Ion Sensors

A Fluorescent Self-Amplifying Wavelength-Responsive Sensory Polymer for Fluoride Ions[**]

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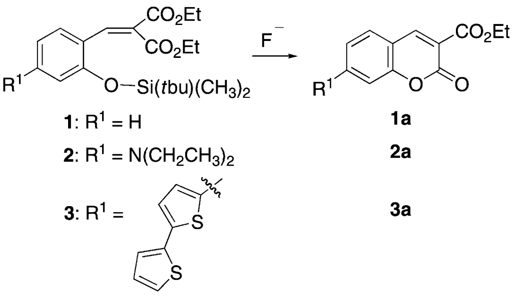
Fluoride, the smallest anion, has unique chemical properties and its recognition and detection are of growing interest because it is associated with nerve gases and the refinement of uranium used in nuclear weapons manufacture. As a result, there is a need to develop new selective and sensitive methods for fluoride detection in environments that are not easily served by conventional ion-selective electrodes. Most of the emerging detection methods have focused on receptors that differentiate fluoride from other anions, such as chloride, phosphate, or nitrate and convert the binding into an electrochemical or optical response.[1] These efforts have enjoyed success and in some cases have resulted in the ability to visually detect fluoride ions.[2–4]

An approach to greater sensitivity in fluorescence detection schemes is to use the exciton-transporting properties of semiconducting polymers to amplify perturbations (transduction events) produced by analyte binding. These methods were originally demonstrated using electron-transfer quenching[5a] and variations on this scheme have been used to create a number of chemical and biological sensory methods, most of which involve changes in the emission intensities.[5] In spite of these successes, it is generally preferable for a fluorescence sensory signal to involve a new emission at a different wavelength rather than a modulation of an existing signal. The advantage of the latter approach is that a new signal is inherently easier to detect than an intensity change. Furthermore, nonspecific chemical interactions are more likely to produce intensity changes than new signals, hence we can also expect specificity gains in properly designed sensors that create new emissions. Fluorescence resonance energy transfer (FRET) is broadly used to produce new emissive signals and the amplification of these processes through intramolecular energy transfer from conjugated polymers has been demonstrated.[6] New analyte-triggered emissions, if optimally deployed, offer high specificity and low background. In consideration of how to best construct such a system for the selective detection of fluoride ions we have decided to explore schemes using the unique chemical reactivity of fluoride ions with silicon,[7] rather than elaborate receptors. In a fusion of these different elements, we report herein a fluoride-sensing system in which a fluoride triggered Si–O bond cleavage results in the formation of a highly fluorescent coumarin [Eq. (1)] and show how the interconnection of this transduction element to a conjugated polymer produces a 100-fold sensitivity enhancement.



(1)

Our decision to focus on the fluoride-ion-triggered formation of coumarins, was based upon the fact that coumarins are laser dyes with high radiative quantum yields.[8] To this end we synthesized a series of coumarin derivatives with varying electron-donating groups in the 7-position of the coumarin to tune the absorption and emission wavelengths as shown (compounds **1a**–**3a** in Table 1). The synthesis of the indicators involved a two-step sequence, namely silylation of the corresponding 2-hydroxy benzaldehyde, followed by a condensation reaction under the modified Knoevenagel conditions.[9] The *tert*-butyldimethylsilyl (TBS) group was chosen as the protecting group for the phenols to promote selectivity to fluoride by rendering indicator **2** stable (unreactive) to likely interferents. Indeed **2** is stable in THF solutions containing an excess of chloride ions (tetrabutylammonium salt). To avoid a possible problematic *trans–cis* isomerization of the double bond, we used diethyl malonate to introduce symmetrically substituted double bonds in **1, 2**, and **3**.

Table 1: Photophysical data in dichloromethane.

Compound	Abs. max.[a] (log ε)	Emission max.[a]	Φ [%][b]
1	322 (3.66)	–	< 0.01
2	386 (4.31)	450	0.2
3	384 (4.43)	489	0.8
4	378 (4.76)[c]	482	12
1a	334 (3.71)	415	12
2a	417 (4.39)	450	81
3a	412 (4.64)	529	37
4a	396 (4.80)[c]	517	30

[a] Given in nanometers. [b] Determined with quinine sulfate as a standard. [c] Per monomer unit.

