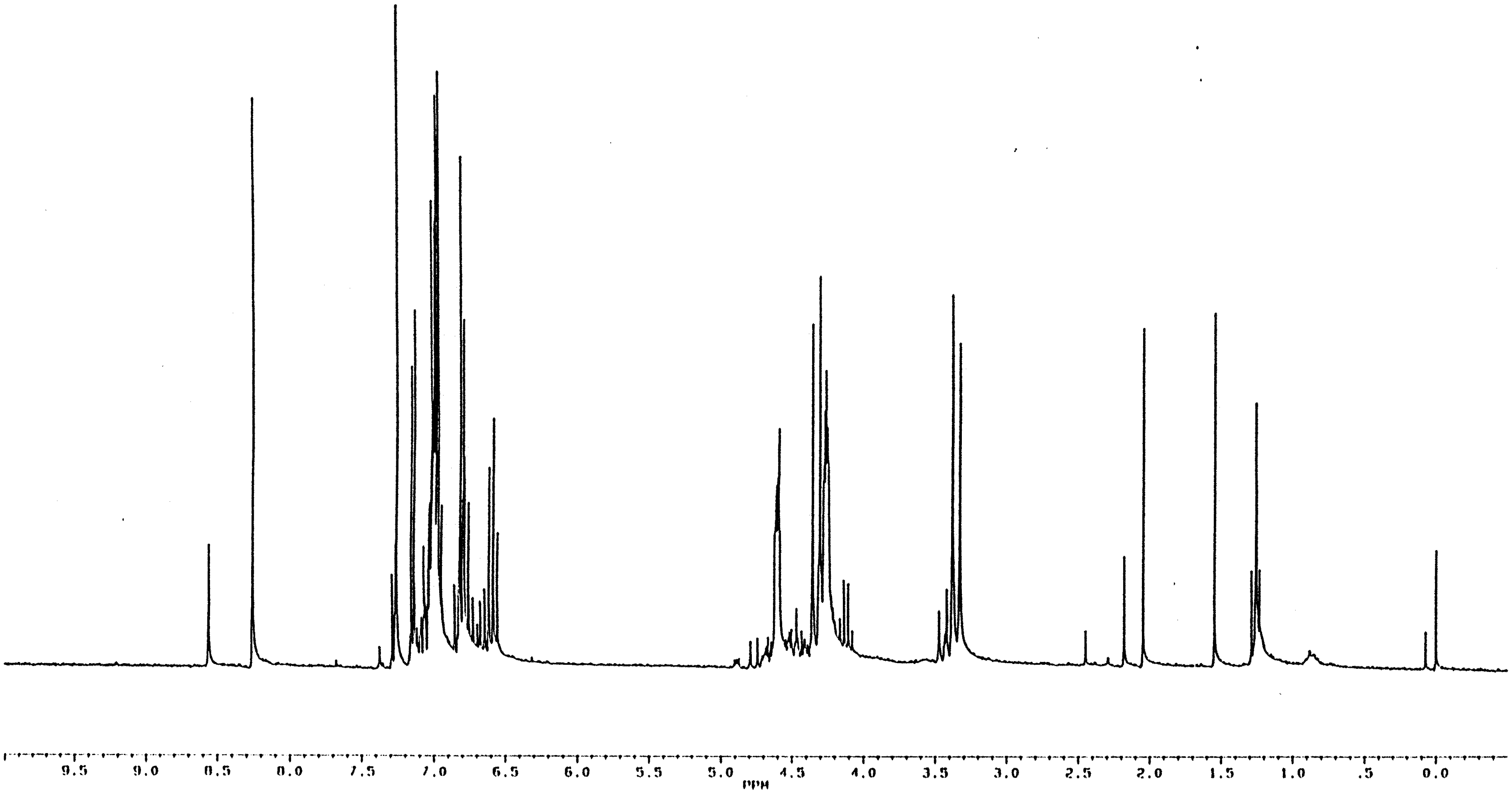


Figure A4. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 9.

