J|A|C|S
ARTICLES
Published on Web 09/28/2002

A Versatile Approach to Affinitychromic Polythiophenes

Stéphanie Bernier, Sébastien Garreau, Maité Béra-Abérem, Catherine Gravel, and Mario Leclerc*

Contribution from the Canada Research Chair in Electroactive and Photoactive Polymers, Centre de recherche en sciences et ingénierie des macromolécules, Département de Chimie, Université Laval, Quebec City, Qc, Canada, G1K 7P4

Received June 20, 2002

Abstract: The preparation of both postfunctionalizable and chromic poly[3-(*N*-succinimido-*p*-phenylcarboxylate(tetraethoxy)oxy)-4-methylthiophene] is reported. The *N*-hydroxysuccinimide ester side group can easily react with different amine-bearing molecules in the solid state to yield a library of new polythiophene derivatives. The resulting polymers can be dissolved in various solvents, and interactions between the side chains (ligands) and different analytes (targets) can be detected from modifications of both the side-chain and the backbone conformations resulting in important color changes (i.e., affinitychromism). This colorimetric polymeric transducer could therefore lead to highly valuable, versatile, and inexpensive tools for highthroughput screening and drug discovery.

Introduction

Combinatorial chemistry has recently revolutionized the pharmaceutical industry because it allows the efficient and parallel synthesis of hundreds of organic compounds.[1−3] However, the large number of chemical compounds synthesized in parallel brings another important problem, which is related to the localization, identification, and determination of the biological activity of one specific compound. For instance, some biological activities can be detected within a library of organic compounds, but the determination of the exact nature of the chemical compound(s) responsible for such an activity is a difficult task. Some solutions have already been proposed. Among them, the (micro)fabrication of positionally addressable two-dimensional arrays of synthetic precursors is a powerful tool for the parallel synthesis of different organic compounds.[4,5] Moreover, it is possible to use these different substrates to verify the interaction or activity of these compounds by tagging, for instance, a fluorescent probe to the target. By utilizing a fluorescence microscope, we found it is then possible to localize onto the surface where interactions are taking place and, consequently, to identify the chemical structure of the organic compound bound to the surface that is responsible for such interactions.

However, this method has the disadvantage of necessitating the addition of a photoactive, electroactive, or radioactive tagging agent onto the target (i.e., the analyte). This problem could be solved by a second generation of active arrays where the substrate is itself colored, luminescent, or electroactive. In other words, we could avoid any tagging process by using a responsive polymer which could serve as a solid-state precursor for the preparation or the covalent attachment of a large number of different chemical compounds but could also have the optical or electrical properties of the resulting polymers modified upon complexation or interaction with a given target. If successful, this approach could easily generate (or bind) a library of potential ligands and have their affinity to different targets directly tested in a few minutes without the use of any sophisticated technique. This ambitious program seems now possible by the utilization of functionalized polythiophenes.[6−8] Indeed, some polythiophenes can detect, transduce, and, sometimes, amplify chemical or physical information into an optical (or electrical) signal. These optical changes are related to a conformational transition of the polymer backbone, between a planar and a nonplanar form, triggered by adequately functionalized and responsive side chains. More precisely, it has been suggested that these optical effects are driven by a delicate balance between repulsive steric interactions and attractive interchain (or intrachain, due to chain folding) interactions, the latter being necessary to get a planar conformation in the case of chromic poly(3-alkoxy-4-methylthiophene)s.[6−8] Recently, the term assisted-planarization mechanism[9] or aggregation-induced

* To whom correspondence should be addressed. E-mail: mario.leclerc@chm.ulaval.ca.

(1) Wilson, S. R., Czarnik, A. W., Eds. *Combinatorial Chemistry: Synthesis and Application*; Wiley & Sons: Toronto, 1997.
(2) Szostak, J., Ed. *Chem. Rev.* **1997**, *97*, 347.
(3) Borman, S. *Chem. Eng. News* **1999**, *77* (10), 33; **2000**, *78* (20), 53.
(4) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. *Science* **1991**, *251*, 767.
(5) Sundberg, S. A.; Barrett, R. W.; Pirrung, M.; Lu, A. L.; Kiangsoontra, B.; Holmes, C. P. *J. Am. Chem. Soc.* **1995**, *117*, 12050.
(6) (a) Faïd, K.; Leclerc, M. *J. Am. Chem. Soc.* **1998**, *120*, 5274. (b) Kumpumbu-Kalemba, L.; Leclerc, M. *Chem. Commun.* **2000**, 1847.
(7) Ho, H. A.; Boissinot, M.; Bergeron, M. G.; Corbeil, G.; Doré, K.; Boudreau, D.; Leclerc, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1548.
(8) (a) Leclerc, M.; Faïd, K. *Adv. Mater.* **1997**, *9*, 1087. (b) Leclerc, M. *Adv. Mater.* **1999**, *11*, 1491. (c) McCullough, R. D. *Adv. Mater.* **1998**, *10*, 93. (d) McQuade, D. T.; Pullen, A. E.; Swager, T. M. *Chem. Rev.* **2000**, *100*, 2537.
(9) (a) Politis, J. K.; Somoza, F. B., Jr.; Kampf, J. W.; Curtis, M. D.; Gonzalez Ronda, L.; Martin, D. C. *Chem. Mater.* **1999**, *11*, 2274. (b) Apperloo, J. J.; Janssen, R. A. J.; Malenfant, P. R. L.; Fréchet, J. M. J. *Macromolecules* **2000**, *33*, 7038.

