# Investigation of Isomerism in Anthracene-Isothiouronium Salts and Application of these Salts for Anion Sensing

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Novel fluorescent anion chemosensors based on anthracene-isothiouronium derivatives were synthesized. Isomerism due to the intramolecular mobility in these isothiouronium salts was detected by ^{1}H NMR spectroscopy. The effect of the substituent, temperature and solvent on the isomerism was also examined. The anthracene-isothiouronium sensor showed significant fluorescent enhancement upon the addition of various anions such as fluoride, acetate, and dihydrogen phosphate, even in the presence of water.

**Key Words**: Anthracene-isothiouronium salts, Anion sensing

## Introduction

The design and synthesis of anion receptors have gained much attention in molecular recognition chemistry, since anions play significant roles in many chemical and biological processes.[1] Recently, the ability of thioureas to form complexes with anions has been thoroughly exploited in the field of molecular recognition due to their binding of anions through hydrogen bonding.[2] The use of isothiouronium groups has not been explored very much in the area of anion binding. Such groups would enhance the acidity of the NH moieties, thereby can

function as a better binder compared to the thiourea group.[3] Therefore we decided to synthesize novel fluorescent anion chemosensors based on anthracene using isothiouronium as an anion binding unit (Scheme 1 and 2).

## Results and Discussion

**Isomerism in the anthracene-isothiouronium salts.** The isothiouronium salt **5a** was first prepared by refluxing thiourea **4a** with benzyl bromide in ethanol. During its spectroscopic characterization, the ^{1}H NMR spectrum of **5a** showed two sets
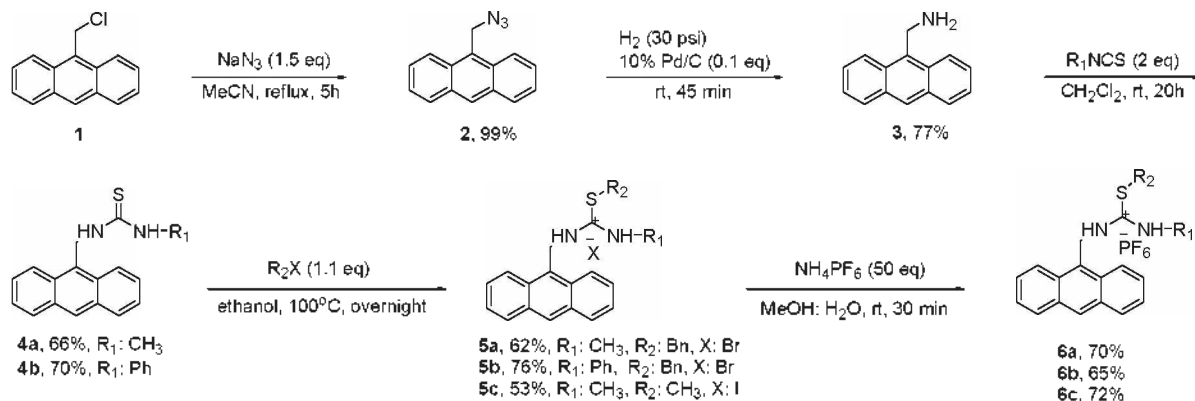


