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Promoting effects of the hydroxymethyl group on the fluorescent signaling recognition of anions by thioureas

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Abstract—A series of novel fluorescent naphthylthioureas **1**–**4** with hydroxymethyl groups was designed and synthesized. Upon complexation with anions, **1**–**4** showed strong fluorescence enhancements in the order: **1**>**2**>**3**≈**4**, which is consistent with the number of hydroxymethyl groups contained in their structures. Hydroxymethyl groups have an important influence on the compounds' *trans–trans* or *trans–cis* conformations, and their action to promote the fluorescence signaling recognition of the thioureas for anions might be caused by their preorganizing the intramolecular protons of the receptor in favor of sites of the *trans–trans* conformation ready for hydrogen bond formation with the anions. Thioureas **1** to **4** had favorable selectivities for certain anions, which relied on the net charge and Brϕnsted basicity of the anions.

Studies on 'host' molecules for recognition of 'guest' anions are of considerable importance in the field of supramolecular chemistry. Anions are ubiquitous throughout biological systems, e.g. DNA and the majority of enzyme substrates.[1] The complexation of a host with an anion can be measured by several methods.[2] Since any change in fluorescence is highly sensitive and easily detectable, the design of fluorescent host molecules for investigating recognition processes has attracted wide interest.

Most host molecules for fluorescent recognition are usually in the 'fluorophore-receptor' format. There are many reports about the utilization of various fluorophores.[3] Many different types of noncovalent interactions are applied to the design of selective anion receptors, and receptors with hydrogen bonding donor groups are widely used, e.g. sulfamide and (thio)urea moieties.[4] Hennrich and co-workers designed iminoylthioureas with naphthyl substituents as fluorescence reporter groups which showed strong selective fluorescence enhancement upon complexation of anions in a 1000-fold excess in methanol.[5] The number of hydrogen bonding donor groups in the receptors are often increased to improve the recognition between host and anion, e.g. by using poly-thiourea or poly-thiouronium receptors.[6] However, reports on anion recognition by receptors with the aid of an auxiliary group are few.

Here, we report the selective fluorescence enhancement of novel naphthylthioureas by anions, and the use of the hydroxymethyl group to promote the recognition ability of the thiourea receptors.

Naphthylthioureas **1**–**4** containing hydroxymethyl groups were designed with the thiourea moiety as the receptor for anions and the naphthyl moiety as the fluorescence reporter. The syntheses of **1**–**4** and their derivatives **5**–**8** are shown in Scheme 1. The condensation in ethyl acetate of 1-naphthylisothiocyanate with 1.1 equiv. of tris(hydroxymethyl)aminomethane, 2-amino-2-ethyl-1,3-propanediol, 2-amino-2-methyl-1-propanol, and 2-hydroxyethylamine gave **1**, **2**, **3** and **4**, respectively. Cyclization in hydrochloric acid of the naphthylthioureas **1**–**4** gave naphthyliminothiazolines **5**–**8**,[7a] which were characterized by ^{1}H NMR, IR, and HRMS.[7b]

The fluorescent signaling recognition ability for anions of **1**–**4** (at 20 μM) was tested in methanol–water (v:v = 4:1) as a polar, protic solution, with the anions added as their sodium salts. As follows from known results,[5] the influence of Na^+ on the spectroscopic behavior of **1**–**4** can be disregarded.[5,8] When free **1**–**4** were excited