planarization[10] was coined to explain these results in solution. In the reverse process, such planar assemblies can be disrupted owing to a disordering of the flexible side chains, a cooperative twisting of the main chain being assumed with this dismantling. In addition to optical transitions induced by heating (thermochromism) or solvent quality changes (solvatochromism), novel phenomena have been generated in solution, including the detection of ions (ionochromism) and molecular recognition of chemical or biological moieties (affinitychromism). Along these lines, we would like to report the development of both postfunctionalizable and chromic polythiophenes and the demonstration of their potential for applications in highthroughput screening and drug discovery.

Experimental Section

Materials. 3-(((2-Iodoethyl)triethoxy)oxy)-4-methylthiophene (**1**) was prepared according to already published procedures,[11] and all other starting materials were purchased from Aldrich Co. and used without further purification.

3-[(Ethyl-4-phenylcarboxylate)-1-(tetraethoxy)oxy]-4-methylthiophene (2). Under argon, 1.20 g (3.0 mmol) of 3-(((2-iodoethyl)-triethoxy)oxy)-4-methylthiophene (**1**) and 0.71 g (4.28 mmol, Aldrich Co.) of *p*-hydroxyethylbenzoate were dissolved in 25 mL of anhydrous acetone. Subsequently, 1.28 g (9.27 mmol) of K_2CO_3 and 0.08 g (0.48 mmol) of KI were added to the solution. The mixture was refluxed for 60 h. After cooling, the precipitate was filtered through a Büchner funnel, and the solid was washed with acetone. The filtrate was evaporated and extracted with water and chloroform. The organic layer was dried over magnesium sulfate, and the residue was purified by column chromatography (silica gel, 20% hexane in diethyl ether as eluent) to give a yellow oil (yield: 90%).

^{1}H NMR (300 MHz, $CDCl_3$, ppm). 1.37 (t, 3H, $J = 7.0$ Hz); 2.08 (s, 3H); 3.67−3.74 (m, 8H); 3.85 (m, 4H); 4.09 (t, 2H, $J = 4.5$ Hz); 4.16 (t, 2H, $J = 4.8$ Hz); 4.34 (q, 2H, $J = 7.0$ Hz); 6.15 (d, 1H, $J = 3.3$ Hz); 6.80 (m, 1H); 6.91 (d, 2H, $J = 8.8$ Hz); 7.98 (d, 2H, $J = 8.8$ Hz).

^{13}C NMR (75 MHz, $CDCl_3$, ppm). 12.68; 14.38; 60.53; 67.56; 69.48; 69.62 (2C); 70.64; 70.65; 70.83 (2C); 96.59; 114.12 (2C); 119.96; 123.00; 129.00; 131.45 (2C); 155.89; 166.16.

HRMS. Calculated for $C_{22}H_{30}O_7S_1$: 438.1712. Found: 438.1718.

3-((4-(*p*-Carboxyphenyl)tetraethoxy)oxy)-4-methylthiophene (3). To a solution of 24 mL of 5 M NaOH (aq)/EtOH (1:1) was added 1.50 g (3.45 mmol) of compound **2**. The resulting mixture was refluxed for 16 h. Afterward, the solvent was evaporated, and the resulting product was dissolved with diethyl ether. The organic layer was extracted with water, and HCl was added to the aqueous layer until the pH reached a value of 3. Finally, the acid layer was extracted with ethyl acetate. The resulting organic layer was dried over magnesium sulfate. The crude product was decolorized on activated carbon with hot acetone and filtered through Celite 521 to obtain a white solid. mp: 74−76 °C (yield: 93%).

^{1}H NMR (300 MHz, $CDCl_3$, ppm). 2.10 (s, 3H); 3.67−3.76 (m, 8H); 3.87 (m, 4H); 4.10 (t, 2H, $J = 4.5$ Hz); 4.19 (t, 2H, $J = 4.4$ Hz); 6.16 (d, 1H, $J = 3.2$ Hz); 6.81 (m, 1H); 6.94 (d, 2H, $J = 9.2$ Hz); 8.04 (d, 2H, $J = 9.2$ Hz).

