Conversion of thioureas to fluorescent isothiouronium-based photoinduced electron transfer sensors for oxoanion sensing

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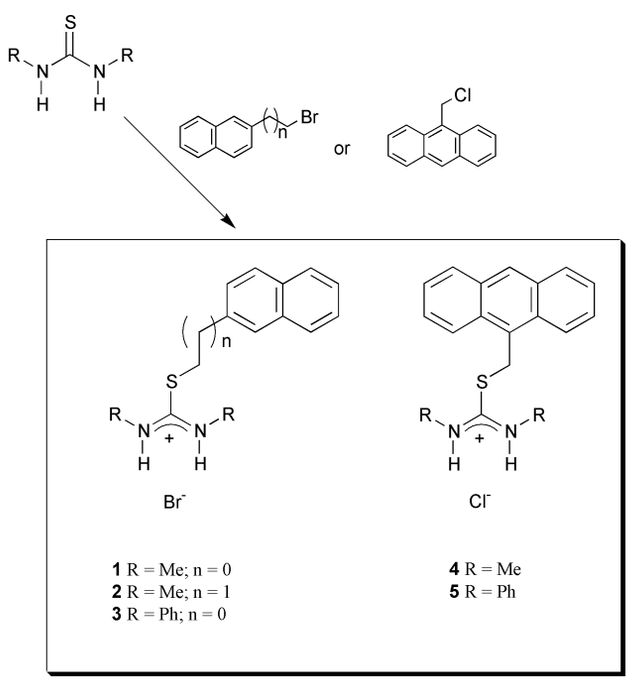
A convenient conversion is described of thiourea-based receptors to fluorescent isothiouronium-based photoinduced electron transfer (PET) sensors for oxoanion sensing. Naphthalene- or anthracene-functionalized mono-isothiouroniums are synthesized from the corresponding thioureas, in which the fluorophore is connected to the sulfur atom of the thiourea moiety by a methylene or an ethylene spacer. Even though all of the isothiouroniums with a methylene spacer readily decompose in MeOH upon excitation of the fluorophore moiety, the isothiouronium with an ethylene spacer shows good stability under identical conditions. The naphthyl isothiouronium with an ethylene spacer shows a significant fluorescence enhancement upon formation of a 1 : 1 complex with oxoanions in MeOH, and the selectivity follows the order of hydrogen phosphate > acetate ≫ dihydrogen phosphate ≫ chloride. The results in the present work indicate that various types of fluorescent PET sensors might be readily obtainable from non-fluorescent thiourea-based receptors by the introduction of appropriate fluorophores at the sulfur atom of thiourea-binding sites.

Introduction

The design and synthesis of abiotic hydrogen-bonding receptors for biologically and/or chemically important anions are of current interest in host–guest chemistry.[1,2] A wide variety of these receptors has been reported for selective anion detection, transport, and catalysis. In these receptors, amides, (thio)ureas, pyrroles, imidazoliums and guanidiniums are utilized as hydrogen-bond forming moieties to obtain selective binding affinities.

Isothiouronium salts have been explored quite recently as a new class of hydrogen-bonding subunit for the purpose of anion recognition.[3–5] The first use of isothiouronium compounds was reported by Yeo and Hong[3] for the binding of 5′-AMP or oxoanions such as phosphates and carboxylates. Suzuki and co-workers[4] described an application of isothiouronium compounds for solvent polymeric membrane ion-selective electrodes with iodide selectivity. Of particular interest is a sophisticated combination of the isothiouronium binding unit and a suitable chromophore as reported by Kubo *et al.*[5] Their anion chemosensor was based on a naphthalene-isothiouronium dyad that was synthesized from the corresponding naphthalene-thiourea, *i.e.*, 2-(1,3-dimethylthioureylene)naphthalene, by reaction with benzyl bromide. This receptor showed a significant increase in fluorescence intensity upon binding with acetate in MeCN, while only a low response was observed in the presence of chloride anion. Although the details of the response mechanisms are not clear for their system, the complexation-induced enhancement in the fluorescence intensity is quite attractive from a practical viewpoint. To date, only a few fluorescent anion sensors exist that allow the detection of anionic species based on chelation-enhanced fluorescence or luminescence.[6–8] Furthermore, due to their high affinity for oxoanions over chloride,[5] isothiouronium-based receptors may be promising candidates for the recognition of biologically relevant substrates such as phosphates and their derivatives under physiological conditions.