The cyclization reaction is irreversible and produces a time-dependent dosimetric response that is controlled by the reaction kinetics. The rate of the cyclization of **2** to **2a** in THF solution was monitored by fluorescence and found to be first order in **2**, independent of fluoride (tetrabutylammonium salt, TBAF), and relatively slow with a rate constant of $k = 2 \times 10^{-4}\ \mathrm{s}^{-1}$. The rate constants do not change for the ranges from

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0.5 to 3 molar ratio of fluoride ion relative to **2**. Hence it appears that the silyl cleavage (or fluoride association with the silyl) is fast and that the cyclization is the slow step. With a higher 10-fold excess of fluoride ion there is an enhancement in the rate, and a saturation of the emission intensity is observed in approximately 2 h (Figure 1 a). The rate acceleration at high fluoride concentrations suggests additional ionic associations with the tetrabutylammonium fluoride (TBAF) salt. The non-innocence of excess fluoride is further revealed by additional peaks in absorbance spectra of **2a** (Figure 1 a inset) that are present at high TBAF concentration but absent after an aqueous extraction.

To impart greater sensitivity to our fluoride-induced-lactonization detection scheme, we designed semiconductor-polymer–indicator conjugates that could amplify the response. Amplification of a turn-on sensor can in principle be performed by bringing a chromophore of the proper spectral characteristics near to the polymer to achieve FRET. Indeed our purpose in synthesizing **3a** which has a longer-wavelength emission was to enable this type of detection scheme. However, in spite of our chromophore engineering, the cyclized coumarins lacked the proper energy matching with poly(phenylene ethynylene)s (PPEs), whose optical and electronic properties are well suited for this fluorescent sensory application.[5]

To overcome the constraints of FRET we pursued a potentially more powerful approach wherein the electronic character of the indicator is strongly electronically coupled to the band structure of the polymer. This approach enables an additional energy-transfer mechanism (known as Dexter energy transfer for small molecules) wherein activation of an indicator locally perturbs the band gap of the polymer. This approach is further attractive because detailed fluorescence-depolarization studies have shown that the strong electronic coupling (band structure) in PPEs contributes more to energy transfer than Förster energy transfer, the basis of FRET schemes.[10] Hence in strongly electronically coupled conjugation schemes a few cyclization events triggered by fluoride ions will produce local minima in the band gap that trap mobile excitons to give a new emission (Figure 2).[11] The facile transport of excitons in semiconductive organic polymers allow these polymers to sample many potential transduction sites and thereby dramatically increase the probability of emission from a lower-energy-trapping (cyclized) site. The result is an amplified turn-on sensory scheme.

In designing PPE-conjugates we sought to develop a general scheme that could be exploited for future indicator systems. In addition, band-gap engineering by the interconnection of pendant chro-