^{13}C NMR (75 MHz, $CDCl_3$, ppm). 12.73; 67.66; 69.66; 69.73; 70.71; 70.72; 70.82; 70.93; 96.61; 114.33 (2C); 119.96; 121.92; 129.17; 132.29 (2C); 155.89; 163.25; 171.53.

HRMS. Calculated for $C_{20}H_{26}O_7S_1$: 410.1399. Found: 410.1403.

3-(*N*-Succinimido-*p*-phenylcarboxylate(tetraethoxy)oxy)-4-methylthiophene (4). First of all, 1.64 g (4.00 mmol) of compound **3** was dissolved in toluene and evaporated two times to remove any trace of water. The acid was stored under nitrogen until use. To a solution of compound **3** in 50 mL of anhydrous CH_2Cl_2 were added 0.46 g (4.00 mmol, Aldrich Co.) of *N*-hydroxysuccinimide, 0.91 g (4.41 mmol, Aldrich Co.) of *N*,*N*′-dicyclohexylcarbodiimide, and 10.00 mg (0.08 mmol, Aldrich Co.) of 4-(*N*,*N*′-dimethyl)aminopyridine. The mixture was stirred for 35 h. The flask of solution was dipped into cold water, and the precipitate was removed by filtration through a Büchner funnel. This operation was repeated three times. The product was purified by column chromatography (silica gel, diethyl ether followed by acetonitrile as eluents) to give a pale yellow oil (yield: 85%).

^{1}H NMR (300 MHz, $CDCl_3$, ppm). 2.09 (s, 3H); 2.90 (s, 4H); 3.68−3.75 (m, 8H); 3.87 (m, 4H); 4.10 (t, 2H, $J = 4.8$ Hz); 4.20 (t, 2H, $J = 4.4$ Hz); 6.16 (d, 1H, $J = 3.3$ Hz); 6.81 (m, 1H); 6.98 (d, 2H, $J = 9.2$ Hz); 8.09 (d, 2H, $J = 8.8$ Hz).

^{13}C NMR (75 MHz, $CDCl_3$, ppm). 12.73; 25.54 (2C); 67.83; 69.46; 69.67; 69.74; 70.71; 70.73; 70.92; 70.95; 96.61; 114.80 (2C); 117.25; 119.97; 129.17; 132.85 (2C); 155.91; 161.47; 164.19; 169.45 (2C).

HRMS. Calculated for $C_{24}H_{29}O_9S_1$: 507.1563. Found: 507.1567.

Poly[3-(*N*-succinimido-*p*-phenylcarboxylate(tetraethoxy)oxy)-4-methylthiophene] (P1). A three-electrode one-compartment cell was employed. The working electrode and the counter electrode were platinum plates, and the $Ag/AgNO_3$ (0.010 M in 0.1 M Bu_4NBF_4/CH_3CN) electrode was chosen as reference. The corresponding monomer was electropolymerized at a concentration of 0.1 M in 0.1 M Bu_4NBF_4/CH_3CN by successive cyclings at 200 mV/s between 0.0 and 1.7 V. After the polymerization, the polymer was rinsed with fresh acetonitrile, acetone, and methanol.

Instrumentation. FTIR spectra were recorded using a Nicolet Magna 560 spectrometer, with a resolution of 4 cm^{-1}, from KBr pellets or films cast from $CHCl_3$ solution on NaCl disks. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AMX300 apparatus in deuterated chloroform solution at 298 K. Number-average (M_n) and weight-average (M_w) molecular weights were determined by size exclusion chromatography (SEC) with an HPLC pump using a Waters 515 differential refractometer. The calibration curve was made with a series of monodispersed polystyrene standards in THF (HPLC grade, Aldrich). UV−vis absorption spectra were recorded on a Hewlett-Packard diode-array spectrophotometer (model 8452A) equipped with a temperature control unit, using 1 mm path length quartz cells. The temperature was measured with a thermocouple, with $\Delta T \approx 2$ °C. Electrochemical measurements have been performed with a Solartron potentiostat-galvanostat, model SI 1287, driven by a Corrview software.

