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Thiazole-based chemosensor III: synthesis and fluorescence sensing of $CH_3CO_2^-$ based on inhibition of ESIPT

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ABSTRACT

Novel fluorogenic sensors based on urea derivative of 2-(2′-aminophenyl)-4-phenylthiazole (**4** and **5**) were prepared and used for recognition of anions with similar basicity and surface charge density. Chemosensor **4** was found to be highly selective to acetate ion over other anions. The selectivity was related to the structure matching between the host and the guest. The evaluation of the chemosensors' interaction with anions was performed by UV–vis and fluorescence titration. This acetate binding affinity was further tuned by varying the acidity of the N–H proton of the urea moiety in chemosensor **5**.

1. Introduction

There exists a large interest in the development of artificial neutral receptors for anions due to their medicinal and environmental potential applications.[1] Such molecules should be able to behave as hydrogen-bond donors toward the envisaged anion, giving rise to a complex that is stable in solution. Beside mere electrostatic interactions, hydrogen-bonds are directional, a feature, which allows the design of receptors capable of differentiating between anions with different geometries and hydrogen-bonding requirements. Neutral receptors that contain N–H fragments can act as hydrogen-bond donors for the anion. One of the most frequently employed neutral receptor containing the N–H fragment is urea. In fact, urea can donate two hydrogen bonds in a parallel fashion, and so it is complementary to Y-shaped oxoanions, such as carboxylates. One of the first examples of anion complexation by urea-based receptors was reported by Wilcox and Hamilton who characterized the receptor–analyte interaction through ^{1}H NMR experiments.[2] In particular, the carboxylate anions exhibit specific biochemical behaviors in the enzymes and antibodies[3] and are also critical components of numerous metabolic processes.[4] So the recognition and sensing of acetate ion is considered to be more important than the other biologically functional anions. Acetate production and oxidation rate has been frequently used as an indicator of organic decomposition in marine sediments.[5] Several anion sensors having strong affinity and selectivity for acetate anions are reported based on phenylhydrazone and benzimidazole moiety.[6]

During the last few years, much attention has been focused on the fluorescent sensing because of the high sensitivity and selectivity of this method.[7] In cell and tissues, fluorescent probes are generally distributed inhomogeneously. As a consequence their fluorescence intensity is dependent on the local concentration of the sensors as well as on other factors, such as illumination intensity, optical path length, and bleaching. In order to eliminate the effects of these factors a ratiometric sensor that exhibits a spectral shift upon reaction or binding to the analyte of interest is generally used. In the case of ratiometric sensors the ratio between the two emission intensities can be used to evaluate the analyte concentration. In this respect, dual fluorescence probes exhibiting two well separated emission bands in organic solvents are of particular interest, since they provide a reliable ratiometric signal independent of the probe concentration.[8] Excited-state intramolecular proton transfer (ESIPT) is very effective for the design of probes with dual fluorescence. ESIPT results in the formation of two tautomeric forms in the excited state of the probe: N*- enol and T*- keto forms.[9] ESIPT is one of the most well known photophysical process occurring in *o*-hydroxy-benzoxazole, benzimidazole, and benzothiazole.[10] It is expected that replacement of the oxygen atom in the oxazole ring with a sulfur atom to form a thiazole ring increases the polarizabilities of the molecule and introduces interesting novel spectral-luminescent properties that

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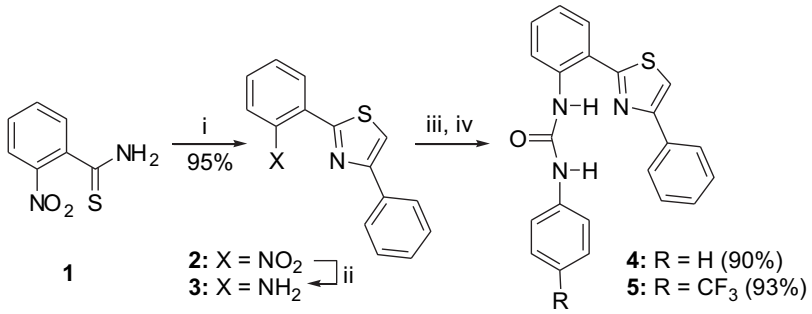


Scheme 1. Synthesis of chemosensors **4** and **5**. Reagents and conditions: (i) 2-bromoacetophenone, EtOH, reflux, 2 h; (ii) 10% Pd/C, H_2, MeOH, 6 h; (iii) phenyl isocyanate, dioxane, reflux, 12 h; (iv) 4-trifluoromethylphenyl isocyanate, dioxane, reflux, 2 h.

are essential for practical applications of the luminophores. Formation of an intramolecular hydrogen bond in these compounds promotes luminescence intensity and results in abnormally large Stokes shifts.[11]

Previously we already exploited the inhibition of ESIPT for cation sensing and ratiometric fluoride sensing in 2-hydroxyphenylthiazole.[12] To prepare an ESIPT-based anion chemosensor, the sensor moiety should form an intramolecular hydrogen bond in the ground state with the adjacent hydrogen-bonding acceptor and the acidity of the receptor should be weak enough to avoid the deprotonation of the sensor upon interaction with the basic anions, such as $CH_3CO_2^-$ or F^-, yet it should be strong enough to induce a fast rate of ESIPT. Therefore we introduced a urea group, which is a good hydrogen-bonding donor and can bind efficiently with the Y-shaped anion, such as acetate. Moreover we have appended an electron-withdrawing substituent ($-CF_3$) to the urea framework in order to polarize the N–H bonds and to increase their hydrogen-bond donor tendencies. Therefore, the strongest interactions are expected to occur between highly basic anions and highly acidic urea fragments.