The present paper discusses an alternative design of such isothiouronium-based fluorescent anion receptors. In contrast to the earlier system based on the conversion of fluorescent thioureas to isothiouroniums in which the fluorophore is linked to the nitrogen atom of the isothiouronium binding site,[5] our strategy is based on the conversion of thioureas to isothiouroniums by attachment of the appropriate fluorophores through the sulfur atom of the thiourea moiety (Scheme 1). Since a number of thiourea compounds are now available as anion-binding reagents,[9–12] our approach makes it possible to



Scheme 1

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easily derive various types of fluorescent receptors from the corresponding thioureas without the need for changes to the receptor skeleton. In order to assess our strategy, very simple naphthalene- or anthracene-functionalized mono-isothiouroniums **1** to **5** were synthesized from the corresponding thioureas in the present study. The photostabilities and binding properties of these isothiouronium-based compounds were examined in MeOH, and the response mechanism was discussed on the basis of photoinduced electron transfer (PET) reactions as a possible operating principle.

Results and discussion

As shown in Scheme 1, the syntheses of the isothiouronium compounds were carried out by nucleophilic substitution of halogenides with the appropriate thioureas. 2-(2-Bromoethyl)naphthalene was prepared from naphthalene-2-acetic acid by reduction using $LiAlH_4$ to give the corresponding alcohol, followed by bromination with CBr_4. All of the isothiouronium compounds could be easily obtained in high yields (~80%) although the purification process lowered final yields to ~50%.

Fig. 1 shows the absorption and fluorescence spectra of **1** and

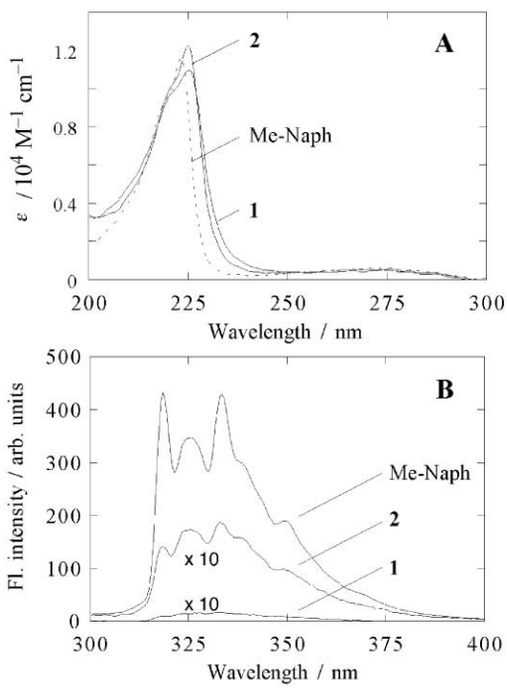

Fig. 1 (A) Absorption and (B) fluorescence spectra of receptors **1**, **2** and 2-methylnaphthalene (Me-Naph) in non-degassed MeOH. The emission intensities of the fluorescence spectra of **1** and **2** are magnified by a factor of 10. [Compound] = 20 μM. Excitation wavelength: 270 nm.

2 in MeOH. For comparison, the absorption and fluorescence spectra of 2-methylnaphthalene (Me-Naph) are also shown. As can be seen from Fig. 1A, compounds **1** and **2** show absorption maxima at 225 nm, accompanied by vibronic absorption bands above 250 nm. These features of the absorption spectra are characteristic of alkyl-substituted naphthalene molecules, and no marked differences are observed as compared with the spectrum of Me-Naph (λ_{max}: 224 nm). This result indicates that there is no significant interaction between naphthalene and the isothiouronium moieties in the ground state. By contrast, as shown in Fig. 1B, the fluorescence spectra of isothiouronium compounds **1** and **2** are clearly different from the spectrum of Me-Naph. While both the shape and position of the emission spectra peaks of **1** and **2** almost coincide with those of Me-Naph (*cf.* Fig. 2), the intensity at 333 nm is reduced to 1/260 and 1/23 for **1** and **2**, respectively, as compared with that of