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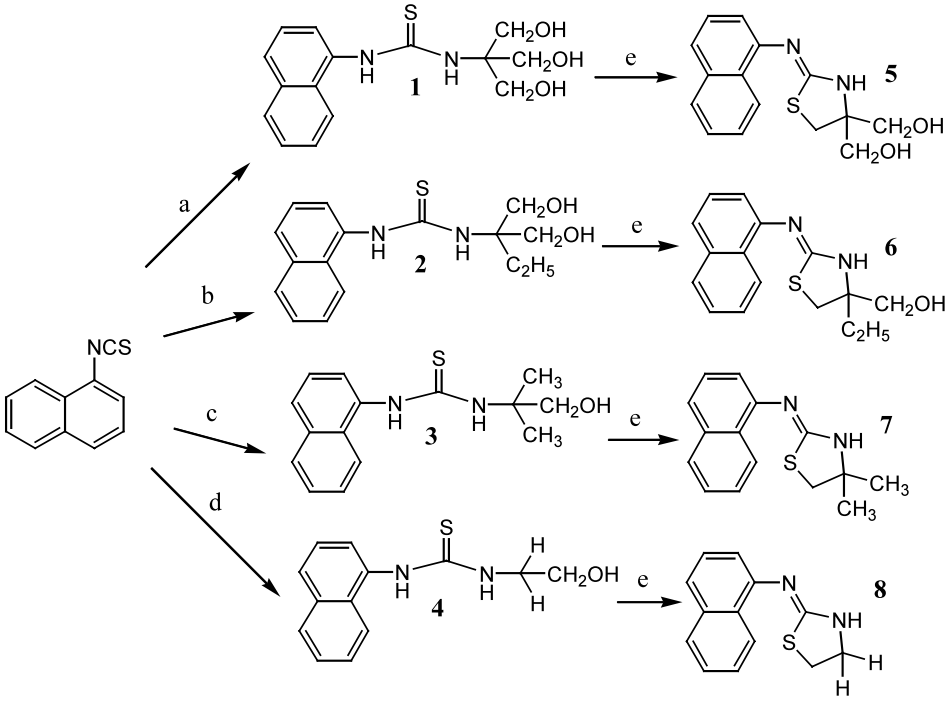

Scheme 1. *Reagents and conditions*: (a) tris(hydroxymethyl)aminomethane, reflux, 62%; (b) 2-amino-2-ethyl-1,3-propanediol, rt, 55%; (c) 2-amino-2-methyl-1-propanol, rt, 52%; (d) 2-hydroxylethylamine, rt, 79%; (e) conc. HCl, 95°C, 4 h; **5**, 63% **6**, 39% **7**, 23%, **8**, 61%.

at about 284 nm of their maximal absorptions, **1** and **2** showed broad structureless emission bands with a maximum at 372 nm, **3** at 425 nm with a shoulder at 372 nm, and **4** at 372 nm with a shoulder at 434 nm (Fig. 1).

All free naphthylthioureas **1**–**4** showed very weak fluorescence, however, after the addition of various anions their fluorescence intensities were selectively enhanced. In particular, upon addition of CO_3^{2-} to the solution of **1** in a 500-fold and 100-fold excess, remarkable fluorescence enhancement was achieved (30.6-fold and 14.7-fold, see Fig. 1), which is comparable to 53-fold for CO_3^{2-} in 1000-fold excess in methanol.[5] This fluorescence enhancement can be attributed to the incremental rigidity of the naphthylthioureas brought about by hydrogen bonding between the N–H of the thiourea and the anions.[5] A minor fluorescence enhancement was obtained for complexation of **1** with HPO_4^{2-} (6.5-fold). In the presence of the same anions the fluorescence enhancement of **2** was weaker than that of **1**. The weakest fluorescence enhancements were observed for **3** and **4** (see Table 1). Upon complexation, no remarkable changes in the absorption spectra were observed for **1**–**4** and no wavelength-shift in the emission for **1** and **2** was evident. However, upon complexation, the emission of **3** at 425 nm disappeared and the shoulder at 372 nm remained and became the maximum, while that of **4** at 372 nm remained as the maximum with the disappearance of the shoulder at 434 nm. The common emission at 372 nm means that, in the structure of the fluorophore's **1**–**4** complex, the binding with the anions was the same, and is very similar to that of free **1** and **2**. In addition, the above changes in fluorescence are strongly time dependent, reaching a constant after approximately 72 h,[5] which implied the complexation of the thiourea moiety with the anions through a two intermolecular hydrogen-bonding mode.[5]

Obviously, the signaling recognition ability of the naphthylthioureas for anions is in the order: **1**>**2**>**3**≈**4**. Especially, binding abilities of **1** and **2** are prominently superior to those of **3** and **4**. The major difference in the structures of **1** to **4**, is the number of hydroxymethyl groups contained in the host molecules, which is consistent with the recognition ability of these host molecules (**1**–**4** possessing three, two, one and one $-CH_2OH$ groups, respectively).

The number of $-CH_2OH$ groups would appear to be very important for the recognition. We do not speculate that the fluorescence enhancement might be mainly ascribed to some action between the hydroxymethyl group and the anion, instead of the interaction between the N–H of the thiourea and the anion. Due to the distance between the hydroxymethyl group and the naphthalene ring and as the hydroxymethyl group is not directly connected with the fluorophore through a conjugated chain, it is impossible that the interaction between the hydroxymethyl group and the anions influences the fluorescence.