2. Results and discussion

Chemosensors **4** and **5** were prepared as described in Scheme 1 starting from thionation of 2-nitrobenzamide with Lawesson's reagent. The Hantzsch condensation of 2-nitrobenzthioamide with 2-bromoacetophenone in dry ethanol gave **2** in good yield. Hydrogenation of the latter with 10% Pd/C in methanol afforded 2-(2′-aminophenyl)-4-phenylthiazole **3** that was used for the preparation of **4** and **5** without further purification. The structures of **4** and **5** were confirmed by ^{1}H NMR, ^{13}C NMR, and elemental analysis.

The binding and recognition abilities of **4** and **5** toward various anions in dry CH_3CN were studied by UV–vis and fluorescence spectroscopy. The receptor **4** produces an absorption band at 339 nm, which is attributed to the π–π^* transition favored by the planar orientation enforced by the intramolecular hydrogen bonding (Fig. 1).[12,13] It shows that the F^- and the $CH_3CO_2^-$ (10 equiv) only produce a blue shift with slight decrease in the absorbance spectra at 339 nm. No other anions (Cl^-, Br^-, I^-, ClO_4^-, NO_3^-, $H_2PO_4^-$, HSO_4^-) produce any significant change in absorption.

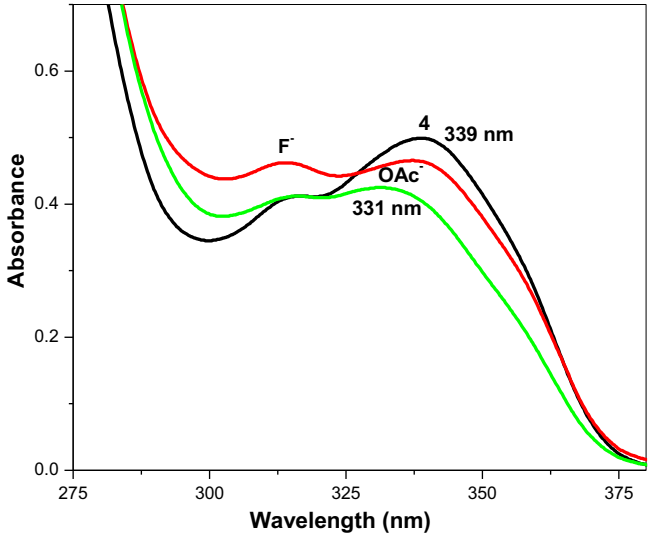


Figure 1. UV–vis spectra of **4** (50 μM) upon addition of 10 equiv of F^- and $CH_3CO_2^-$ anions.

Spectrophotometric titration was carried out by slow addition of the tetrabutylammonium acetate to a dry CH_3CN solution of **4**. The addition of the Y-shaped $CH_3CO_2^-$ produces a slight blue shift from

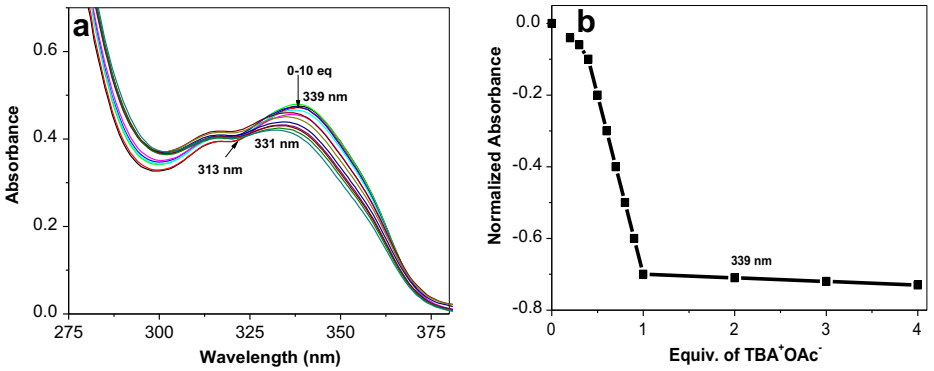


Figure 2. (a) UV–vis spectra of **4** (50 μM) upon successive addition of $CH_3CO_2^-$ (0–10 equiv) in CH_3CN. (b) Normalized absorbance changes at 339 nm versus equiv of TBA^+OAc^- added.