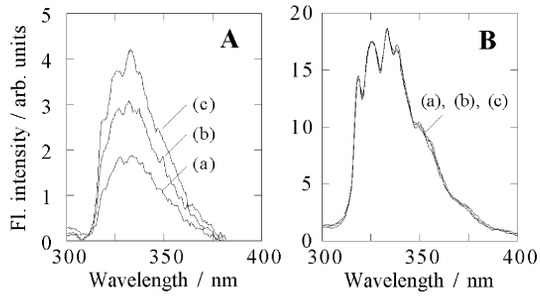

Fig. 2 Fluorescence spectra of (A) receptor **1** and (B) receptor **2** under repeated scan conditions. [**1**] = [**2**] = 20 μM in MeOH. Excitation wavelength: 270 nm. Scan speed: 100 nm min^{-1}. Scan range: 300–450 nm. (a): 1st; (b) 2nd; (c) 3rd scans.

Me-Naph. Even though the observed quenching may be partly ascribable to a heavy-atom effect from the bromide ion, it is most likely that, as expected from the results of electrochemical measurements (*vide infra*), the fluorescence of the naphthalene moiety in **1** and **2** is quenched by a PET mechanism,[13–15] in which the naphthalene and isothiouronium moieties act as electron donor and acceptor, respectively.

The feasibility of PET between the naphthalene (Naph) and isothiouronium (TU) moieties can be assessed according to the Rehm–Weller equation:[14,15]

$$\Delta G/\text{kcal mol}^{-1} = 23.06[E_{ox}(\text{D}) - E_{red}(\text{A})] - \omega_p - G_{00}(\text{D})$$

where ΔG, E_{ox}(D), E_{red}(A), ω_p, and G_{00}(D) are the free energy change of electron transfer, the oxidation potential of the donor (D), the reduction potential of the acceptor (A), the ion-pairing energy, and the excitation energy of the donor (D), respectively. The oxidation potential of naphthalene, E_{ox}(Naph), is 1.6 V *vs.* SCE, and G_{00}(Naph) is 92 kcal mol^{-1}.[15] The value of ω_p is usually estimated to be −1.3 kcal mol^{-1} in MeCN.[15] E_{red}(TU) is *ca.* −1.83 V *vs.* Ag/Ag^+, which was measured in MeCN solution by cyclic voltammetry. Although accurate determination of the free energy change of electron transfer was impossible due to the irreversibility of the TU reduction, the ΔG within the present system calculated from the above values is indeed negative. This is clear evidence that the naphthalene and isothiouronium moieties act as electron donor and acceptor, respectively.

The difference in the emission intensities between **1** and **2** seems to be another piece of evidence for quenching due to the PET mechanism. It is reasonable that the fluorescence intensity of **1** with the CH_2 spacer is weaker than that of **2** with the CH_2CH_2 spacer because of the smaller distance separating the terminal groups, *i.e.*, the naphthalene and isothiouronium moieties. Use of the CH_2 spacer is therefore desirable in terms of obtaining fast PET rates, since it allows efficient fluorescence signalling, *i.e.* 'switched off–switching on'.[13,16] The CH_2 spacer may also contribute to the suppression of exciplex emissions, thus simplifying the fluorescence behaviour,[13] although this type of emission benefits the ratiometric analysis in well-designed systems.[17] Additionally the CH_2 spacer is more convenient for synthesis *via* benzylic functionalities.[13] However, as shown in Fig. 2A, the fluorescence intensity of **1**, with the CH_2 spacer, increased uniformly after repeated scans, indicating the instability of receptor **1** under the conditions of photo-irradiation (excitation wavelength λ_{ex}: 270 nm). Similar results were obtained for all the isothiouronium-based compounds with the CH_2 spacer. Again, the fluorescence intensities of receptors **3** to **5** increased uniformly upon continuous excitation of the fluorophore moiety (λ_{ex}: 270 nm for **3**; 349 nm for **4** and **5**). It seems likely that, under the photo-irradiation conditions, photodissociation of the CH_2–S bond occurs in all the compounds with the CH_2 spacer when considering the photochemistry of arylmethyl compounds.[18] It is well recognized that