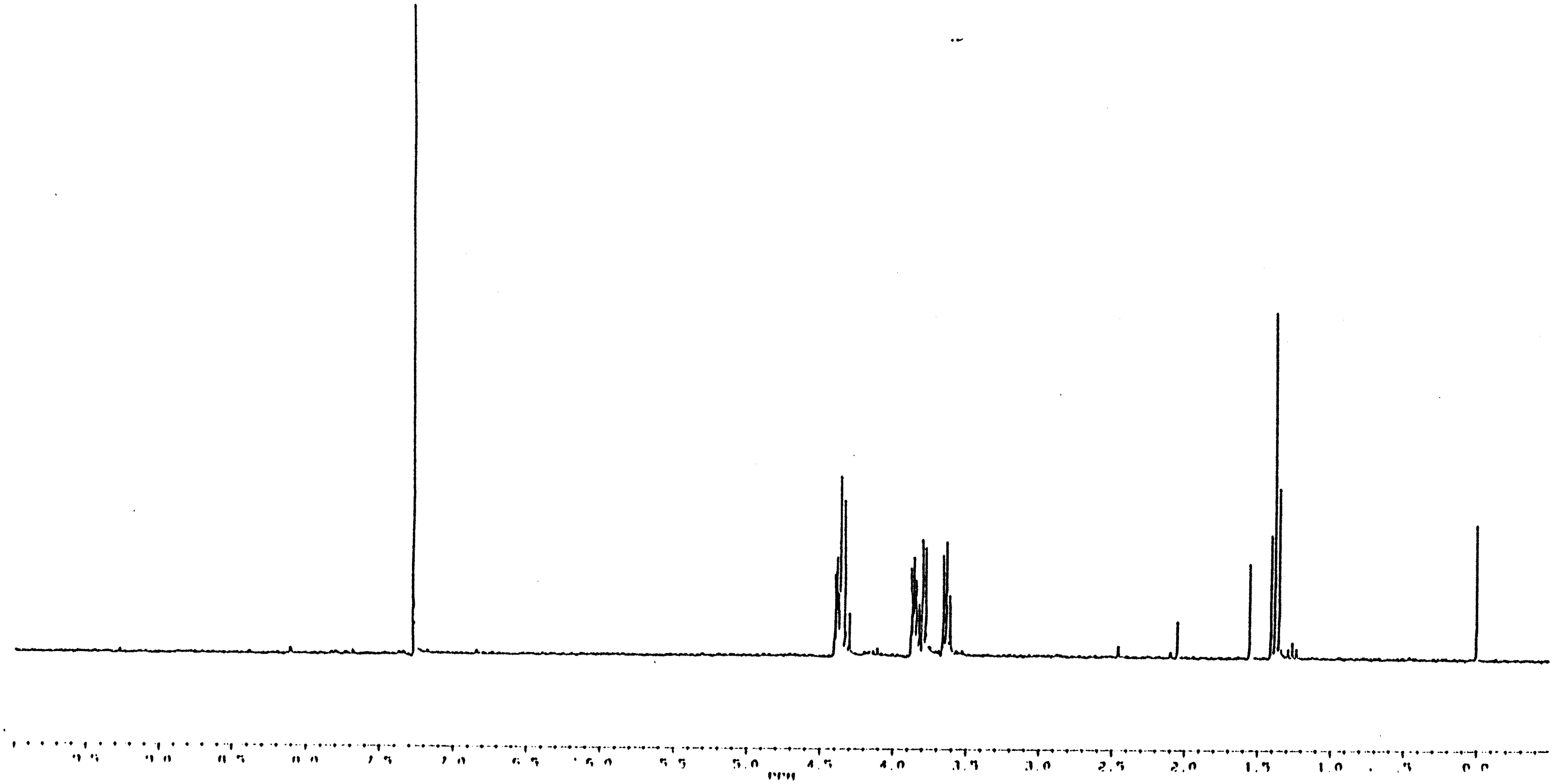


Figure A5. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 16.