The anion complexation of the non-thioureas **5**–**8** with hydroxymethyl groups, which were derived from **1**–**4**, did not show any obvious fluorescence change. This

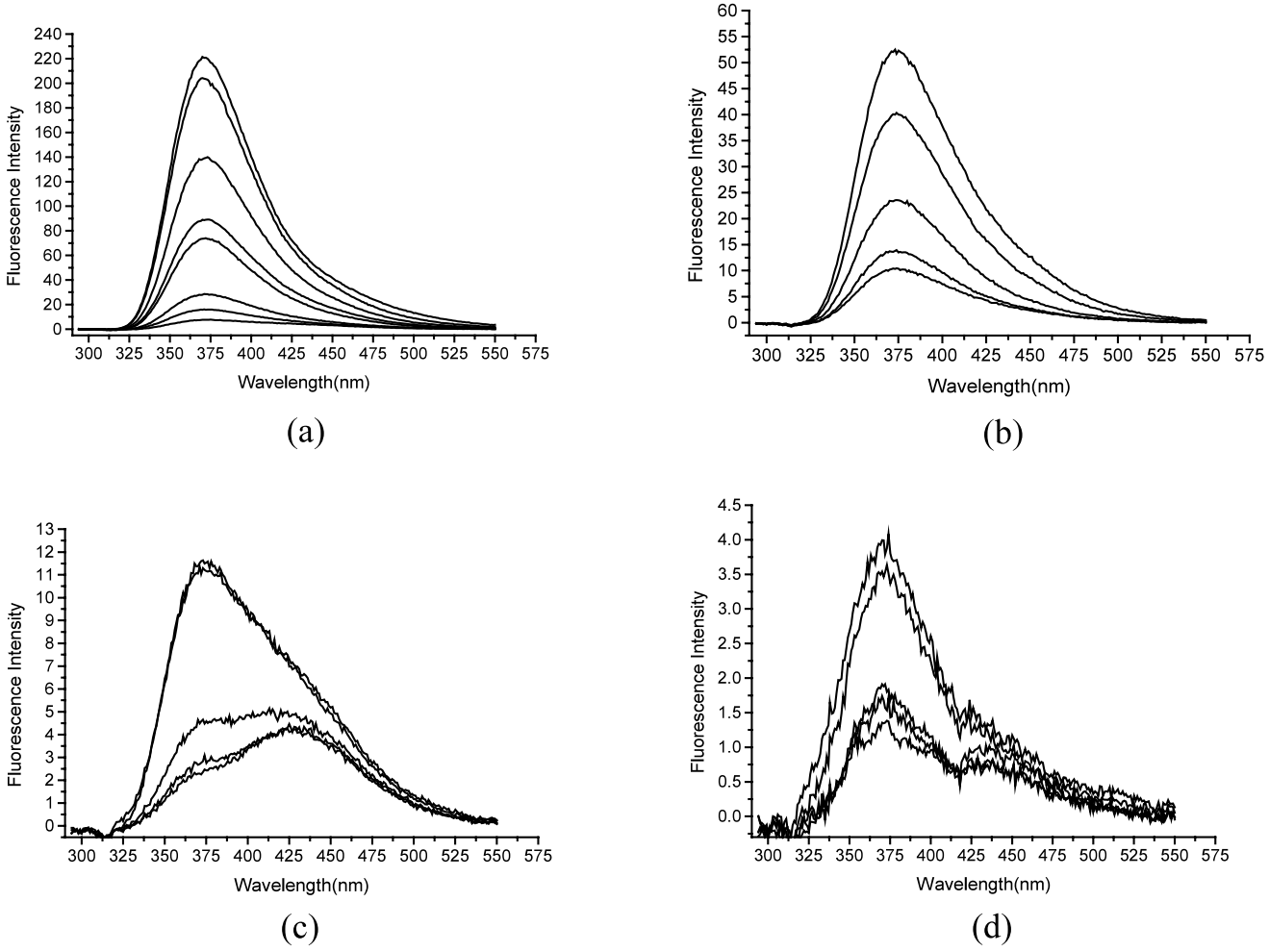

Figure 1. (a) Emission of **1** (20 μM) upon addition of CO_3^{2-} (excited at 284 nm): The concentrations of CO_3^{2-} are (from bottom to top): 0, 20, 200, 500, 1000, 2000, 4000, 10000 μM. (b–d) Emission of **2**, **3** and **4** (20 μM) upon addition of CO_3^{2-} (excited at 284 nm): the concentrations of CO_3^{2-} are (from bottom to top): 0, 20, 200, 500, 1000, 2000 μM.

means that the naphthyl fluorophore or hydroxymethyl group did not result in any direct fluorescent response to the anions, apparently, for **1**–**4** the thiourea still is the real receptor for anions.