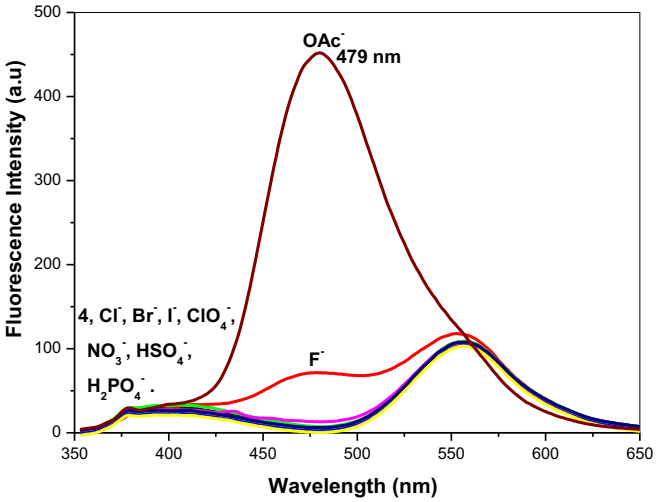
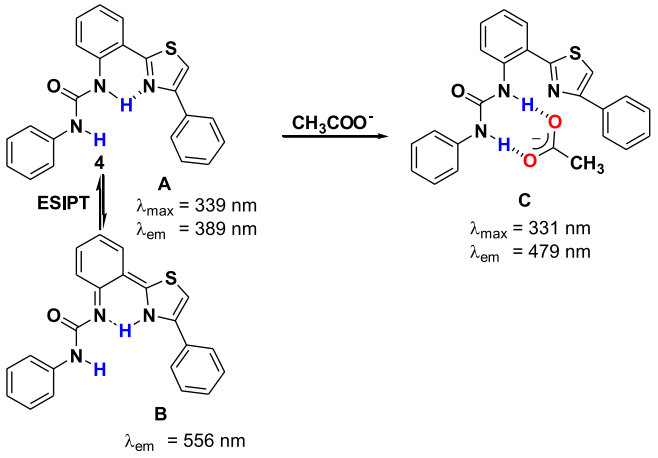


Figure 3. Fluorescence spectra of **4** (50 μM) upon addition of 10 equiv of various anions in CH_3CN (λ_{ex}=339 nm).



Scheme 2. The possible ESIPT in **4** and binding of $CH_3CO_2^-$ in a 1:1 binding stoichiometry.

339 to 331 nm with decrease in absorbance (Fig. 1). The presence of a well defined isosbestic point at 313 nm indicates that only one acetate anion can form hydrogen bonds with the urea subunit of **4** during the entire titration. This intermolecular hydrogen bond formation can disturb the intramolecular hydrogen bonding and destroy the rigidity of the molecule, so the blue shift and decrease in the absorption band at 339 nm is observed.[14a] Moreover the absorption band at 339 nm linearly decreased, up to 1 equiv of $CH_3CO_2^-$ addition (Fig. 2a and b), indicating the formation of a 1:1 complex.

The fluorescence responses of **4** with different anions were recorded in dry acetonitrile with excitation at 339 nm i.e., the absorption band maximum of **4** for the purpose of avoiding specific solvent effects.[14] From Figure 3 it can be seen that only $CH_3CO_2^-$ produces a new enhanced peak at 479 nm on binding with **4**, while complexation with the F^- produces a small change in the emission spectra. None of any other anions produce any noticeable change in the emission spectra.

Spectrofluorimetric titrations were also investigated with an excitation at 339 nm. The sensor **4** undergoes ESIPT and produces a normal emission at 389 nm (Form **A**) and a tautomer emission of 556 nm (Form **B**). On the slow addition of $CH_3CO_2^-$, the peaks at 389 and 556 nm disappears and a new peak is formed at 479 nm (Form **C**) as shown in Scheme 2 and Figure 4.

The ESIPT is inhibited by the hydrogen bonding of the urea N–H with the $CH_3CO_2^-$, which causes fluorescence enhancement that results in the formation of emission peak between the normal and tautomer emissions burying the normal emission and quenching the tautomer emission with an isoemission point at 556 nm (Fig. 4a). The peak at 479 nm showed a linear enhancement with the increase of acetate ion concentration when the ratio of acetate ion and **4** concentrations is below or equal to the ratio of 1:1. When the ratio has reached 1:1, however, higher acetate ion concentration did not lead to any further emission enhancement (Fig. 4b).

This is supported by the Job's plot of **4** with $CH_3CO_2^-$, which also indicates the formation of a ratio of 1:1 complex (Fig. 5). From this titration experiment, the association constant of **4** with $CH_3CO_2^-$ in CH_3CN was calculated to be $1.2\times10^4\ M^{-1}$ (error limit $\leq$10%)[15] (Table 1).