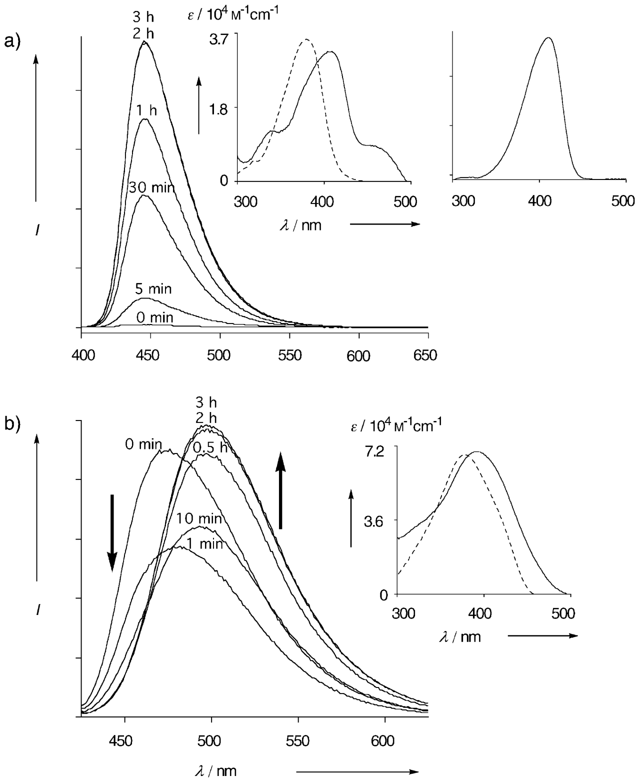


Figure 1. Emission changes of indicator **2** (a) and sensory polymer **4** (b) upon addition of TBAF. The insets show the respective absorption spectra of the initial solution (0 min, -----) and after exposure to TBAF (2 h, ——). The second inset (top right) is the absorption spectrum of **2a** after aqueous extraction, which removes absorptions that appear to be the result of interactions with fluoride ion. Experimental conditions: 298 K in all cases. a) **2**, 3.2×10^{-6} M in THF and TBAF, 33×10^{-6} M; b) **4**, 1.5×10^{-6} M in CH_2Cl_2 (repeating group concentration) and TBAF, 1.6×10^{-7} M. For the polymer **4** $\lambda_{max}=378$ nm, $\varepsilon=57600\,M^{-1}cm^{-1}$; emission $\lambda_{max}=482$ nm and **4a** $\lambda_{max}=396$ nm, $\varepsilon=63400\,M^{-1}cm^{-1}$; emission $\lambda_{max}=517$ nm.