It is known that *N*,*N*′-disubstituted thioureas can adopt the *trans–cis*, *trans–trans*, and *cis–cis* conformations.[10] Molecular mechanics calculations (PCMODEL 6.0) gave the preferential conformations of free **1**–**4**. Compounds **1** and **2** showed a *trans–trans* conformation that is 5.1, 3.8 kJ/mol lower in energy than the *trans–cis* conformation, respectively, whereas **3**, **4** showed a *trans–cis* conformation that is 10.1, 11.9 kJ/mol lower than the *trans–trans* conformation (see Fig. 2), respectively. According to the two intermolecular hydrogen-bonding modes,[5] the *trans–trans* conformation of the receptor should form hydrogen bonding with anions owing to the appropriate site of the H–N- and fitting distance **r** between the two protons (**1**: 2.195 Å; **2**: 2.173 Å), which closely match the distance of about 2.1–2.2 Å (calculated) between the two oxygens of anions (e.g. $^-$O–CO–O$^-$). In contrast, the *trans–cis* conformation does not possess a proper site and the distance **r** (**3**: 2.7445 Å; **4**: 2.6781 Å) between the two protons, which does not favor the formation of hydrogen bonding between the receptor and the anion. Therefore, we believe that the hydroxymethyl group might play a role of pre-organizing the protons to facilitate recognition of the receptor for the anions. The above description provides an explanation for the binding ability of **1** and

Table 1. Fluorescence enhancement of **1**–**4** upon the addition of anions in 100 times excess

Anions	pK_a of anion[9]	I/I_0[a]			
		1	**2**	**3**	**4**
CO_3^{2-}	10.33	14.7	5.2	2.5	2.6
HPO_4^{2-}	7.21	6.5	3.0	2.5	1.1
HCO_3^-	6.73	2.2	2.3	1.4	1.0
CH_3COO^-	4.76	3.8	1.3	1.0	1.0
$H_2PO_4^{2-}$	2.16	3.1	1.2	1.0	–
NO_3^-	−1.4	1.5	1.2	1.0	–
HSO_4^-	−3.1	1.0	1.1	1.5	–

[a] I_0: fluorescence intensity of free compounds; I: fluorescence intensity of compounds after the addition of anions.

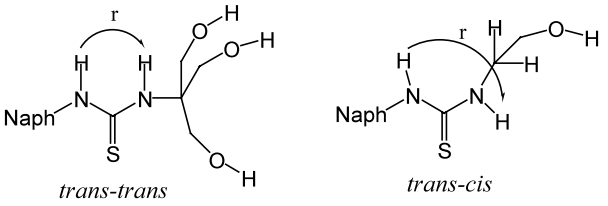

Figure 2. Descriptions for the different conformations of the receptors.

2 being superior to those of **3** and **4**. It is also consistent with changes of the fluorescence spectra for **1**–**4** (Fig. 1a–d), where **1** and **2** mainly in the *trans–trans* conformation, were easily bound with anions without changes of shape, with the increase of the concentration of the anions, **3** and **4** have to change their *trans–cis* conformations to *trans–trans* for complexation with an obvious change of fluorescence shape (for free **4** the fluorescence intensity at 434 nm was weaker than that at 372 nm, which might be caused by the relative lower ability of fluorescence emission for its *trans–trans* conformation). In fact, the SCF-MO-CI calculation at the ZINDO/s level (Hyperchem 5.5) did show that the fluorescence maximum of **3** and **4** in the *trans–cis* conformations were longer than those in the *trans–trans* conformation.

Similarly, the calculations showed that the difference in energy between the *trans–trans* and *trans–cis* conformations of **1** was larger than that of **2**, that is, the amount of **1** in the *trans–trans* conformation was also more than that of **2**. Therefore, it resulted in that **1** displayed the stronger fluorescence enhancement and the obvious difference in the recognition ability in the order: **1**>**2**> **3**≈**4**.