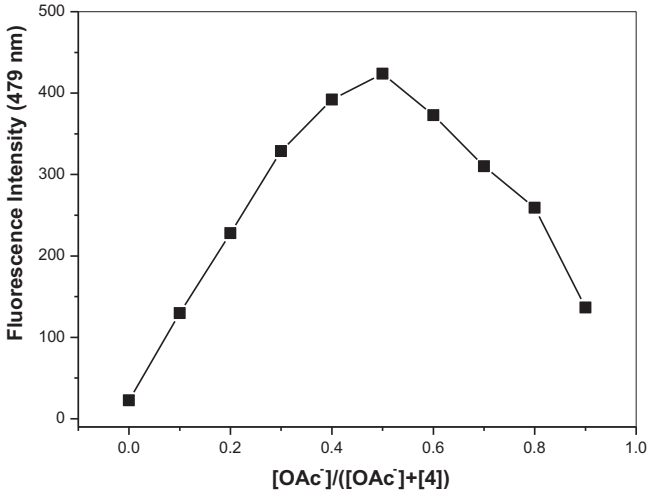


Figure 5. Fluorescence Job's plot of **4** (100 μM) with $CH_3CO_2^-$ (100 μM) in CH_3CN.

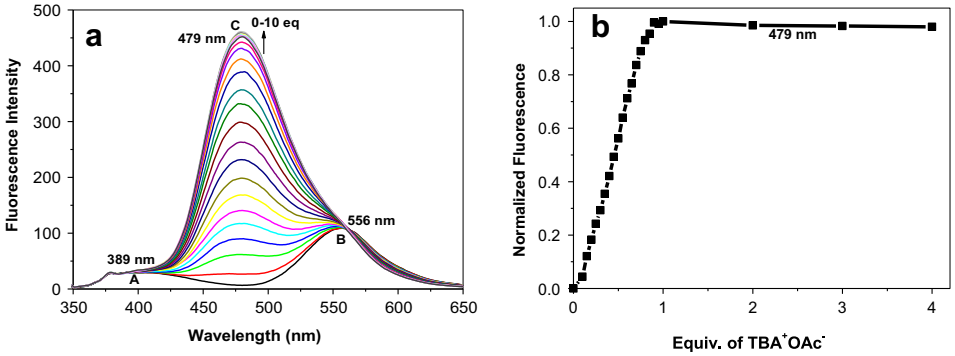


Figure 4. (a) Changes in fluorescence spectra of **4** (50 μM) upon successive addition of $CH_3CO_2^-$ (0–10 equiv) in CH_3CN. (λ_{ex}=339 nm) (b) Normalized fluorescence changes at 479 nm versus equiv of TBA^+OAc^- added.

Table 1
Photophysical properties and association constants of **4** and **5** in CH_3CN

Sensor	UV–vis (nm, log ε)			Fluorescence (nm)			Association constant K_a (M^{-1})[a]	
	Host	OAc^-	F^-	Host	OAc^-	F^-	OAc^-	F^-
4	317 (3.61) 339 (3.70)	317 (3.61) 331 (3.63)	314 (3.67) 339 (3.66)	389 (N*) 556 (T*)	479	389 480 556	1.2×10^4	4.2×10^2
5	317 (3.68) 336 (3.76)	317 (3.66)	388 (3.59)	390 (N*) 553 (T*)	473	Nd[b]	2.5×10^4	Nd[b]

N*=normal emission, T*=tautomer emission.
[a] Calculated from fluorescence titration, error estimated to be ≤10%.
[b] Not determined.

The reason for the high selectivity of $CH_3CO_2^-$ over F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, NO_3^-, ClO_4^-, and HSO_4^- is related to the configuration of the $CH_3CO_2^-$ matching with the chemosensor and the alkalescence of the anion, as well as the acidity of urea N–H protons in chemosensor. Because acetate anion is a Y-shaped oxyanion and planar triangular with the angle of O–C–O is about 120°, the distance of the two oxygen atoms may fit to two hydrogen atoms on recognition sites of the receptor **4** (Scheme 2). This increases its binding affinity than the fluoride ion though the latter has smaller size and higher basicity (Table 1 and Fig. 6). This is also confirmed by the geometry optimized structure according to the density functional theory using B3LYP/6-31G(d), which shows that there exists a strong hydrogen-bond, with bond length of 1.61 and 2.05 Å between the N–H of the urea and the acetate oxygen (Fig. 7). Moreover, the angle of O–P–O in $H_2PO_4^-$ is about 108° (tetrahedral configuration), and the distance of two oxygen atoms of acetate ion is longer than that of the $H_2PO_4^-$, and so two oxygen atoms of $H_2PO_4^-$ could not match well with two hydrogen atoms of **4**.[6a] The alkalescence of acetate anion is also stronger than the other halide anions (Cl^-, Br^-, I^-). Thus appropriate multiple hydrogen bonding interactions and high alkalescence cause high affinity for $CH_3CO_2^-$ over other anions.