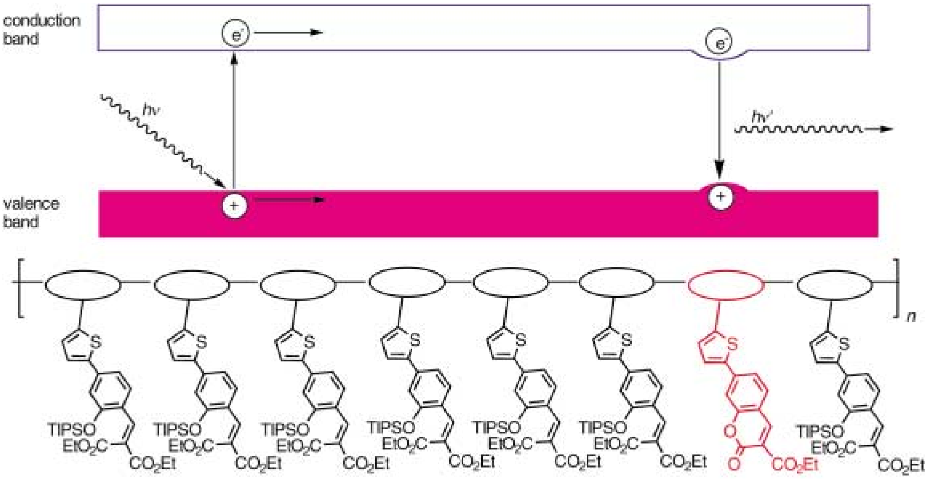


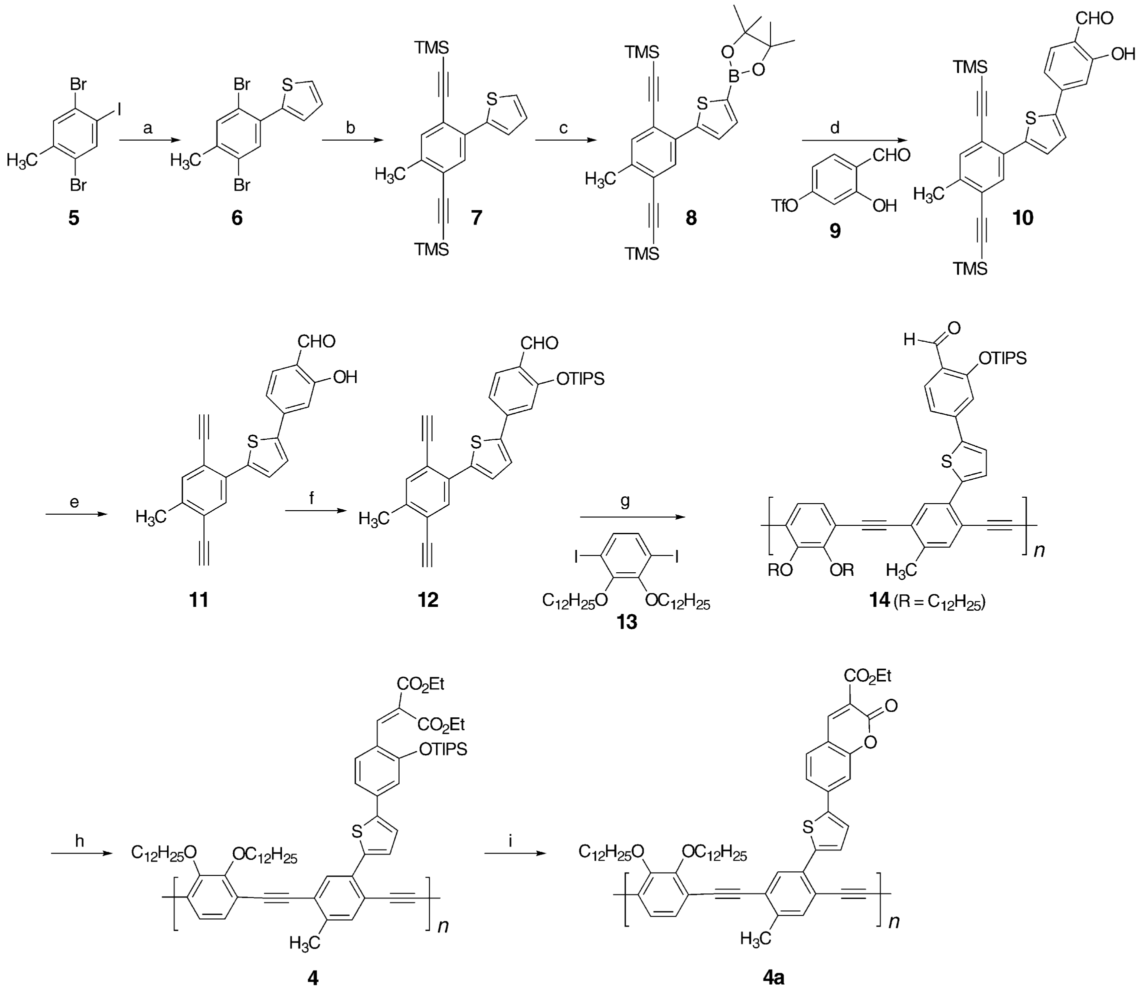
Figure 2. Schematic band diagram illustrating the mechanism by which a semiconductive polymer can produce an enhancement in a new fluorescence chemosensory response. The horizontal dimension represents the position along the polymer backbone shown schematically at the bottom. Excitons are created by absorption of a photon ($h\nu$) and then migrate along the backbone. Fluoride-induced lactonization in the side-chains produces a trapping site with a smaller band gap (E_g) and recombination of excitons at that site results in a new amplified emission.

mophores to semiconducting polymers is applicable to other electrooptical technologies. Our semiconductive-sensory-polymer designs have focused on the PPE-based material **4** (Scheme 1), in which a thiophene-bridge connects the sensory *o*-silyloxybenzylidene malonate moiety with the polymer backbone.[12] Thiophene is the linkage of choice because its strong π-electron delocalizing nature will relay electronic perturbations in the side-chains to the conjugated backbone and it is synthetically versatile.

The synthesis of sensory polymer **4** is shown in Scheme 1.[13] Bis(trimethylsilylethynyl)phenyl thiophene **7**, obtained from **5** by selective Stille cross-coupling and subsequent Sonogashira cross-coupling reactions, was derivatized to the corresponding dioxaborolane **8**. A further cross-coupling reaction with the appropriate triflate **9**[14] produced the thiophene-bridged diaryl compound **10**. Desilylation of diethynylenes using TBAF, followed by silylation of phenol with TIPSCl, gave the monomer **12**.[15] A Sonogashira cross-coupling polymerization provided polymer **14**.[16] As a final step we modified polymer **14** using a titanium-mediated Knoevenagel reaction with diethyl malonate to produce the desired sensory polymer **4**.

The effect of coumarin formation on the band gap of polymer **4** is readily apparent by inspection of the absorption and emission spectra before and after quantitative conversion into **4a** by treatment with an excess of TBAF. As expected, both absorbance and emission spectra of the coumarin-containing form **4a** in dichloromethane solution were red-shifted compared to those of its precursor **4** (Figure 1b). Moreover, the emission change from blue to blue-green is readily detected visually. Cyclization also caused a significant increase in the fluorescence quantum yield of the conjugated polymer (**4**: $\Phi = 0.12$; **4a**: $\Phi = 0.30$). These results indicate that we can trigger a strong change in photophysical properties of PPEs using an electronic perturbation from the appended indicator. The gel permeation chromatography (GPC) analysis of the polymer **4** and **4a** revealed molecular weights of $M_n = 1.06 \times 10^4$ and $M_n = 1.05 \times 10^4$, respectively.