Compounds **1**–**4** had favorable selectivity for various anions in the order: CO_3^{2-}>HPO_4^{2-}>HCO_3^-> CH_3COO^->$H_2PO_4^{2-}$>NO_3^->HSO_4^-. The selectivity relied on net charge and Brϕnsted basicity of the anions, as shown in Table 1. The recognition of CO_3^{2-} with the strongest basicity by receptors is the best. But an exception is the interaction of HCO_3^- with **1**.

We can conclude that the hydroxylmethyl moiety as an auxiliary group has the ability to promote the recognition of the thioureas for the anions, which may give a new alternative for the rational design of anion fluoroionophores.

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7. (a) Jackman, L. M.; Jen, T. *J. Am. Chem. Soc.* **1975**, *97*, 2811; (b) **1**: mp 159–160°C; ^{1}H NMR (500 MHz, CD_3COCD_3): δ=7.83–8.10 (m, 3H, naph), 7.49–7.63 (m, 4H, naph), 3.88 (s, 6H); HR-MS (EI) found: 306.1025; calcd for $[C_{15}H_{18}N_2O_3S]^+$: 306.1038. **2**: mp 121–122°C; ^{1}H NMR (500 MHz, CD_3COCD_3): δ=7.80–8.12 (m, 3H, naph), 7.45–7.65 (m, 4H, naph), 3.70 and 3.83 (Abq, J=10.7 Hz, 4H), 2.00 (m, 2H), 0.90 (brs, 3H); HR-MS (EI) found: 304.1280; calcd for $[C_{16}H_{20}N_2O_2S]^+$: 304.1245. **3**: mp 144–145°C; ^{1}H NMR (500 MHz, CD_3COCD_3): δ=7.80–8.08 (m, 3H), 7.47–7.63 (m, 4H), 3.60 (s, 2H), 1.50 (s, 6H); HR-MS (EI) found: 274.1158; calcd for $[C_{15}H_{18}N_2OS]^+$: 274.1140. **4**: mp 169–171°C; ^{1}H NMR (500 MHz, CD_3COCD_3): δ=7.85–8.03 (m, 3H, naph), 7.49–7.63 (m, 4H, naph), 3.71 (t, 2H), 3.64 (s, 2H); HR-MS (EI) found: 246.0824; calcd for $[C_{13}H_{14}N_2OS]^+$: 246.0827. **5**: mp 199–200°C; ^{1}H NMR (500 MHz, CD_3COCD_3): δ=8.2 (d, J=8.3 Hz, 1H), 7.83(d, J=7.7 Hz, 1H), 7.55(d, J=8.1 Hz, 1H), 7.37–7.49 (m, 4H), 3.78 and 3.70 (ABq, J=10.7 Hz, 4H), 3.25 (s, 2H); MS(EI): m/z (%), 288 (M^+, 39.58), 257 (100), 227 (35.27). **6**: mp 143–144°C; ^{1}H NMR (500 MHz, CD_3COCD_3): δ=8.1 (d, J=8.2 Hz, 1H), 7.83 (d, J=7.7 Hz, 1H), 7.55 (d, J=8.1 Hz, 1H), 7.37–7.49 (m, 4H), 3.70 and 3.62 (ABq, J=11 Hz, 2H), 1.82 (q, J=7.2 Hz, 2H), 1.05 (t, J=7.2 Hz, 3H); MS(EI): m/z (%), 286 (M^+, 39.58), 256 (100), 255 (35.27). **7**: mp 162–164°C; ^{1}H NMR (500 MHz,

CD_3COCD_3): $\delta = 8.1$ (d, $J = 8.2$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.60 (d, $J = 8.1$ Hz, 1H), 7.38–7.45 (m, 4H), 3.15 (s, 2H); 1.48 (s, 6H); MS(EI): m/z (%), 256 (M^+, 94.68), 257 (14.80), 241 (100). **8**: mp 153–154°C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.1$ (m, 1H), 7.85 (m, 1H), 7.7 (d, $J = 8.0$ Hz, 1H), 7.25–7.54 (m, 4H), 3.85 (t, 2H); 3.35 (t, 2H); MS(EI): m/z (%), 228 (M^+, 100), 257 (95.44), 229 (16.79).

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