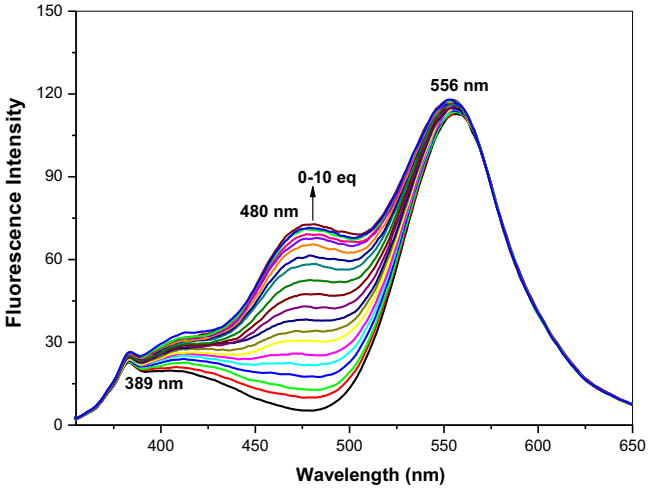


Figure 6. Changes in fluorescence spectra of **4** (50 μM) upon successive addition of F^- (0–10 equiv) in CH_3CN (λ_{ex}=339 nm).

More evidences for the notion that the formation of hydrogen bonds between urea N–H and $CH_3CO_2^-$ came from ^1H NMR titration carried in DMSO-d_6. From Figure 8 we can see that both the N–H signals shift downfield over the course of the titration from δ 9.58 to 10.37 and δ 10.40 to 10.85. However, the N–H signals were observable throughout the titration, and were consistent with a hydrogen-binding process, and not deprotonation, involving the receptor. The downfield shift of the N–H protons take place till

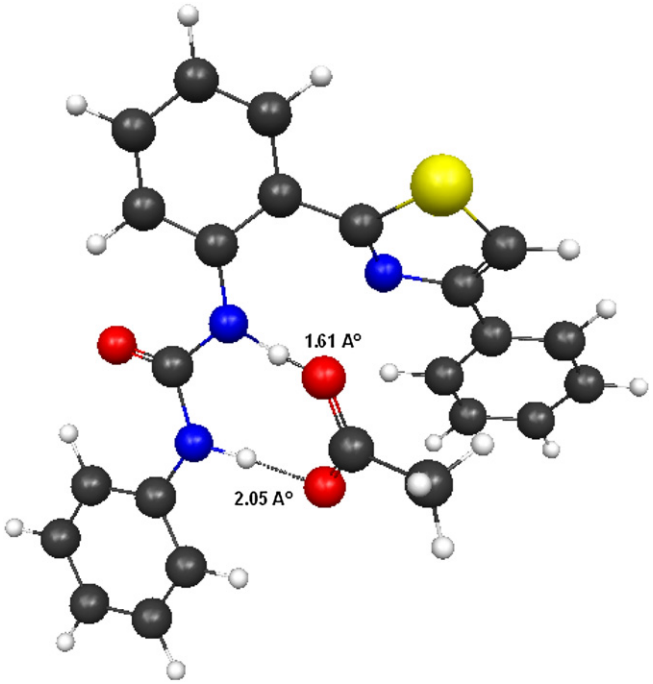


Figure 7. Optimized structure (B3LYP/6-31G) of **4**-$CH_3CO_2^-$.

1 equiv of $CH_3CO_2^-$ is added. Further addition only causes broadening of the peak.

For the ^1H NMR titration spectrum, two effects are responsible for the spectral changes upon N–H···anion hydrogen bond formation: (a) through-bond effects, which increase the electron density of the phenyl ring and promote upfield shifts in the case of H_a ($\Delta\delta$=0.07), H_b ($\Delta\delta$=0.23), and H_c ($\Delta\delta$=0.06), and (b) through-space effects, which polarize the C–H bond in proximity to hydrogen bonds, creating a partial positive charge on the proton, and causing a downfield shifts in the case of H_d ($\Delta\delta$=0.06), H_e ($\Delta\delta$=0.5), and H_f ($\Delta\delta$=0.05).

Deprotonation of the N–H proton of urea shows that the electron density of the phenyl *para* position is enhanced as shown in Scheme 3. This indicates that the acidity of this kind of chemosensors can be tuned by changing the electronic property of the substituent at the *para* position.

Thus by introducing an electron-withdrawing substituent (CF_3) at the *para* position of the phenyl ring, the acidity and thus the hydrogen-bond donor property of the N–H moiety is increased.

Similarly UV–vis titration was carried out by the slow addition of tetrabutylammonium acetate salt to a dry CH_3CN solution of **5**. The addition of the $CH_3CO_2^-$ produces a blue shift from 336 to 317 nm with decrease in absorbance (Fig. 9). The presence of a well defined isosbestic point at 307 nm indicates that during the entire titration only one $CH_3CO_2^-$ can form hydrogen bonds with the urea