the photochemical reactions of arylmethyl compounds with leaving groups ($ArCH_2$–LG) give various products from both the intermediate arylmethyl radical ($ArCH_2^{\bullet}$ $^{\bullet}$LG) as well as ion pairs ($ArCH_2^{+}$:LG^{-}).[18] One of possible processes in protic and nucleophilic solvents like alcohols (ROH) is photosolvolysis where the ion pair is trapped by the solvent to give substitution products ($ArCH_2$–OR and HLG).[18] On the other hand, as shown in Fig. 2B, no changes in the fluorescence spectra of **2** with the CH_2CH_2 spacer appeared after repeated scans, indicating the good photostability of **2** under identical conditions (λ_{ex}: 270 nm). On the basis of these results, we conclude that the CH_2 group is not suitable as a spacer for the design of isothiouronium-based PET systems when the fluorophores are attached through the sulfur atom of the isothiouronium moiety. Thus, all subsequent binding studies were performed with the isothiouronium-naphthalene with a CH_2CH_2 spacer, receptor **2**.

The effect of HPO_4^{2-} as [K^+–18-crown-6] salts on the absorption and fluorescence spectra of receptor **2** was examined in MeOH. While the absorption spectra above 260 nm did not change at all in the presence or absence of this anion, significant changes occurred in the fluorescence spectra. Fig. 3 shows the

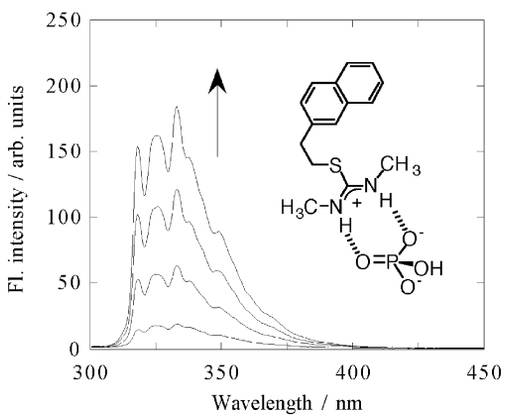

Fig. 3 Changes in the fluorescence spectra of **2** (20 μM) upon addition of HPO_4^{2-} (0, 20, 100, 400 μM) as the [K^+–18-crown-6] salt in non-degassed MeOH. Excitation wavelength: 270 nm.

fluorescence spectra of **2** as a function of HPO_4^{2-} concentration, when excited at 270 nm. Increasing the HPO_4^{2-} concentration results in a marked enhancement of the fluorescence intensity while the spectral shape and position of fluorescence are independent of the HPO_4^{2-} concentration. This signalling action, in which only one parameter (fluorescence quantum yield) is anion-controlled, is typical of fluorescent PET-based molecular sensors. In spite of the use of the ethylene group as a spacer, the fluorescence intensity at 333 nm in the HPO_4^{2-} complex is indeed higher by a factor of 10 than that in the free receptor. This indicates that use of the CH_2CH_2 spacer does not cause any serious problems for fluorescent signalling. A non-linear fitting shows that the changes in the fluorescence spectra can be explained by the formation of a 1 : 1 complex (*cf.* Fig. 4),[19] and the association constant between **2** and HPO_4^{2-} is calculated to be $1.1 \pm 0.1 \times 10^4$ M^{-1}. This corresponds to approximately half the value obtained with a bis-guanidinium receptor in the same solvent (1.83×10^4 M^{-1}),[20] indicating that the binding affinity of isothiouronium is indeed comparable to that of biologically important guanidinium groups,[21] which have been extensively utilized as anion-binding subunits in artificial systems.[1]