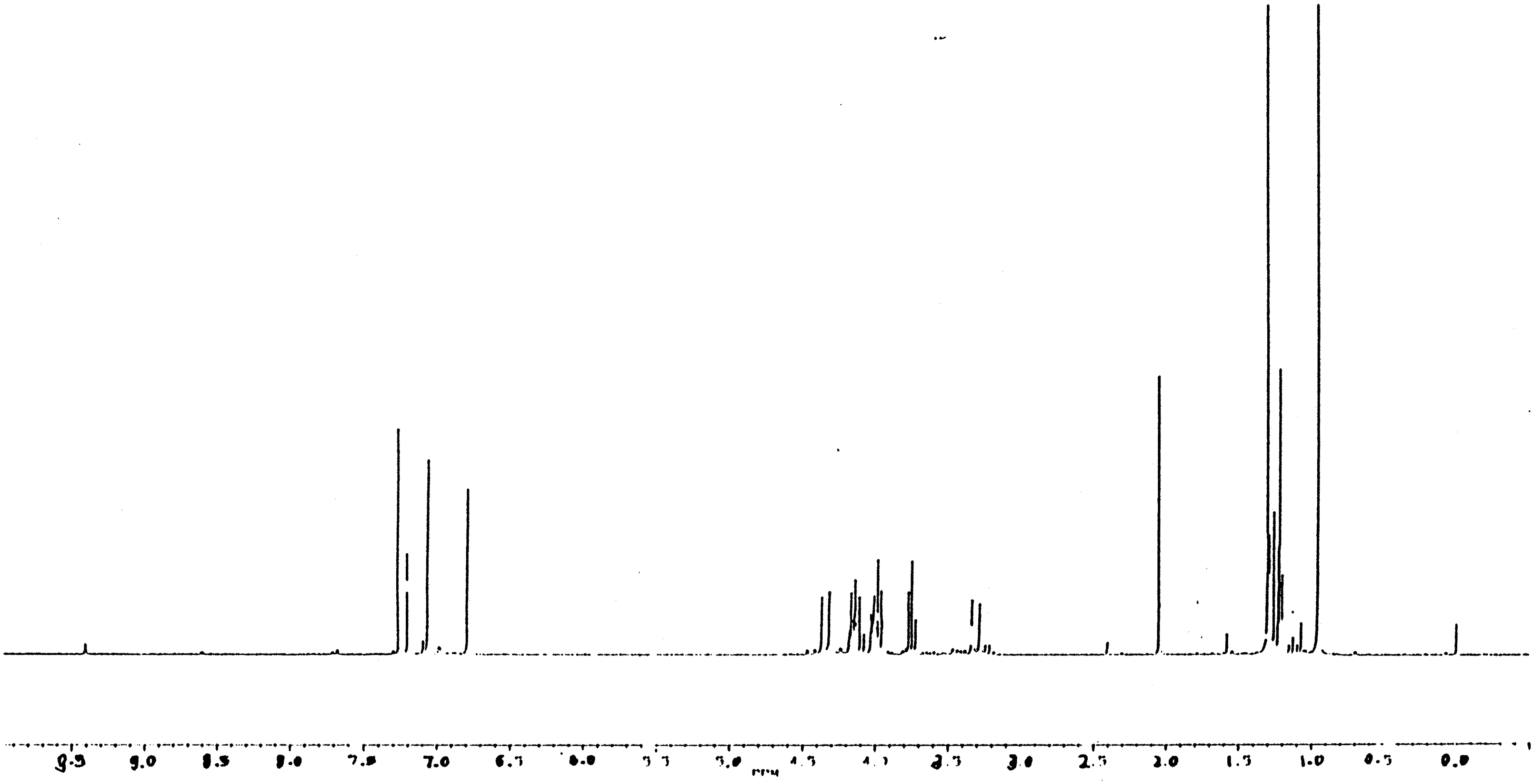


Figure A6. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 17.