Results and Discussion

As shown in Scheme 1, the desired thiophene monomer has been easily prepared in three straightforward steps, starting from 3-(((2-iodoethyl)triethoxy)oxy)-4-methylthiophene.[11] The present substitution pattern of the thiophene unit has been designed on the basis of our previous investigations,[6−8] which have shown that the presence of an alkoxy substituent at the 3-position combined with a methyl group at the 4-position leads, upon oxidative polymerization, to regioregular (>95% head-to-tail coupled) and chromic polythiophenes. The relatively long and hydrophilic spacer is there to allow easy postfunctionalization reactions and possible electroactivity in aqueous and polar organic solutions. Finally, a *N*-hydroxysuccinimide (NHS) ester group has been incorporated because it can support oxidative electropolymerization of pyrrole or thiophene units.[12−14] This

(10) Levitus, M.; Schmieder, K.; Ricks, H.; Shimizu, K. D.; Bunz, U. H. F.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 4259.
(11) Lévesque, I.; Leclerc, M. *Macromolecules* **1997**, *30*, 4347.
(12) Bäuerle, P.; Hiller, M.; Scheib, S.; Sokolowski, M.; Umbach, E. *Adv. Mater.* **1996**, *8*, 214.
(13) Korri-Youssoufi, H.; Garnier, F.; Srivastava, P.; Godillot, P.; Yassar, A. *J. Am. Chem. Soc.* **1997**, *119*, 7388.
(14) Li, G.; Kossmehl, G.; Hunnius, W.; Zhu, H.; Kautek, W.; Plieth, W.; Melsheimer, J.; Doblhofer, K. *Polymer* **2000**, *41*, 423.

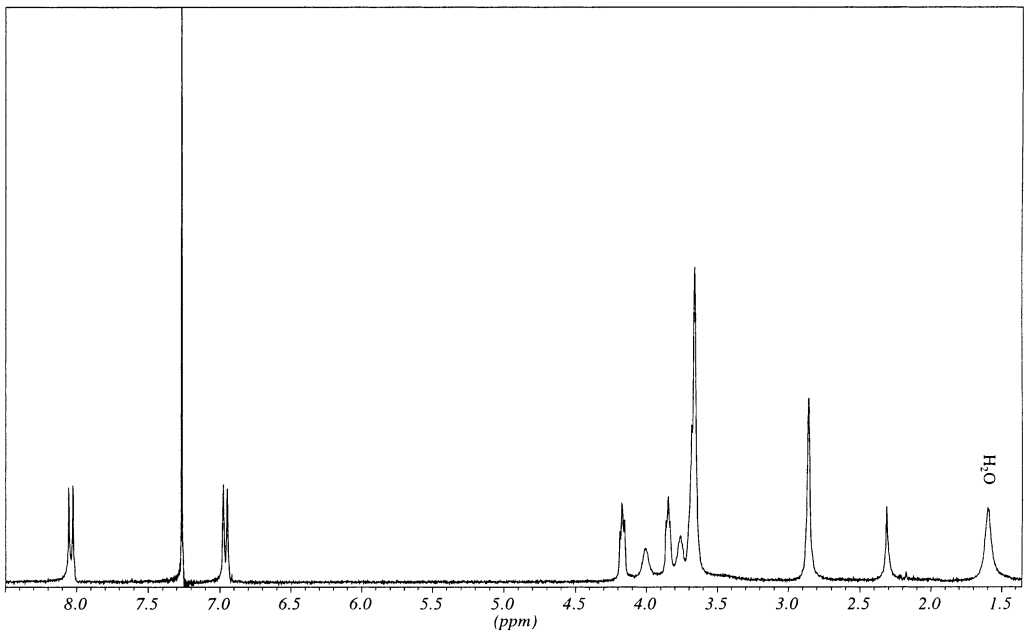
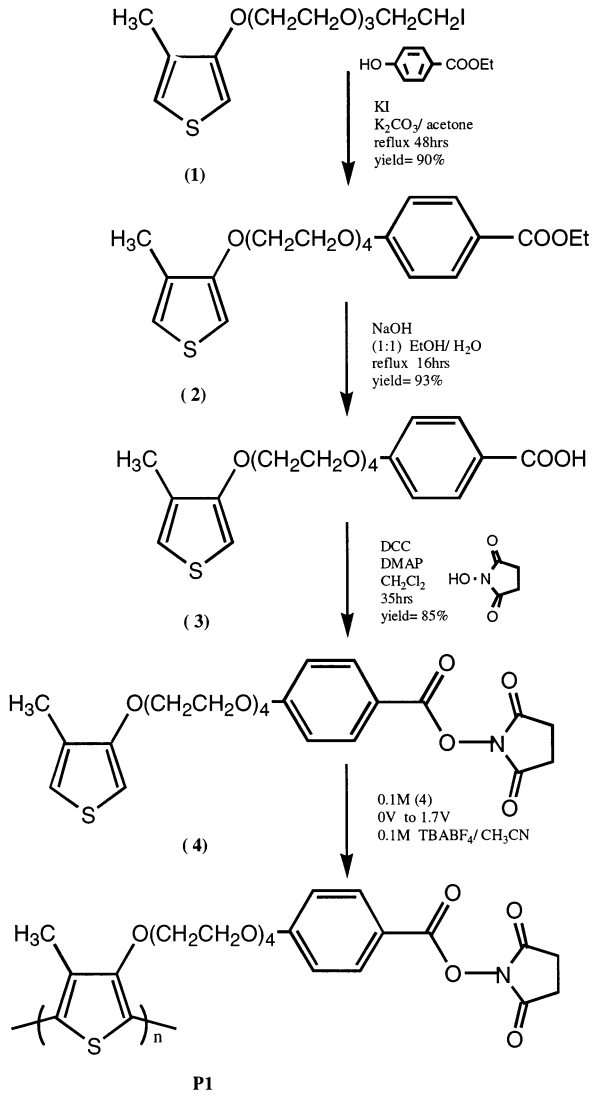