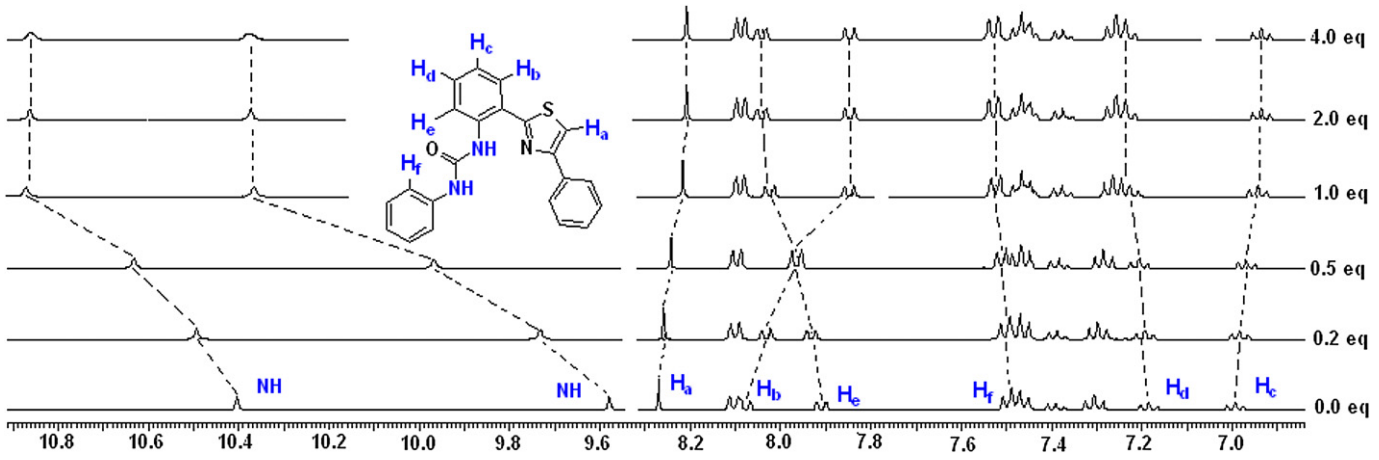
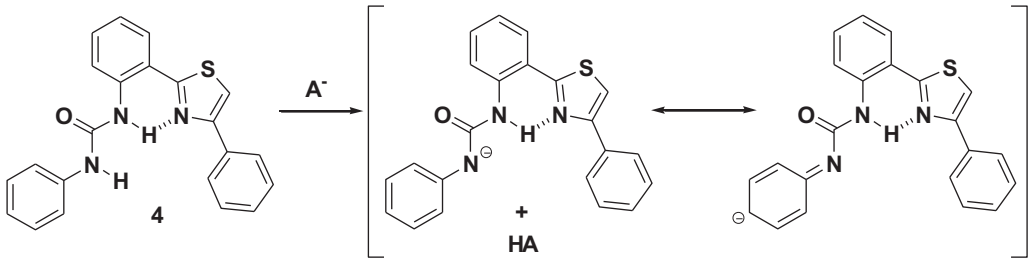


Figure 8. Partial ^{1}H NMR spectra of **4** with $CH_3CO_2^-$ in DMSO-d_6.



Scheme 3. Resonance representation of the deprotonated form of **4**.

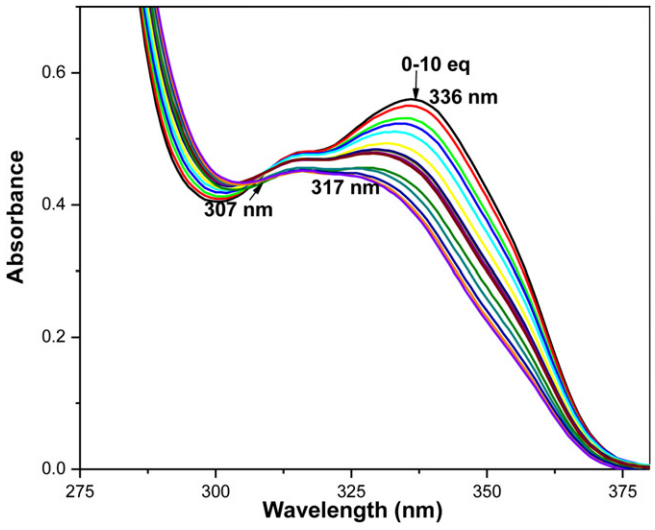


Figure 9. Changes in UV–vis spectra of **5** (50 μM) upon successive addition of $CH_3CO_2^-$ (0–10 equiv) in CH_3CN.

subunit of **5**. This intermolecular hydrogen bond formation with the anion can disturb the intramolecular hydrogen bond more strongly than **4**, leading to the destruction of the molecular rigidity so there is a larger blue shift and more decrease in the absorbance on acetate binding as compared to **4** (Table 1).[14a]

The receptor **5** undergoes ESIPT and produces a normal emission at 390 nm and tautomer emission at 553 nm when excited at 336 nm (Fig. 10). On slow addition of $CH_3CO_2^-$, a new peak is formed at 473 nm that buries both the normal and tautomer emissions. Thus by increasing the acidity and the hydrogen bonding affinity of the urea moiety, the fluorescence intensity and the binding capacity with the anion is enhanced (Table 1).