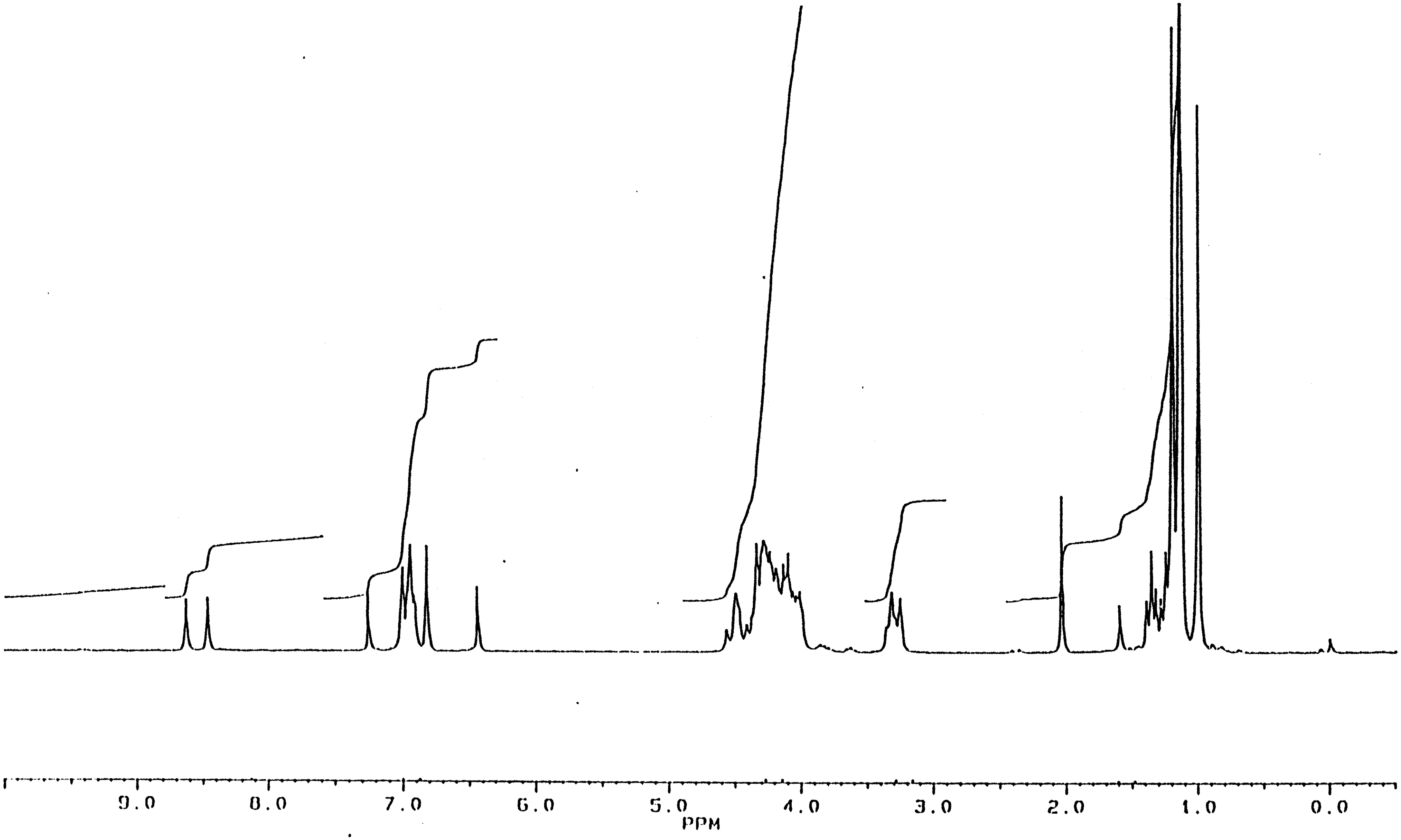


Figure A7. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 18.

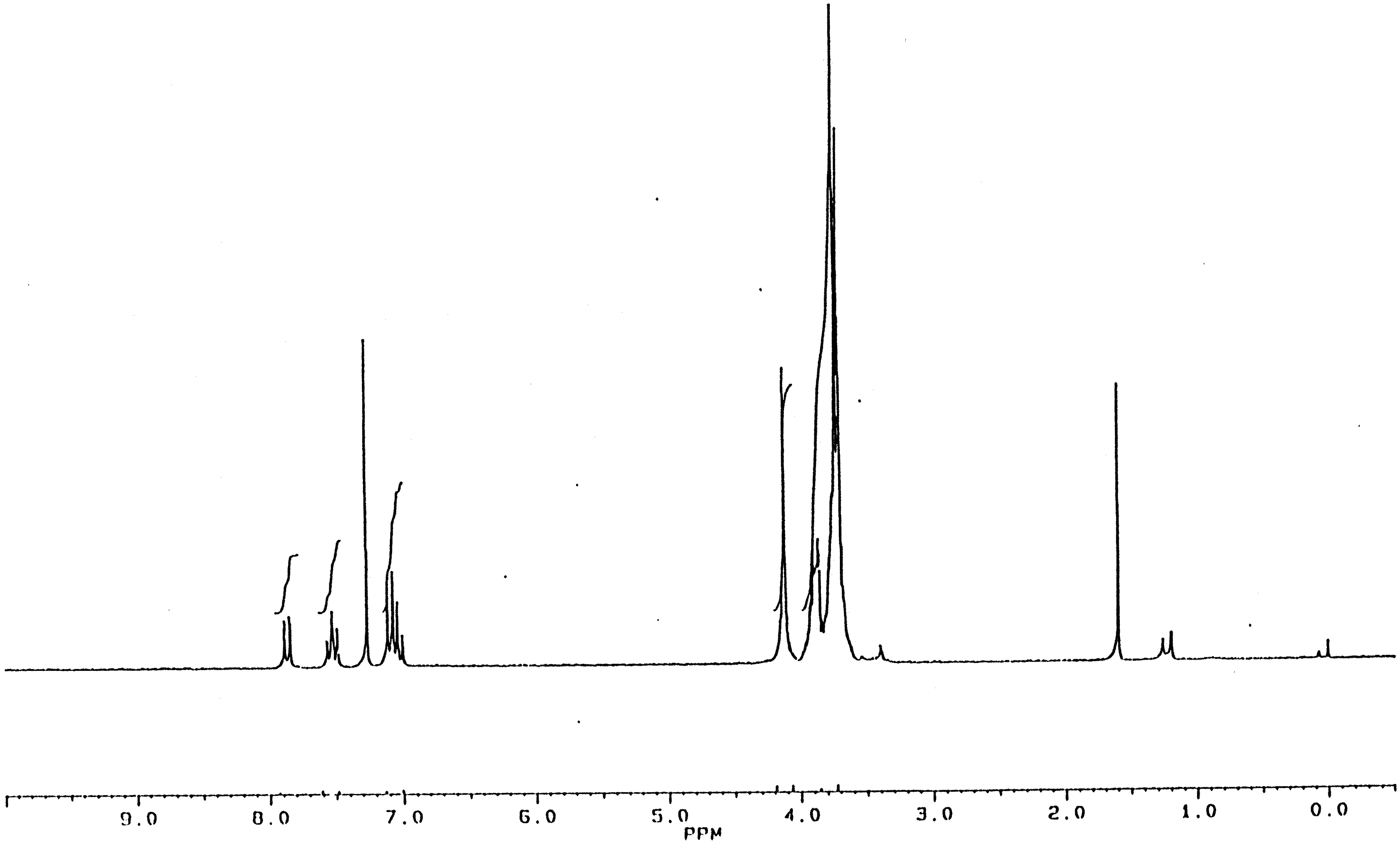


Figure A8. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 22.