The selectivity of receptor **2** was also examined in MeOH. Similar, but less pronounced, responses were observed upon addition of other monovalent anions ($H_2PO_4^-$, $MeCO_2^-$, Cl^-). Fig. 4 shows the dependence of the intensity ratio F/F_0 (F and F_0 are the fluorescence intensities of the receptor in the presence and absence of guest anions, respectively) at 333 nm on the concentration of anion in MeOH. We can see that acetate is the

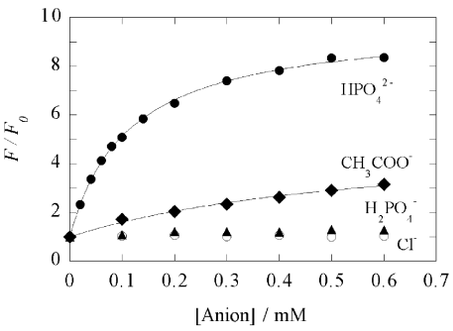

Fig. 4 Dependence of the intensity ratio, F/F_0, at 333 nm of **2** (20 μM) on the concentrations of (●) HPO_4^{2-}, (◆) CH_3COO^-, (▲) $H_2PO_4^-$ and (○) Cl^- in non-degassed MeOH. Anions are added as the [K^+–18-crown-6] salts. (—): Non-linear fitting based on the equation for 1 : 1 complexation.

only other anion to be bound substantially under these conditions. When **2** forms a 1 : 1 complex with acetate ($K_{11} = 1.7 \pm 0.2 \times 10^3$ M^{-1}), the fluorescence intensity at 333 nm increases by a factor of 5.0, which corresponds to half the value observed for HPO_4^{2-} binding. In the presence of $H_2PO_4^-$, only a slight change in the fluorescence spectrum is observed so that determination of the association constant between **2** and $H_2PO_4^-$ is impossible. In the case of Cl^-, **2** does not show any obvious spectral changes even with a 30-fold excess. Thus, **2** shows selectivity in the order of $HPO_4^{2-} > MeCO_2^- \gg H_2PO_4^- \gg Cl^-$. As has been found previously,[5] the lack of binding affinity for Cl^- seems quite desirable for the sensing of oxoanions.

In summary, we have examined the conversion of thiourea-based receptors to fluorescent isothiouroniums by introduction of appropriate fluorophores at the sulfur atom of the thiourea moiety. Whereas all the isothiouroniums with a methylene spacer readily decomposed in MeOH upon excitation of the fluorophore moiety, receptor **2** with an ethylene spacer, exhibited good stability and could function as a fluorescent PET sensor for oxoanions such as HPO_4^{2-} and $MeCO_2^-$. In addition to the strong anion-binding affinity, another promising feature of the isothiouronium was its electron-acceptor ability [E_{red}(TU): *ca.* −1.83 V], which makes anion detection possible on the basis of fluorescence enhancement. Although both the isothiouroniums reported here and by Kubo *et al.*[5] are naphthalene-functionalized receptors, the Rehm–Weller equation predicted that various fluorophores such as pyrene [E_{ox}(Py): 1.20 V; G_{00}(Py): 77 kcal mol^{-1}][15] and anthracene [E_{ox}(An): 1.16 V; G_{00}(An): 76.3 kcal mol^{-1}][15] were suitable for the design of isothiouronium-based PET sensors. Our approach would thus allow easy derivation of various types of fluorescent receptors from the corresponding thioureas; such work is now in progress in our laboratory.

Experimental

Reagents and apparatus

All the guest anions were commercially available as K^+ salts and used as-received. 18-Crown-6 from Wako Pure Chemical Industries (Tokyo, Japan) was used to dissolve the K^+ salts. Tetrabutylammonium perchlorate from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan) was purified four times by recrystallization from ethyl acetate. Spectrometric grade methanol from Nacalai Tesque, Inc. (Kyoto, Japan) was used as-received. Dry acetonitrile (for organic synthesis, Wako) was used without further purification for electrochemical measurements. Dimethyl sulfoxide-d_6 (DMSO-d_6) and chloroform-d_1 were purchased from E. Merck (>99.8%, Darmstadt, Germany).