An absorbance study of **5**, with 1 equiv of F^-, produces a new red-shifted band at 388 nm, which matches well with the absorption band formed from tetrabutylammonium hydroxide by deprotonation. This imply that highly basic F^- causes the deprotonation of **5** (Fig. 11), leading to a red-shift in the absorbance spectra, making it an acid–base reaction, and so the association constant (K_a) cannot be calculated.[16,17]

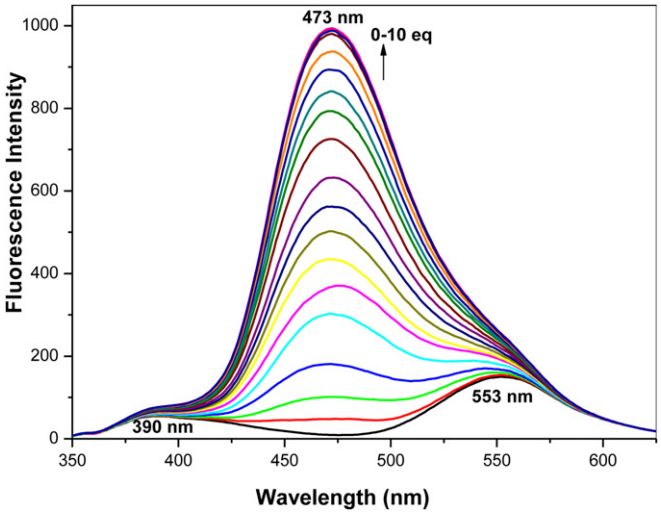


Figure 10. Changes in fluorescence spectra of **5** (50 μM) upon successive addition of $CH_3CO_2^-$ (0–10 equiv) in CH_3CN (λ_{ex}=336 nm).

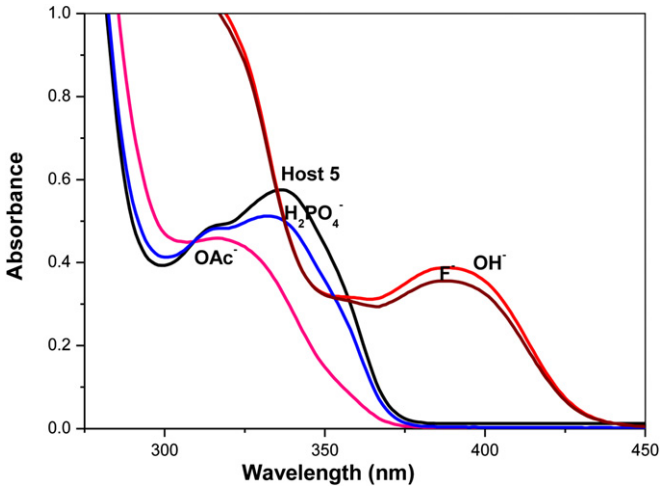


Figure 11. UV–vis spectra of **5** (50 μM) upon addition of 10 equiv of various anions in CH_3CN.

3. Conclusion

In this study, we have developed a chemosensor that can selectively detect acetate anion from anions with similar basicity and surface charge density such as F^- and $H_2PO_4^-$. An investigation of the binding patterns of chemosensors by a series of structurally different anions provided this very important information that the chemosensor preferred structure matching anions, such as acetate. We also tuned the acidity of the N–H in the urea moiety by introducing an electron withdrawing group that not only increased the fluorescence, but also enhanced the binding ability.

4. Experimental section

4.1. General methods

Melting points were determined using a Standford Research System model Opti Melt- MPA100 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400 FT-NMR spectrometer using Me_4Si as the internal standard. Unless otherwise specified, DMSO-d_6 was used as NMR solvent. UV–vis absorption spectra were determined on a Shimadzu UV-1650PC spectrophotometer. Fluorescence spectra were measured on a Shimadzu RF-5301 fluorescence spectrometer equipped with a xenon discharge lamp, 1 cm quartz cells. All of the measurements were carried out at 298 K. ^1H NMR titrations were run with a Bruker AM-400 FT-NMR spectrometer (400 MHz) at concentration levels of 4.5 mM concentrations, with aliquots of a 45 mM $(^nBu)_4N^+X^-$ salts solution added. Association constants were calculated from fluorescence titration according to the literature procedure.[15] Analytical grade acetonitrile was purchased from Merck and dried with calcium hydride. All other materials used for synthesis were purchased from Aldrich Chemical Co. and used without further purification. The solutions of anions were prepared from their tetrabutylammonium salts of analytical grade, and then subsequently diluted to prepare working solutions. Structure of **4** with acetate was optimized using density functional theory with B3-LYP functional at the 6-31G (d,p) basis set.[18]

*4.1.1. 2-Nitrobenzthioamide (**1**).* Lawesson's reagent (608 mg, 1.5 mmol) was added to a solution of 2-nitrobenzamide (200 mg, 1.23 mmol) in dry THF (15 mL) and refluxed for 1 h. The reaction mixture was evaporated in vacuo. The residue was then washed with saturated solution of sodium bicarbonate and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified using SiO_2 column chromatography (EtOAc–hexane, 1:2) to give **1** in 82% yield. Mp: 153–155 °C (CH_2Cl_2–hexane); ^1H NMR δ 7.48 (d, J=7.2 Hz, 1H), 7.59 (t, J=7.2 Hz, 1H), 7.72 (t, J=4.0 Hz, 1H), 7.99 (d, J=8.0 Hz, 1H), 9.92 (s, 1H, NH), 10.21 (s, 1H, NH); ^{13}C NMR δ 124.4, 128.5, 129.9, 133.8, 138.8, 145.6, 198.9. Anal. Calcd for $C_7H_6N_2O_2S$: C, 46.14; H, 3.32; N, 15.38; S, 17.60; found: C, 46.26; H, 3.32; N, 15.27; S, 17.62.