**Scheme 1.** Synthesis of the isothiouronium salts **6**
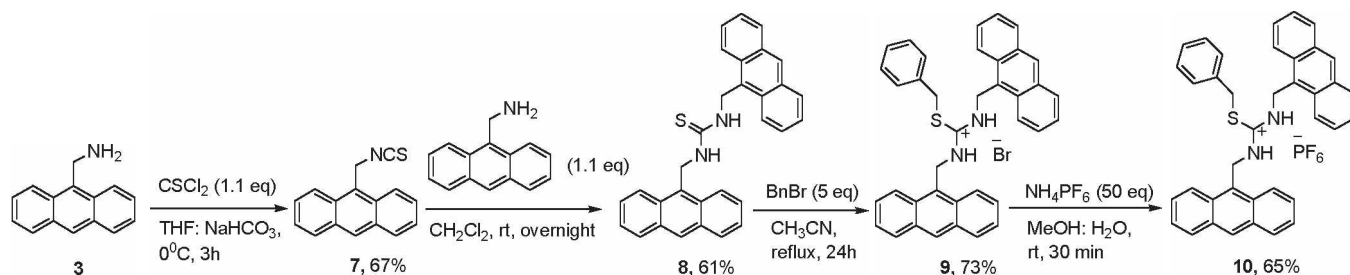


**Scheme 2.** Synthesis of the isothiouronium salts **10**

of peaks for the protons. thus indicating the existence of different two isomers. The ratio of the isomers. as deduced from the integration of the proton signals, was approximately 3:1 in CDCl$_3$ (see Experimental Section). While very similar isothiouronium structures based on naphthalene had a single form and no isomerism at room temperature.[3a] the configurational and electronic structure of our isothiouronium salts presented complexities and remained a subject for investigation. Consequently, the following three possibilities of isomerism in substituted isothiouronium salts need to be discussed (R$_1$ ≠ R$_3$).
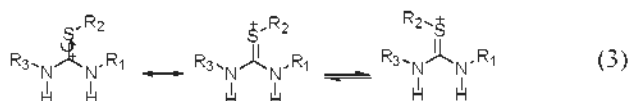
1. The oscillation of the carbon-nitrogen double bond contributes to the resonance structure of the isothiouronium ion including two imonium, one carbonium, and one sulfonium ions (eq. 1).[4]



$$(1)$$
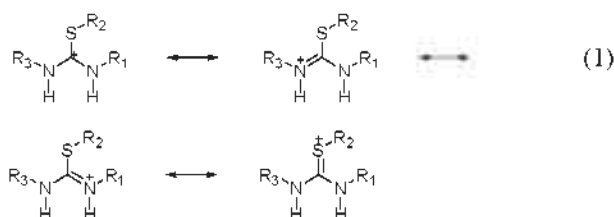
2. Hindered rotation at the C = N bond arises from the resonance effect (eq. 2).[5]



$$(2)$$
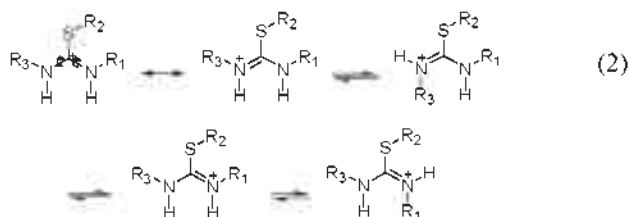
3. *Syn-anti* isomerism due to restricted rotation at the C = S bond (eq. 3).[6]



$$(3)$$

It is known that in a few cases single bond rotation is so slow and restricted that isomers can be differentiated even if no double bond exists. because resonance gives the single bond some double bond character.[7g] While *cis* and *trans* isomerism at the isoelectronic C=N double bond in amides[7] is well known, the possibility of isomerism at the isoelectronic C=S double bond in thioketonium ions has only been examined by Horst Kesskor and Hans-Otto Kalinowski at low temperature.[6] To the best of our knowledge, this is the first time isomerism in the more complex structures of isothiouronium salts has been detected at room temperature.

**Effect of substituent on the isomerism in anthracene-isothiouronium salts.** By varying the substituents R$_1$, R$_2$ and X of compound **5a** while R$_3$ is fixed at 9-methylanthracene, the ratio

of the two isomers was changed (Table 1). This can be explained by the steric hindrance between R$_1$, R$_2$, and 9-methylanthracene during the rotation. When R$_1$ and R$_2$ were methyl moieties (compound **5c**). a small group, the effect of steric hindrance was very small. Therefore, the ratio of the two isomers was 1:1. When R$_1$ or R$_2$ was the benzyl moiety (compounds **5a** and **5b**), a more bulky group, the ratio of the two isomers was changed. due to the steric interaction with other functional groups. Another point of note here is the effect of the counter anion. The counter anions such as bromide, iodide, and hexafluorophosphate had no effect on the ratio of the two isomers, which remained the same when it was changed from the bromide and iodide moiety of **5a-5c** to the hexafluorophosphate of **6a-6c**. That can be explained by the low interaction between these counter anions and positive moiety of isothiouronium which accounts for isomerism.

The examination of isomerism becomes increasing problematic with increasing dissimilarity in the structure of the compounds. Therefore, we tried to simplify the structure of the isothiouronium salts by synthesizing compounds **9** and **10**, in which R$_1$ is the same as R$_3$. Only one set of peaks was observed in the $^1$H NMR spectra of **9** and **10**. It can be inferred that the two isomers of compound **5a-5c** and **6a-6c** may be from the *syn-anti* isomerism due to restricted rotation at the C=S bond (eq. 3).