Fluorescence studies reveal that our amplification scheme is highly effective. Kinetic studies for the polymer **4** were not



Scheme 1. Reagents and conditions: a) 2-tributylstannylthiophene, $[PdCl_2(PPh_3)_2]$, DMF, 80 °C, 12 h, 76 %; b) TMSA, $[Pd(PPh_3)_4]$, CuI, toluene/DIPA 4:1, 80 °C, 20 h, 76 %; c) *t*BuLi, THF, −70 °C, 90 min, then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, RT, 4 h, 59 %; d) $[Pd(PPh_3)_4]$, triethylamine, DMF, 100 °C, 24 h, 64 %; e) TBAF, THF, RT, 1 h; f) TIPSCl, imidazole, DMF, RT, 2 h, 75 % over two steps; g) $[Pd(PPh_3)_4]$, CuI, toluene/DIPA 4:1, 65 °C, 24 h, 43 %; h) $TiCl_4$ in CCl_4 to THF, 0 °C, then **14** and diethylmalonate in THF, then pyridine in THF, 0 °C, 1 h and RT, 2 h, 88 %; i) TBAF, THF, RT, 3 h, 98 %. TMSA = trimethylsilylacetylene, DIPA = diisopropylamine.

possible in the same way as for the small molecule **2**, because the fluorescence quantum yield of the polymer varies as a function of conversion and at low conversion we observe less efficient emission. Nevertheless, it is clear that the polymer **4** has a faster response to fluoride ion (Figure 1 b). The enhanced fluoride sensitivity of **4** relative to **2** is clearly evident when one considers that exposure of **4** (1.5×10^{-6} M based upon the repeating group) to fluoride (1.6×10^{-7} M, TBAF in THF) results in a complete transformation of the fluorescence intensity maximum of **4** in 2 h, whereas **2** required a 100-fold higher fluoride concentration to achieve a complete fluorescence transformation over the same time with all other conditions the same (Figure 1). Hence we conclude that **4** is approximately 100-times more sensitive than its small-molecule-based counterpart **2**. This amplification factor is in accord with our previous determination of exciton diffusion in isolated polymers.[5a] We further note that energy migration within isolated polymers (i.e. dilute solutions) is inherently inefficient owing to the one-dimensional exciton diffusion.[17] Thin films that display two- and three-dimensional transport characteristics exhibit more favorable transport statistics and also benefit from improved Förster energy-transfer process between polymer chains. Unfortunately **4** is strongly quenched in thin films, however, it should be possible to generate related indicator materials with desirable solid-state properties and much larger amplification factors in the future.

In summary, we have introduced a new system for the detection of fluoride ion and successfully amplified the response using exciton migration in a semiconducting organic polymer. In contrast to most semiconductive-polymer sensor schemes that rely on changes in emission intensity, this sensory system utilizes a new fluorescence signal. The approach of directly interconnecting the indicator electronically with the polymer's band structure is a promising alternative to FRET schemes and we intend to apply this approach to other analytes of interest.

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[1] a) C. Dusemund, K. R. A. S. Sandanayake, S. Shinkai, *J. Chem. Soc. Chem. Commun.* **1995**, 333; b) H. Yamamoto, A. Ori, K. Ueda, C. Dusemund, S. Shinkai, *Chem. Commun.* **1996**, 407; c) C. R. Cooper, N. Spencer, T. D. James, *Chem. Commun.* **1998**, 1365; d) M. Nicolas, B. Fabre, J. Simonet, *Chem. Commun.* **1999**, 1881; e) C. B. Black, B. Andrioletti, A. C. Try, C. Ruiperez, J. L. Sessler, *J. Am. Chem. Soc.* **1999**, *121*, 10438, and references therein; f) H. Miyaji, W. Sato, J. L. Sessler, *Angew. Chem.* **2000**, *112*, 1847; *Angew. Chem. Int. Ed.* **2000**, *39*, 1777; g) S. Mason, J. M. Llinares, M. Morton, T. Clifford, K. Bowman-James, *J. Am. Chem. Soc.* **2000**, *122*, 1814; h) M. Takeuchi, T. Shioya, T. M. Swager, *Angew. Chem.* **2001**, *113*, 3476; *Angew. Chem. Int. Ed.* **2001**, *40*, 3372; i) For a recent review on anion recognition, see: P. D. Beer, P. A. Gale, *Angew. Chem.* **2001**, *113*, 502; *Angew. Chem. Int. Ed.* **2001**, *40*, 486.