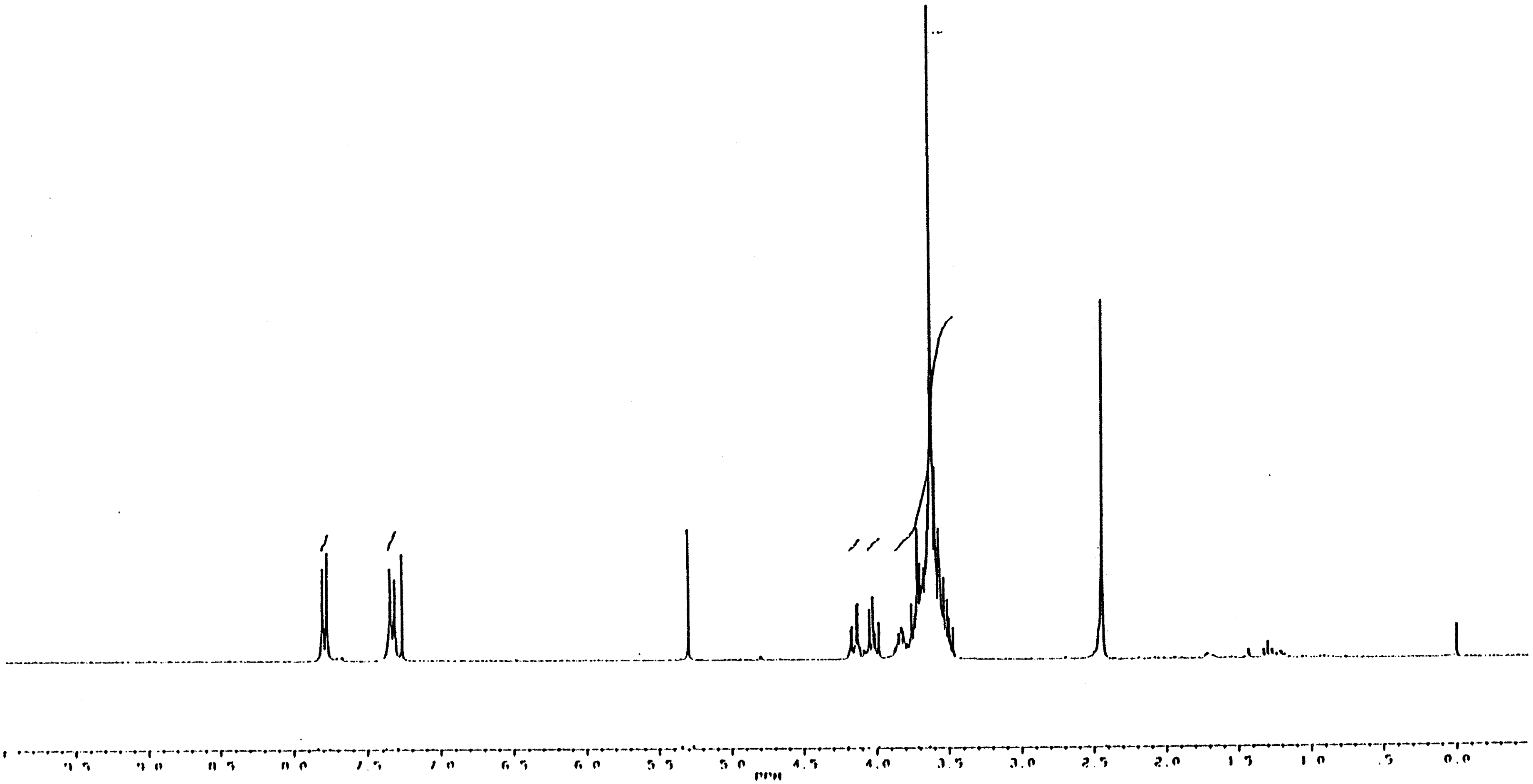


Figure A9. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 23a.