**Effect of temperature on the isomerism in anthracene-isothiouronium salts.** As mentioned above, the isomerization in isothiouronium salts results from the restricted rotation. By increasing the temperature, the available thermal energy can be changed and, in this way, the rate of rotation can be mani-

**Table 1.** Effect of substituent on the ratio of the two isomers in CDCl$_3$

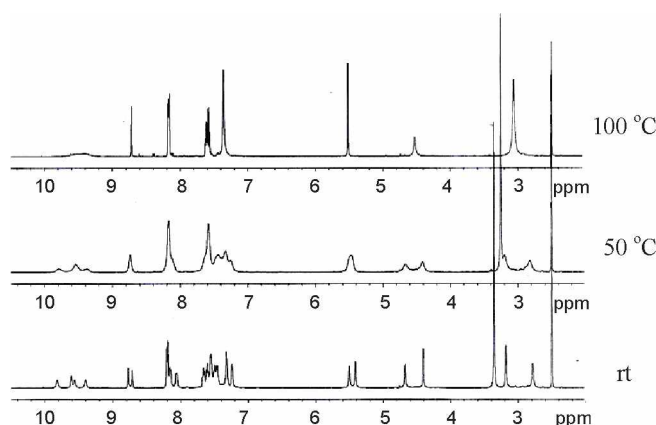| Compound | R$_1$ | R$_2$ | X | Ratio of two isomers |
|---|---|---|---|---|
| **5a** | CH$_3$ | Bn | Br$^-$ | 3 : 1 |
| **5b** | Ph | Bn | Br$^-$ | 3 : 2 |
| **5c** | CH$_3$ | CH$_3$ | I$^-$ | 1 : 1 |
| **6a** | CH$_3$ | Bn | PF$_6^-$ | 3 : 1 |
| **6b** | Ph | Bn | PF$_6^-$ | 3 : 2 |
| **6c** | CH$_3$ | CH$_3$ | PF$_6^-$ | 1 : 1 |



**Figure 1.** Effect of temperature on the isomerism of **5a**.

pulated. When the exchange processes become sufficiently rapid to reduce the residence time in any environment far below the time scale of a nuclear transition, the peaks begin to coalesce. As seen in Figure 1, in the $^1$H NMR spectra of compound **5a** in DMSO-$d_6$, the two sets of peaks merged to form one set of peaks when the temperature was increased to 100 °C.

**Effect of solvent on the isomerism in anthracene-isothiouronium salts.** The dependence of the ratio of the two isomers of compound **5a** on the solvent was observed in the $^1$H NMR spectra (Table 2). This might be due to the fact that the isothiouronium salts are dipoles and that the equilibrium between the two isomers involves dipolar isomers and solvent interactions. Polar solvents can stabilize various conformations of the molecule, resulting in the observation of isomers having different energy levels.[8] The isomer with the higher dipole moment becomes more favored due to the stability as the dielectric constant of the solvent increases.[8b] It is rare to find compounds having such an unstable equilibrium, which gives rise to different conformation isomers in different solvents.

**Application of anthracene-isothiouronium salts for anion sensing.** Although consisting of two isomers, isothiouronium salt **6a** was utilized to investigate the anion sensing ability by fluorescent spectrometry. Table 3 shows the change in the fluorescence intensity of the host **6a** upon adding 9 equivalents of fluoride in various solvents. Among the common solvents, acetonitrile was the best one for the host **6a**-guest binding in fluorescent spectrometry. A mixture of 5% water in acetonitrile also resulted in a good change in the fluorescence intensity. Obviously, isothiouronium receptors bind to the anion through hydrogen bonding and electrostatic interactions. Therefore, these receptors can overcome the competition from protic solvents for the binding sites due to the positive charge of the isothiouronium moiety. This finding is useful for the synthesis of water-soluble artificial anion receptors and important in analytical chemistry.

The binding affinities of the host **6a** for various anions, viz. F⁻, Cl⁻, Br⁻, I⁻, H₂PO₄⁻, OAc⁻, and HSO₄⁻, were examined in a mixture of acetonitrile and water (95:5 v/v) (Figure 2). Similar to the receptors based on anthracene-thiourea,[2a] the fluorescence intensity of **6a** increased significantly upon the addition of F⁻ and OAc⁻ and changed slightly upon the addition of H₂PO₄⁻ and the other anions. The fluorescent titration of the host **6a** and anion fluoride was also examined. Figure 3 shows that the change in the fluorescence intensity of the host **6a** was linearly proportional to the fluoride concentration when the concentration ratio of fluoride to **6a** was lower than one. However, due to the existence of two isomers in the host **6a**, the determination of the binding constant by the fluorescence spectrometry method was quite complicated.[9]