Fluorescence spectra were measured at 25 °C with a JASCO FP-777W spectrophotometer (Japan Spectroscopic Co. Ltd.,

Tokyo, Japan); the slits for the excitation and emission monochromators were 3.0 and 1.5 nm, respectively. All emission spectra were uncorrected. Absorption spectra were recorded at 25 °C with a HITACHI U-3000 UV-VIS spectrophotometer (Hitachi, Ltd., Tokyo, Japan) by using a quartz cell of 0.1 cm path length. ^{1}H NMR spectra were obtained on a JEOL α-270 spectrometer (270 MHz; JEOL Datum, Tokyo, Japan). All chemical shift values (δ) are reported in parts per million (ppm), using the residual solvent signal of DMSO (δ 2.49) or $CHCl_3$ (δ 7.24) as a reference.

Synthesis

***S*-(2-Naphthylmethyl)-*N*,*N*′-dimethylisothiouronium bromide (1).** 2-(Bromomethyl)naphthalene was added to a stirred solution of 1,3-dimethylthiourea (0.24 g, 2.26 mmol) in dry ethanol (30 ml) under a nitrogen atmosphere. The reaction solution was stirred for 1 h at 80 °C, and then the solvent was evaporated. Purification by silica gel column chromatography with $CHCl_3$–CH_3OH (10 : 1) as eluent gave the product as a white solid (0.34 g, 46%). ^{1}H NMR (270 MHz, DMSO-d_6): δ 9.24 (br, 2H, NH), 7.96–7.89 (4H, Naph), 7.57–7.52 (3H, Naph), 4.70 (s, 2H, -CH_2-), 2.92 (s, 6H, -CH_3). Anal. Calcd for $C_{14}H_{17}N_2SBr$ (325.27): C, 51.7; H, 5.27; N, 8.61; S, 9.86; Br, 24.57%. Found: C, 51.49; H, 5.37; N, 8.53; S, 10.13; Br, 24.61%.

2-(2-Naphthyl)ethanol. Naphthalene-2-acetic acid (1.0 g, 5.4 mmol) was added to a stirred solution of $LiAlH_4$ (0.25 g, 6.6 mmol) in freshly distilled THF (50 ml), keeping the reaction mixture at 0 °C under a nitrogen atmosphere. After stirring at 0 °C for 30 min, ethyl acetate, diethyl ether saturated with water, and water were added successively. The organic phase was dried over Na_2SO_4, and then the solvent was evaporated. Purification by silica gel column chromatography with CH_2Cl_2–CH_3OH (10 : 1) as eluent gave the product as a white solid (0.4 g, 43%).

2-(2-Bromoethyl)naphthalene. Naphthalene-2-ethanol (0.2 g, 1.16 mmol) and CBr_4 (0.58 g, 1.74 mmol) were dissolved in CH_2Cl_2 (purified by passage through a column of basic alumina, 20 ml), and triphenylphosphine (0.37 g, 1.39 mmol) was gradually added. The reaction solution was stirred for 1 h at room temperature under a nitrogen atmosphere, followed by washing with water several times. The organic phase was dried over Na_2SO_4, and then the solvent was evaporated. Purification by column chromatography (silica gel, $CHCl_3$) gave the product as a white solid (0.2 g, 73%).

***S*-(2-Naphthylethyl)-*N*,*N*′-dimethylisothiouronium bromide (2).** This compound was synthesized analogously to **1** from 1,3-dimethylthiourea and 2-(2-bromoethyl)naphthalene. It was purified by silica gel column chromatography with $CHCl_3$–CH_3OH (10 : 1) as eluent, giving the product as a pale yellow solid (yield: 55% as calculated for *S*-alkylation of 1,3-dimethyl-2-thiourea). ^{1}H NMR (270 MHz, DMSO-d_6): δ 9.03 (s, 2H, NH), 7.90–7.79 (4H, Naph), 7.53–7.44 (3H, Naph), 3.61 (t, J = 7.3 Hz, 2H, -CH_2-), 3.13 (t, J = 7.3 Hz, 2H, -CH_2-), 2.90 and 2.82 (6H, -CH_3). Anal. Calcd for $C_{15}H_{19}N_2SBr$ (339.30): C, 53.1; H, 5.64; N, 8.26; S, 9.45; Br, 23.55%. Found: C, 53.16; H, 5.63; N, 7.84; S, 9.48; Br, 23.75%.