Figure 1. ^{1}H NMR spectrum of poly(3-[*N*-succinimido-*p*-phenylcarboxylate(tetraethoxy)oxy]-4-methylthiophene) (**P1**) in $CDCl_3$.

chemical moiety is also known to react with amines under very mild conditions to form the corresponding amides in high yields. Therefore, as anticipated, the electropolymerization of monomer **4** has led to the formation of a thin film of the corresponding electroactive polymer (**P1**) on diverse electrodes (ITO, Pt, etc.). Moreover, this polymer is soluble in $CHCl_3$, THF, and DMSO and can be (re)cast to yield thin polymer films with good mechanical properties. The number-average molecular weight of this polymer is 14 kDa with a polydispersity index of 1.2. NMR and IR data are in good agreement with its expected structure. In particular, as shown in Figure 1, the ^{1}H NMR spectrum of polymer **1** exhibits a well-defined and sharp signal at 2.3 ppm which is related to the methyl group at the 4-position and is in agreement with the presence of a regioregular head-to-tail backbone.[15] Moreover, the absence of peaks near 6.2 and 6.8 ppm (characteristic of protons at the 2- and 5-positions, respectively) indicates a relatively high molecular weight with a degree of polymerization higher than 20.

The resulting polythiophene derivative is electroactive in a 0.1 M KCl aqueous solution, with an oxidation potential around +0.7 V versus SCE. As observed with other regioregular poly(3-alkoxy-4-methylthiophene)s,[6−8,15] polymer **1** is thermochromic (a violet-to-yellow color transition) in the solid state, exhibiting an absorption maximum at 550 nm (with the presence of two vibronic bands at 543 and 584 nm) at room temperature, which shifts to 423 nm at 150 °C. A near-isosbestic point is observed in these temperature-dependent optical measurements, which has been explained by the coexistence of only two conformational structures: one being related to a highly conjugated and coplanar conformation of the backbone and the other one to a twisted, nonplanar conformation of the main chain. This polymer is also solvatochromic, giving a yellow solution

Scheme 1



(15) (a) Daoust, G.; Leclerc, M. *Macromolecules* **1991**, *24*, 455. (b) Lévesque, I.; Leclerc, M. *Chem. Mater.* **1996**, *8*, 2843. (c) Lévesque, I.; Bazinet, P.; Roovers, J. *Macromolecules* **2000**, *33*, 2952. (d) Brustolin, F.; Goldoni, F.; Meijer, E. W.; Sommerdijk, N. A. J. M. *Macromolecules* **2002**, *35*, 1054.