To understand inside about the association between the host **6a** and fluoride, the NMR titration method was employed in DMSO-$d_6$ (Figure 4). The $^1$H NMR spectrum of **6a** showed large downfield shifts of the NH protons of the thiouronium moiety from 9.4 and 9.6 ppm to 9.9 and 11.26 ppm upon adding fluoride, indicating the formation of hydrogen bonding, while the other protons tended to shift slightly toward the upfield region. Upon adding over one equivalent of fluoride to the
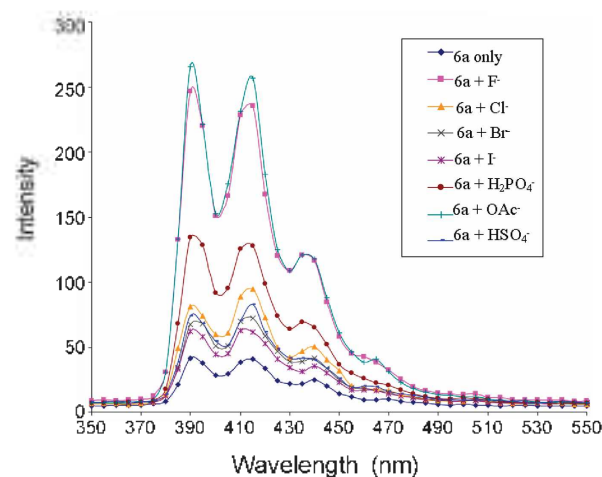


**Figure 2.** Fluorescent emission changes of **6a** ($10^{-5}$ M) upon the addition of tetrabutylammonium salts of F⁻, Cl⁻, Br⁻, I⁻, H₂PO₄⁻, OAc⁻, and HSO₄⁻ (9 equiv) in acetonitrile: water (95:5 v/v) at excitation wavelength of 255 nm.

**Table 2.** Effect of solvent on the ratio of the two isomers of **5a**

| Solvent | Ratio of two isomers |
|---------|---------------------|
| CD₃Cl | 3 : 1 |
| CD₃CN | 1 : 1 |
| DMSO-$d_6$ | 1 : 1 |
| MeOD | 1 : 1 |
| CD₃Cl + MeOD | 2 : 1 |
| CD₃Cl + D₂O | 1 : 0 |
| MeOD + D₂O | 1 : 0 |

**Table 3.** Effect of solvent on the binding of host **6a**-fluoride

| Solvent | CHCl₃ | MeOH | DMSO | CH₃CN | CH₃CN: H₂O (95:5 v/v) |
|---------|-------|------|------|-------|----------------------|
| I/I₀[a] | 3.31 | 1.19 | 1.15 | 6.35 | 5.78 |

[a] I: fluorescence intensity of only host **6a** at $10^{-5}$ M. I₀: fluorescence intensity after adding 9 equivalents of fluoride to **6a**.
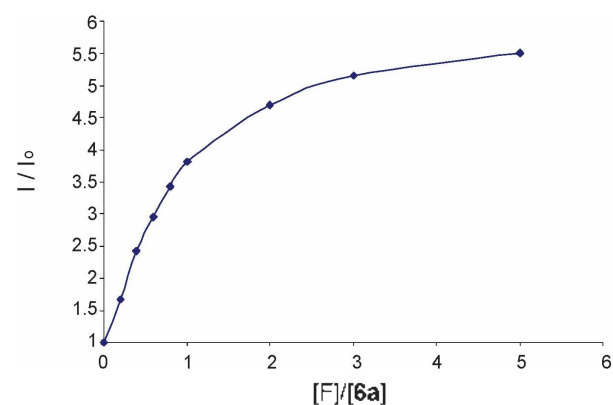