***S*-(2-Naphthylmethyl)-*N*,*N*′-diphenylisothiouronium bromide (3).** This compound was synthesized analogously to **1** from 2-(bromomethyl)naphthalene and 1,3-diphenylthiourea (pale yellow solid). ^{1}H NMR (270 MHz, DMSO-d_6): δ 7.93–7.89 (2H, Ar), 7.80 (d, J = 6.5 Hz, 2H, Ar), 7.54–7.44 (3H, Ar), 7.32–7.13 (10H, Ar), 4.58 (s, 2H, -CH_2-).

***S*-(9-Anthrylmethyl)-*N*,*N*′-dimethylisothiouronium chloride (4).** This compound was synthesized analogously to **1** from 9-(chloromethyl)anthracene and 1,3-dimethylthiourea (yellow solid, yield: 48%). ^{1}H NMR (270 MHz, $CDCl_3$): δ 10.09 (br, 1H, NH), 9.72 (br, 1H, NH), 8.34 (s, 1H, Naph), 8.19 (d, J = 8.1 Hz, 2H, Naph), 7.92 (d, J = 8.1 Hz, 2H, Naph), 7.50 (t, J = 8.1 Hz, 2H, Naph), 7.40 (t, J = 8.1 Hz, 2H, Naph), 5.68 (s, 2H, -CH_2-), 3.48 (s, 3H, -CH_3), 2.95 (s, 3H, -CH_3).

***S*-(9-Anthrylmethyl)-*N*,*N*′-diphenylisothiouronium chloride (5).** This compound was synthesized analogously to **1** from 9-(chloromethyl)anthracence and 1,3-diphenylthiourea (yellow solid). ^{1}H NMR (270 MHz, DMSO-d_6): δ 10.09 (s, 2H, NH), 8.64 (s, 1H, Naph), 8.41 (d, J = 8.1 Hz, 2H, Naph), 8.11 (d, J = 8.1 Hz, 2H, Naph), 7.63–7.08 (14H, Ar), 5.56 (s, 2H, -CH_2-).

Determination of association constants by fluorescence spectroscopy

To determine the 1 : 1 association constant K_{11}, a series of methanol solutions was prepared that contained the guest anions (as their [K^+–18-crown-6] salts) and receptor **2**. The concentration of **2** was fixed at 20 μM, and the concentration of guest anions ranged from 0 to 2.0 mM. The changes in fluorescence intensity at 333 nm were monitored as a function of the guest concentration. The resulting titration curves were analyzed by a non-linear regression based on a 1 : 1 binding isotherm model:[19]

$$F/F_0 = \{1 + \Delta F K_{11}[G]\}/\{1 + K_{11}[G]\} \quad (1)$$

where F and F_0 are the fluorescence intensities of the receptor in the presence and absence of guest anions, respectively, and ΔF is the complexation-induced maximum change in the fluorescence intensity ratio. The free guest concentration, [G], can be related to known initial concentrations of guest (G_0) and receptor (R_0), by the following equation:

$$G_0 = [G] + \{R_0 K_{11}[G]\}/\{1 + K_{11}[G]\} \quad (2)$$

Together, eqns. (1) and (2) describe the system.

Electrochemical measurements

Cyclic voltammograms of receptor **2** (1.0 mM) were measured at 25 °C in MeCN containing 0.1 M $N(C_4H_9)_4ClO_4$ as a supporting electrolyte. A sweep rate of 100 mV s^{-1} was used. A potentiostat (Solatron 1286, Schlumberger Technologies, Hampshire, England) equipped with an X-Y recorder was used with a three-electrode configuration: 1 mm ϕ glassy carbon electrode as the working electrode, an Ag/Ag^+ electrode as the reference electrode, and a platinum wire as the auxiliary electrode. Sample solutions were degassed by Ar gas bubbling before measurements.

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