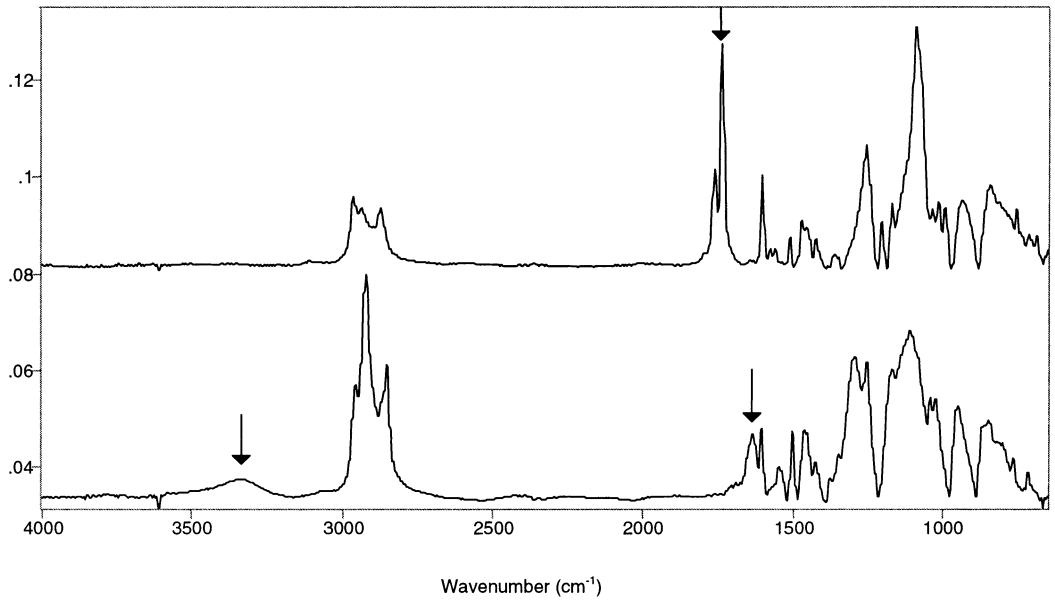
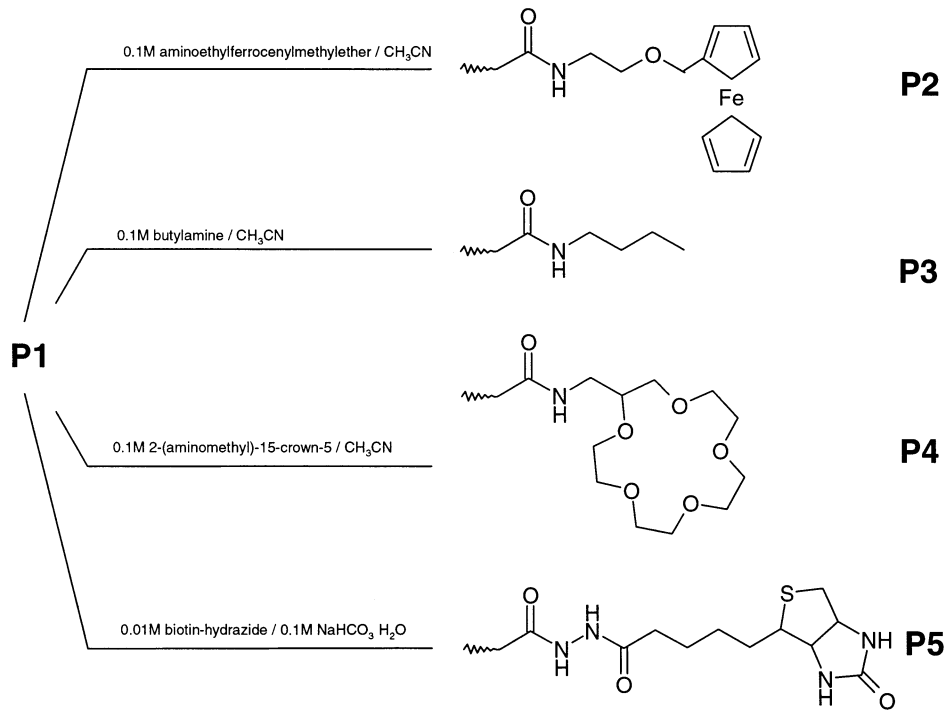


Figure 2. FTIR spectra of pristine polymer **1** (top) and polymer **3** (after treatment with butylamine for 15 min) (bottom).

Scheme 2



in a good solvent (i.e., chloroform) and leading to a violet solution upon the addition of a poor solvent (i.e., methanol).

The possibility of postfunctionalization through a reaction between the NHS group and different amine-bearing molecules has been verified by electrochemistry and infrared spectroscopy. As mentioned above, preformed polymer **1** exhibits an oxidation wave at +0.7 V versus SCE in a 0.1 M KCl aqueous solution. Upon treatment with a 0.1 M 2-aminoethylferrocenylmethyl ether[12] acetonitrile solution, the cyclic voltammogram of the resulting polymer (polymer **2**, see Scheme 2) exhibits a second reversible redox wave at +0.35 V versus SCE, characteristic of the ferrocene unit. Interestingly, polymer **2** and other similar polymers could be used in different catalytic reactions. IR analyses have been also carried out to verify the postfunctionalization of the polymeric precursor. Pristine polymer **1** shows two strong absorption bands at 1760 and 1734 cm^{-1} which are characteristic of the NHS group. Upon treatment with a 0.1 M solution of butylamine in acetonitrile for 15 min, these infrared bands disappeared, whereas two new bands appeared at 1632 and 3314 cm^{-1}, characteristic of the newly formed amide bond in polymer **3** (see Scheme 2 and Figure 2).