**Figure 3.** Fluorescence intensity at 415 nm of **6a** ($10^{-5}$ M) in acetonitrile: water (95:5 v/v) exited at 255 nm as a function of anion fluoride concentration.
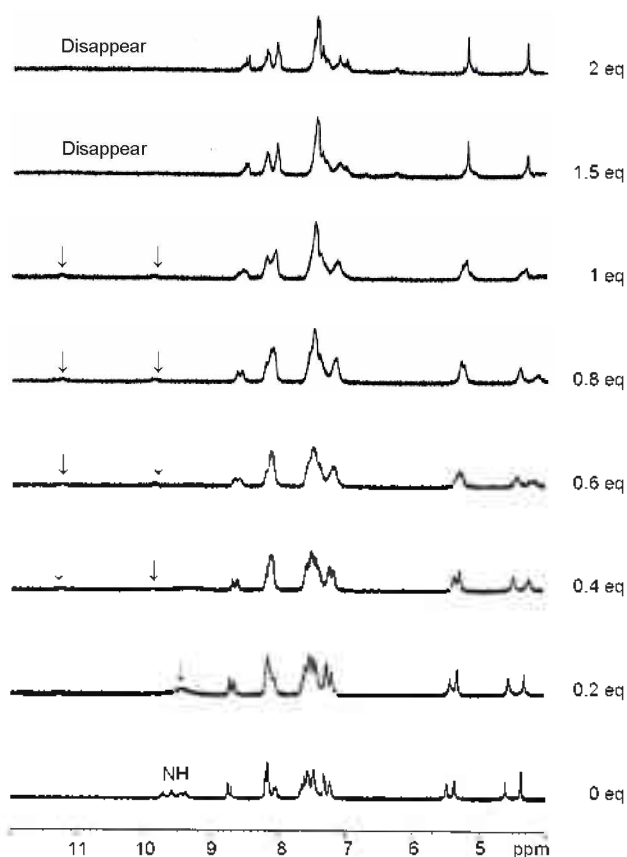
**Figure 4.** $^1$H NMR titration of **6a** ($5 \times 10^{-3}$ M) with fluoride in DMSO-$d_6$.

host, the peaks of the two conformers tended to merge into one another. This means that some degree of conversion took place between the two isomers during the binding. Judging from the titration results, we can conclude that the two isomers of the host **6a** bound the fluoride anion in equilibrium.

To solve the problem of isomerism, the structure of the host **10**, which has only one set of peaks in $^1$H NMR, was introduced with the hope that it would give some interesting results, such as improving the selectivity of the anion due to the steric hindrance, as well as the sensitivity due to the presence of two anthracene groups which should facilitate the detection of the fluorescent signal. Contrary to our expectations, the fluorescence intensity of **10** showed no significant change upon the addition of F$^-$, Cl$^-$, Br$^-$, I$^-$, H$_2$PO$_4^-$, OAc$^-$, and HSO$_4^-$. This means that the two fluorophores gave rise to significant steric strain, which resulted in a decrease in the sensitivity for the recognition of the anion.[10]

## Conclusions

In summary, we prepared isothiouronium salts based on anthracene for anion sensing. These isothiouroniums contain two isomers in equilibrium, which were affected by the substituent, temperature and solvent. The isomerism is may be due to the restricted rotation at the C=S bond of the isothiouronium salts. In addition, the anthracene-isothiouronium sensor showed significant fluorescence enhancement upon adding fluoride.

acetate and dihydrogen phosphate, even in the presence of water. This finding is useful for the synthesis of water-soluble artificial anion receptors and important in analytical chemistry.

## Experimental Section

**Typical procedure for the synthesis of isothiouronium salts.** Thiourea compounds **4a-c** were dissolved in absolute ethanol and heated to reflux under an inert atmosphere of argon. Then, benzyl bromide (1.1 eq.) was added dropwise. The reaction mixture was stirred overnight. The solvent was removed by the evaporation and the organic products were purified by the precipitation in methanol and diethyl ether to yield the pure powder compounds **5a-c**.

**9-[(S-Benzyl-N'-methyl-N-isothiouronio)methyl]anthracene bromide (5a).** The $^1$H NMR spectrum of compound **5a** (62%) contains two sets of peaks for the two isomers, a and b, in CDCl$_3$ at a ratio of 3:1. For isomer a. $^1$H NMR (300 MHz, CDCl$_3$) δ 10.986 (1H, s), 6.726-8.602 (14H, m), 5.792 (2H, s), 4.015 (2H, s), 3.257 (3H, s). For isomer b. $^1$H NMR (300 MHz, CDCl$_3$) δ 10.425 (1H, s), 6.726-8.602 (14H, m), 5.493 (2H, s), 4.928 (2H, s), 3.004 (3H, s). ESI-Mass (positive mode) [M$^+$] 371, [2M$^+$-Br$^-$] 822.9. ESI-Mass (negative mode) [M$^-$-2Br$^-$] 530.8.