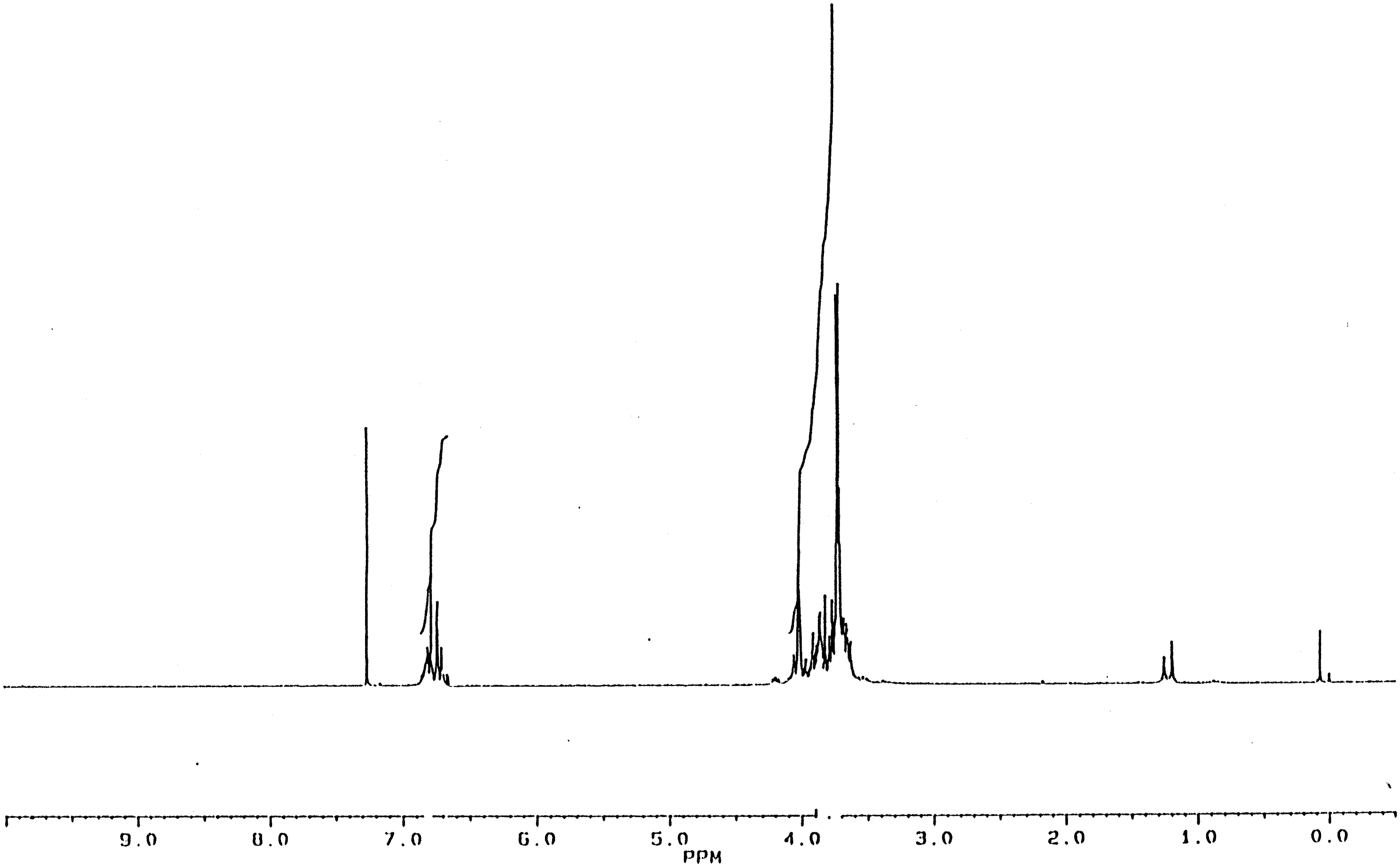


Figure A11. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 24.