*4.1.2. 2-(2′-Nitrophenyl)-4-phenylthiazole (**2**).* A mixture of **1** (182 mg, 0.99 mmol) and 2-bromoacetophenone (244 mg, 1.2 mmol) in ethanol (15 mL) was refluxed for 2 h. The solvent was removed under vacuo and the residue was washed with water, neutralized with 1 N NaOH solution, and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified using SiO_2 column chromatography (EtOAc–hexane,1:9) to give **2** in 95% yield. Mp: 66–67 °C (CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$) δ 7.36 (t, J=6.4 Hz, 1H), 7.43 (d, J=7.6 Hz, 2H), 7.53 (t, J=7.6 Hz, 2H), 7.58 (s, 1H), 7.78–7.73 (m, 3H), 7.93 (d, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 114.6, 124.1, 126.4, 127.0, 128.5, 128.8, 130.4, 131.0, 132.0, 133.8, 148.7, 156.5, 161.6. Anal. Calcd for $C_{15}H_{10}N_2O_2S$: C, 63.81; H, 3.57; N, 9.92; S, 11.36; found: C, 63.64; H, 3.51; N, 9.87; S, 11.42.

*4.1.3. 1-Phenyl-3-(2-(4-phenylthiazol-2-yl)phenyl)urea (**4**).* A solution of **2** (146 mg, 0.80 mmol) in methanol (10 mL) was hydrogenated with 10% Pd/C under hydrogen atmosphere for 6 h. After the catalyst was removed by filtration through the Celite pad, the filtrate was concentrated and dried to give crude amino product **3**. Without further purification, to the solution of the crude amine (100 mg, 0.39 mmol) in dioxane (15 mL) phenyl isocyanate (72 mg, 0.60 mmol) was added and refluxed for 12 h. The solid precipitated on cooling the reaction mixture was filtered and dried to give **4** in a 90% yield. Mp: 220–222 °C (DMSO); ^1H NMR δ 6.99 (t, J=7.4 Hz, 1H), 7.17 (t, J=7.6 Hz, 1H), 7.31 (t, J=8.0 Hz, 2H), 7.38 (t, J=7.0 Hz, 1H), 7.46 (t, J=7.6 Hz, 3H), 7.51 (d, J=8.0 Hz, 2H), 7.90 (d, J=7.6 Hz, 1H), 8.10 (d, J=8.0 Hz, 3H), 8.24 (s, 1H), 9.57 (s, 1H, NH), 10.41 (s, 1H, NH); ^{13}C NMR δ 115.3, 119.4, 119.5, 121.6, 122.0, 123.0, 123.6, 127.3, 129.3, 129.7, 129.9, 131.5, 134.3, 137.9, 140.8, 153.8, 155.4, 167.8. Anal. Calcd for $C_{22}H_{17}N_3OS$: C, 71.14; H, 4.61; N, 11.31; S, 8.63; found C, 70.78; H, 4.75; N, 10.95; S, 8.30.

*4.1.4. 1-Trifluoromethylphenyl-3-(2-(4-phenylthiazol-2-yl)phenyl) urea (**5**).* 4-(Trifluoromethyl)phenyl isocyanate (90 mg, 0.48 mmol) was added to the solution of the crude amine **3** (100 mg, 0.39 mmol) in dioxane (15 mL) and refluxed for 2 h. The solid precipitated on cooling the reaction mixture was filtered and dried to give **5** in 93% yield. Mp: 250–251 °C (DMSO); ^1H NMR δ 7.21 (t, J=6.0 Hz, 1H), 7.38 (t, J=8.0 Hz, 1H), 7.46 (t, J=8.0 Hz, 3H), 7.68 (dt, J=8.5, 12.0 Hz, 4H), 7.92 (d, J=8.0 Hz, 1H), 8.09 (m, 3H), 8.25 (s, 1H), 8.10 (d, J=8.0 Hz, 3H), 10.00 (s, 1H, NH), 10.52 (s, 1H, NH); ^{13}C NMR δ 114.9, 118.4, 121.3, 122.1, 122.6, 123.5, 126.2, 126.4, 126.7, 128.7, 129.1, 129.3, 130.9, 133.7, 136.8, 143.9, 152.9, 154.8, 167.0. Anal. Calcd for $C_{23}H_{16}F_3N_3OS$: C, 62.86; H, 3.67; N, 9.56; S, 7.30; found C, 62.39; H, 3.61; N, 9.41; S,7.42.

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Supplementary data

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