**9-[(S-Benzyl-N'-phenyl-N-isothiouronio)methyl]anthracene bromide (5b).** The $^1$H NMR spectrum of compound **5b** (76%) contains two sets of peaks for the two isomers, a and b, in CDCl$_3$ at a ratio of 3:2. For isomer a. $^1$H NMR (300 MHz, CDCl$_3$) δ 6.753-8.62 (19H, m), 5.569 (2H, s), 4.051 (2H, s). For isomer b. $^1$H NMR (300 MHz, CDCl$_3$) δ 6.726-8.602 (19H, m), 6.089 (2H, s), 4.705 (2H, s). ESI-Mass (positive mode) [M$^+$] 433.1, [2M$^+$-Br$^-$] 946.8.

**9-[(S-Methyl-N'-methyl-N-isothiouronio)methyl]anthracene iodide (5c).** The $^1$H NMR spectrum of compound **5c** (53%) contains two sets of peaks for the two isomers in CDCl$_3$ at a ratio of 1:1. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.258-8.602 (18H, m), 5.842 (2H, s), 5.46 (2H, s), 3.12 (3H, s), 2.96 (6H, s), 2.338 (3H, s).

**9-[(S-Benzyl-N'-(9-methyl-anthracene)-N-isothiouronio) methyl]anthracene bromide (9).** For the synthesis of compound **9**, the above procedure was modified, using acetone nitrile as solvent instead of ethanol and 5 eq. of benzyl bromide. The $^1$H NMR spectrum of compound **9** (73%) contains one sets of peaks. $^1$H NMR (300 MHz, CD$_3$CN) δ 7.203-8.657 (23H, m), 5.584 (2H, s), 5.282 (2H, s), 4.43 (2H, s).

**Typical procedure for the synthesis of hexafluorophosphate salts.** The bromide or iodide salts **5a-c** and **9** were dissolved in MeOH. During the dropwise addition of aqueous NH$_4$PF$_6$ solution (50 eq.), the precipitates were formed. After washing the precipitates several times with water, the desire products **6a-6c** and **10** were obtained as pure compounds.

**9-[(S-Benzyl-N'-methyl-N-isothiouronio)methyl]anthracene hexafluorophosphate (6a).** The $^1$H NMR spectrum of compound **6a** (70%) contains two sets of peaks for the two isomers, a and b, in CDCl$_3$ at a ratio of 3:1. For isomer a. $^1$H NMR (300 MHz, CDCl$_3$) δ 6.746-8.602 (14H, m), 5.350 (2H, s), 3.992 (2H, s), 3.317 (3H, s). For isomer b. $^1$H NMR (300 MHz, CDCl$_3$) δ 6.746-8.602 (14H, m), 5.462 (2H, s), 4.549 (2H, s), 2.951 (3H, s). ESI-Mass (positive mode) [M$^+$] 371, [2M$^+$-PF$_6^-$] 886.9. ESI-Mass (negative mode) [M$^+$-2Br$^-$] 660.8.

**9-[(*S*-Benzyl-*N*''-phenyl-*N*-isothiouronio)methyl]anthracene hexafluorophosphate (6b).** The $^1$H NMR spectrum of compound **6b** (65%) contains two sets of peaks for the two isomers, a and b, in CDCl$_3$ at a ratio of 3:2. For isomer a, $^1$H NMR (300 MHz, CDCl$_3$) δ 6.60-8.517 (19H, m), 5.710 (2H, s), 3.980 (2H, s). For isomer b, $^1$H NMR (300 MHz, CDCl$_3$) δ 6.60-8.517 (19H, m), 5.551 (2H, s), 4.630 (2H, s).

**9-[(*S*-Methyl-*N*''-methyl-*N*-isothiouronio)methyl]anthracene hexafluorophosphate (6c).** The $^1$H NMR spectrum of compound **6c** (72%) contains two sets of peaks for the two isomers in CDCl$_3$ at a ratio of 1:1. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.258-8.602 (18H, m), 5.842 (2H, s), 5.46 (2H, s), 3.12 (3H, s), 2.96 (6H, s), 2.338 (3H, s).

**9-[(*S*-Benzyl-*N*''-(9-methyl-anthracene)-*N*-isothiouronio) methyl]anthracene hexafluorophosphate (10).** The $^1$H NMR spectrum of compound **10** (65%) contains one sets of peaks. $^1$H NMR (300 MHz, CD$_3$CN) δ 7.150-8.689 (23H, m), 5.649 (2H, s), 5.179 (2H, s), 4.343 (2H, s).

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