[2] a) H. Miyaji, J. L. Sessler, *Angew. Chem.* **2001**, *113*, 158; *Angew. Chem. Int. Ed.* **2001**, *40*, 154.

[3] a) J. J. Lavigne, E. V. Anslyn, *Angew. Chem.* **1999**, *111*, 3903; *Angew. Chem. Int. Ed.* **1999**, *38*, 3666.

[4] S. Yamaguchi, S. Akiyama, K. Tamao, *J. Am. Chem. Soc.* **2001**, *123*, 11372.

[5] a) Q. Zhou, T. M. Swager, *J. Am. Chem. Soc.* **1995**, *117*, 12593; b) J.-S. Yang, T. M. Swager, *J. Am. Chem. Soc.* **1998**, *120*, 5321; c) J.-S. Yang, T. M. Swager, *J. Am. Chem. Soc.* **1998**, *120*, 11864; d) T. M. Swager, *Acc. Chem. Res.* **1998**, *31*, 201; e) D. T. McQuade, A. E. Pullen, T. M. Swager, *Chem. Rev.* **2000**, *100*, 2537; f) for a recent review, see: T. M. Swager, J. H. Wosnick, *MRS Bull.* **2002**, *27*, 446.

[6] D. T. McQuade, A. H. Hegedus, T. M. Swager, *J. Am. Chem. Soc.* **2000**, *122*, 12389.

[7] For another sensor approach that used the affinity of fluoride to silicon see: S. Yamaguchi, S. Akiyama, K. Tamao, *J. Am. Chem. Soc.* **2000**, *122*, 6793.

[8] K. D. Drexhage in *Dye Lasers, Vol. 1* (Ed.: F. P. Schäfer), Springer, New York, **1977**.

[9] a) W. Lehnert, *Tetrahedron Lett.* **1970**, 4723; b) M. Black, J. I. G. Cadogan, H. McNab, A. D. MacPherson, V. P. Roddam, C. Smith, H. R. Swenson, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2483.

[10] A. Rose, C. G. Lugmair, T. M. Swager, *J. Am. Chem. Soc.* **2001**, *123*, 11298.

[11] T. M. Swager, C. J. Gil, M. S. Wrighton, *J. Phys. Chem.* **1995**, *99*, 4886.

[12] The alternative approach to develop PPE based on the 3,6-diethynyl-2-hydroxy-benzaldehyde was not pursued, as *o*-phenoxyacetylenes could undergo tandem cyclization to the corresponding benzofuran by use of TBAF or CsF, for example, see: A. Sakai, T. Aoyama, T. Shioiri, *Heterocycles* **2000**, *52*, 643.

[13] See Supporting Information for details.

[14] 2-Hydroxy-4-(trifluoromethanesulfonyl) benzaldehyde (**9**) was obtained by treating 4-hydroxy-2-methoxybenzaldehyde with triflic anhydride in pyridine (95 %), followed by demethylation involving BBr$_3$ in CH$_2$Cl$_2$ at −40 °C (79 %). See also Supporting Information.

[15] Triisopropylsilyl group (TIPS) was used instead of *tert*-butyldimethylsilyl (TBS) as the thermal polymerization conditions required a more stable protecting group for phenol.

[16] 1,4-Diiodobenzene with *ortho*-dialkoxy side-chains **13** was chosen as a comonomer to produce a sensory polymer with higher frequencies (blue-shifted). Z. Zhu, T. M. Swager, *Org. Lett.* **2001**, *3*, 3471.

[17] I. A. Levitsky, J. Kim, T. M. Swager, *J. Am. Chem. Soc.* **1999**, *121*, 1466.