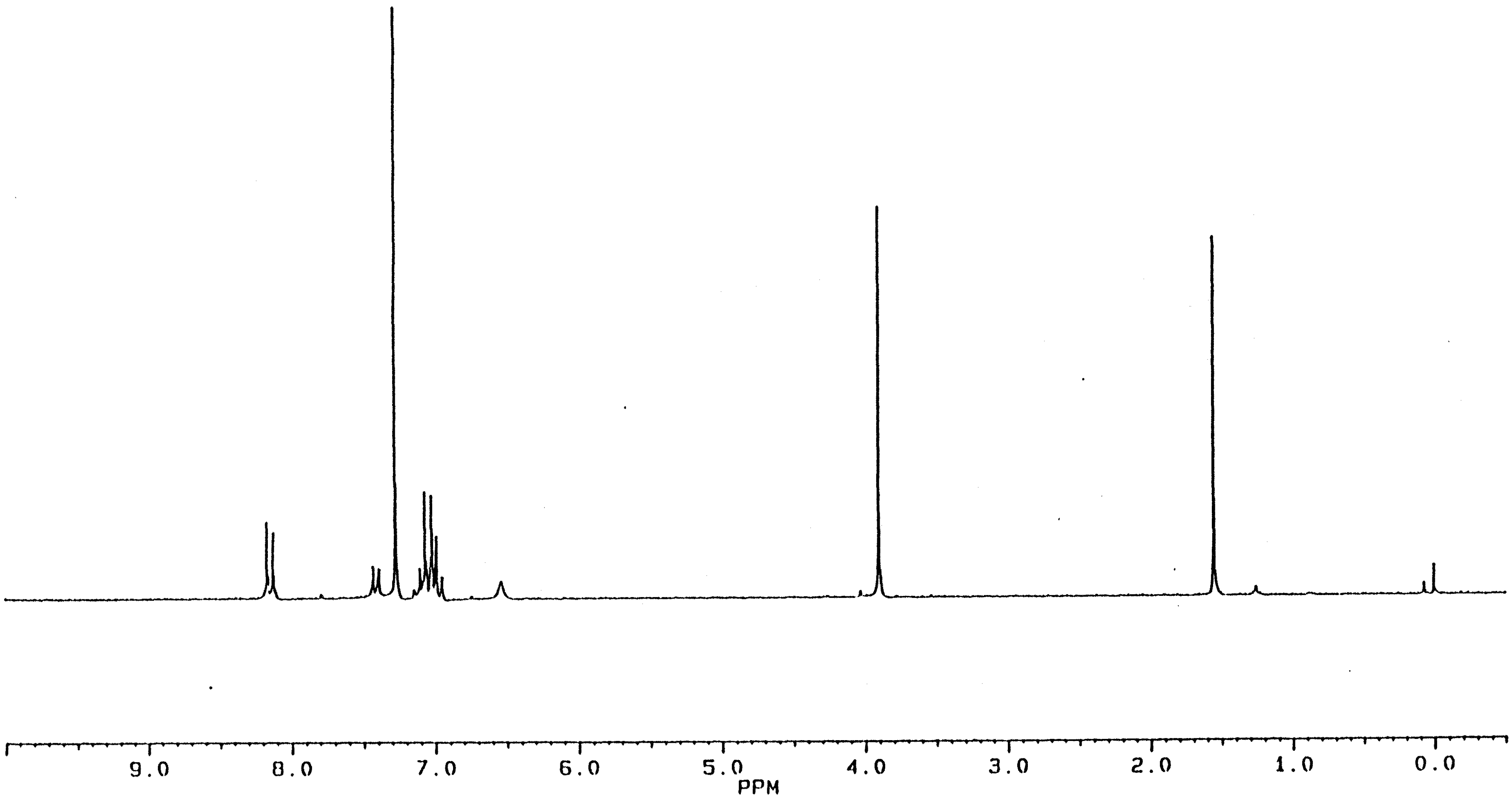


Figure A12. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 28.