Moreover, it is possible to dissolve polymer **1** in chloroform and to cast (from 100 μL of a 0.01 M polymer solution in chloroform) a thin film in the bottom of a glass or polymeric well. Solid-state postfunctionalization of different wells has then been carried out by using 100 μL of a 0.1 M acetonitrile solution of butylamine or 2-(aminomethyl)-15-crown-5 (see Scheme 2). After 15 min, careful washing of the treated surfaces was carried

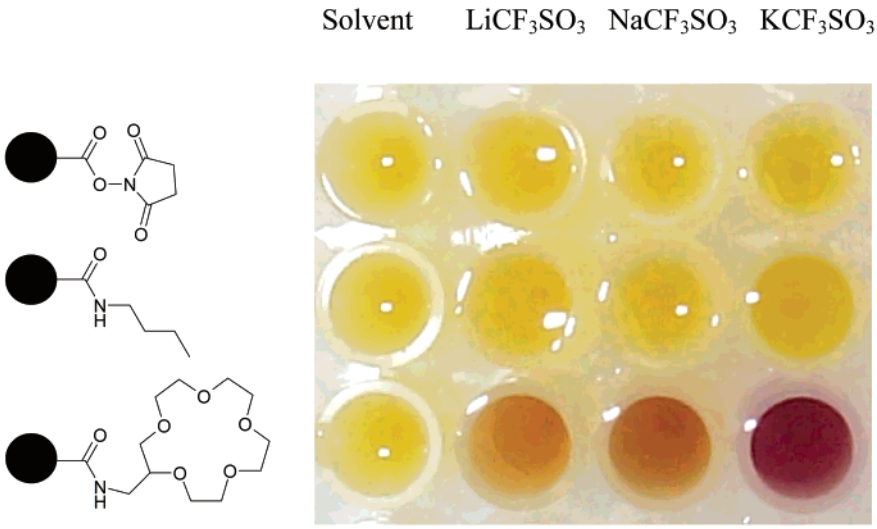


Figure 3. Visual detection of ionochromic effects with polymer **1**, polymer **3**, and polymer **4** in the presence of different salts in THF.

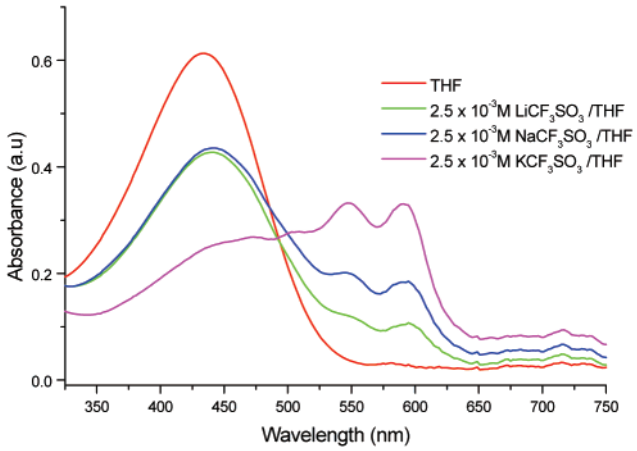


Figure 4. UV−visible absorption spectra of polymer **4** (2.5×10^{-3} M) in different THF solutions.

out with dry acetonitrile. The modified polymeric film is then dissolved in a given solvent (THF, DMSO, chloroform), and the affinity of the modified side chains is then evaluated against different targets. For instance, polymer **4** has been evaluated in THF solutions containing different alkali metal salts. Polymer **1** and butylamine-treated, polymer **3** have also been tested for comparison purposes. As shown in Figures 3 and 4, the yellow solution of 15-crown-5 modified polymer (polymer **4**) exhibits a maximum of absorption at 435 nm in THF. However, upon addition of different alkali metal salts (10^{-6} mol in a 400 μL of THF solution), the absorption spectra exhibit new absorption bands at 548 and 589 nm which are the optical signature of a coplanar and presumably aggregated structure for the polymer. These results are essentially the same as those observed on parent polymers directly obtained from the corresponding monomers:[16] the lithium salt showing the weakest effect and the potassium salt leading to the strongest ionochromic effect. These different behaviors can be explained by the formation of a more stable complex between two 15-crown-5 ligands and one potassium ion,[16,17] which forces the aggregation of the conjugated backbone. Interestingly, polymers **1** and **3** did not show any ionochromic effect, their respective absorption maximum being constant at 435 nm in the different THF solutions.