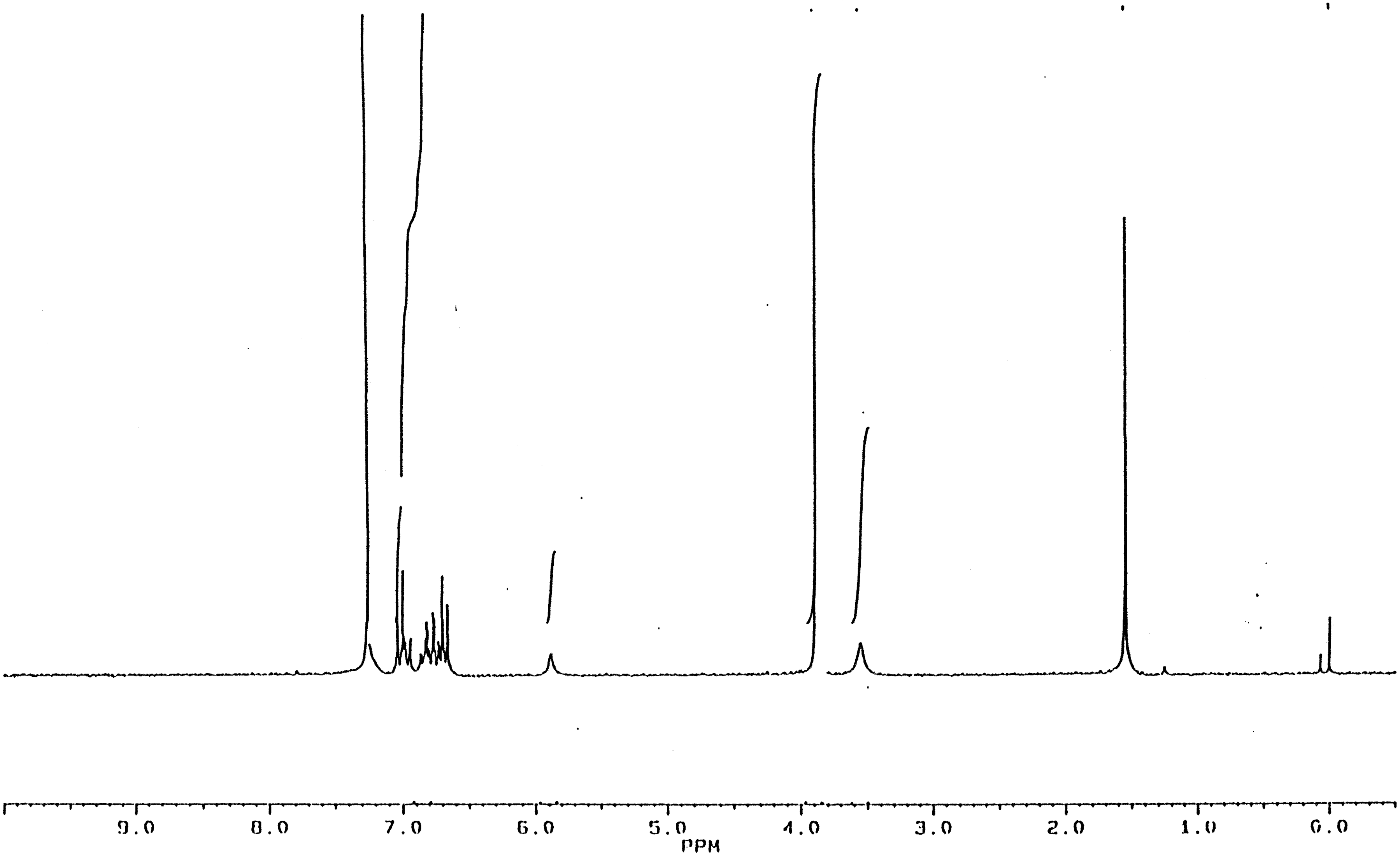


Figure A13. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 29.

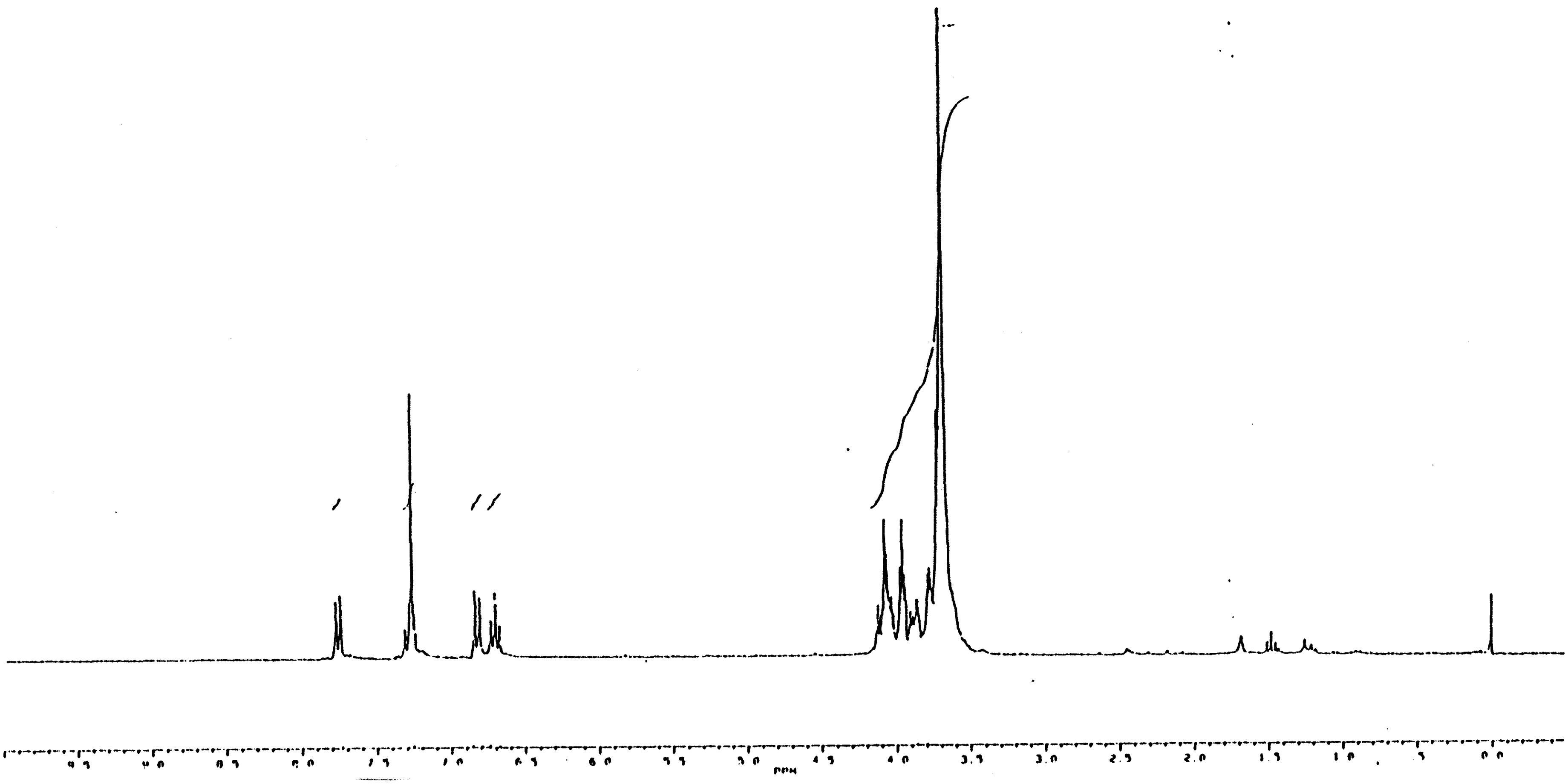


Figure A14. 1H-NMR Spectrum (250 MHz, CDCl3) of compound 30.