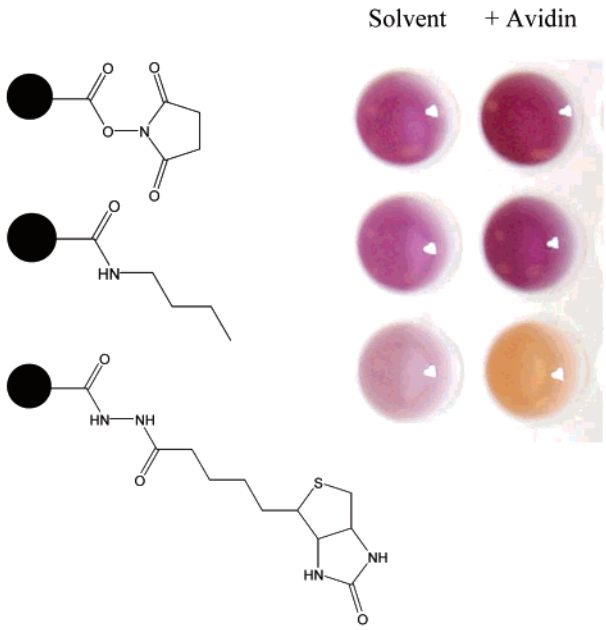


Figure 5. Visual detection of affinitychromic effects with polymer **1**, polymer **3**, and polymer **5** in the absence or presence of the protein avidin, in a DMSO/H_2O (3:1) solution.

Furthermore, and following the same procedures of those previously described, polymer **1** has been treated with 0.01 M biotin hydrazide (Pierce) dissolved in 0.1 M $NaHCO_3$ aqueous solution. The resulting and dried polymer **5** has then been dissolved in 400 μL of a 3:1 (v/v) mixture of DMSO/H_2O. This combination of solvents is a right compromise for the solubilization of both the protein avidin and the polythiophene derivatives. As reported in Figure 5, polymer **5** solution is pale pink, whereas polymers **1** and **3** are violet in the same solution. This indicates a stronger hydrophilic character for polymer **5** which is better solubilized in this highly polar mixture. Interestingly, in the presence of avidin (Pierce), which is known to specifically and strongly interact with the biotin moiety,[18] the solution of polymer **5** undergoes, within a period of 1 h, a

(16) Boldea, A.; Lévesque, I.; Leclerc, M. *J. Mater. Chem.* **1999**, *9*, 2133.
(17) (a) Flink, S.; Boukamp, B. A.; van den Berg, A.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1998**, *120*, 4652. (b) Kim, J.; McQuade, D. T.; McHugh, S. K.; Swager, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3868.

significant optical change to a yellow-orange color (presumably due to a better solubilization in the presence of avidin),[19] whereas solutions of polymers **1** and **3** remain violet. It is worth noting here that an amount of only 2.0×10^{-9} mol of avidin can strongly modify a solution containing 1.0×10^{-6} mol of polymer **5** (on a repeat unit basis). These possibilities are directly related to an amplification factor (ca. 250)[6,7,19] which is believed to be related to the difference in size between the protein avidin and one repeat thiophene (binding) unit. Following this model, the interaction of the ligand with a very large target perturbs a significant number of neighboring thiophene units which explains this amplification phenomenon.

All of these results point out the high versatility and ease of this postfunctionalization approach of chromic poly(3-alkoxy-4-methylthiophene)s. This methodology cannot give an absolute evaluation of the binding of a given target, and it cannot be predicted from a new set of host and guest if binding will lead to aggregation (violet form) or to the formation of well-dissolved, isolated species (yellow form), but comparisons within a library of compounds in different solutions can give very valuable information about interactions among chemical and biochemical moieties.

(18) Wilchek, M.; Bayer, E. A. *Anal. Biochem.* **1988**, *171*, 1.
(19) Faïd, K.; Leclerc, M. *Chem. Commun*. **1996**, 2761.

Conclusions

This novel development of both postfunctionalizable and affinitychromic poly(3-alkoxy-4-methylthiophene)s has led to useful colorimetric tools for the rapid and versatile detection of interactions between various combinations of ligands (covalently attached to the polymeric transducer) and targets. The optical detection is based on a conformational transition of the conjugated backbone occurring upon the modification of the side-chain organization. The present results clearly indicate that this postfunctionalization approach gives essentially the same results as those reported for the parent polymers obtained from the direct polymerization of the corresponding monomers. Moreover, this new methodology may allow the covalent binding of chemical or biochemical moieties that could not tolerate the polymerization reactions. Clearly, this new platform, which combines variable triggers, a transducer, and, sometimes, an amplifier, should find applications in the areas of diagnostics, therapeutics, and drug screening.

Acknowledgment. This work was supported by the Canada Research Chair program and a grant from FCAR in Combinatorial Chemistry involving Merck Frosst, Boehringer Ingelheim, Biochem Pharma, and Astra Zeneca. The authors thank Dr. H. A. Ho and M. Bédard for their help in the synthesis of some organic compounds.

JA027387L