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Unique fluoride anion complexation in basic media by 5,5-dioxophenothiazine bis(phenylurea) and bis(phenylthiourea)

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Abstract

The anion recognition properties of the newly synthesised 5,5-dioxophenothiazine bis(phenylurea) and bis(phenylthiourea) were investigated using UV–vis spectroscopy. While most of the studied anions were bound only by the neutral receptors, fluoride and acetate were complexed even by the deprotonated ones.

Keywords: phenothiazine, anion recognition, deprotonation

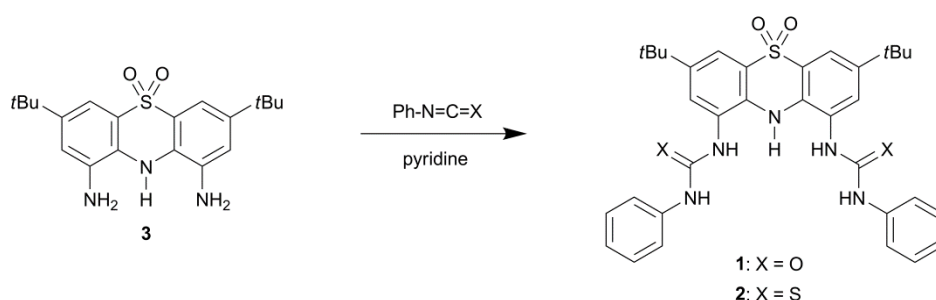
1. Introduction

Sensor molecules capable of selectively recognizing cationic, anionic or neutral species have received a great interest due to their potential applications in pharmaceutical and food industry as well as in environmental chemistry.¹ In the last decade, many efforts have been devoted to the development of anion sensors,^{2,3} among them receptor molecules, which allow optical detection of anionic species.⁴⁻⁹

One of the main groups of anion receptors consists of neutral molecules having slightly acidic groups, which bind anions by hydrogen bond formation. Examples include amide-¹⁰⁻¹² and urea-based¹⁰⁻¹⁴ receptors and host molecules containing heterocycles with slightly acidic NH groups,^{11,12,15-18} among them bis(phenylureas) and bis(phenylthioureas) having tricyclic heterocyclic units like acridone¹⁷ and carbazole.¹⁸ Increasing the acidity of the sensor molecules can lead to the deprotonation of those in the presence of basic anions (such as fluoride, acetate and dihydrogen phosphate) causing large spectral changes.^{19,20}

Sensor molecules having thiazine 1,1-dioxide units were synthesised by Wang and co-workers for the studies of their anion complexing ability.²¹ Recently, we reported the synthesis and anion recognition studies of two 5,5-dioxophenothiazine-1,9-diamides. We demonstrated that fluoride, acetate and dihydrogen phosphate caused the deprotonation of both sensor molecules meaning that the spectral changes were mainly induced by acid–base equilibria.²²

Since increasing the number of binding sites of the receptor molecules may enhance the complexation ability, we synthesised novel phenothiazine-5,5-diones containing urea and thiourea units, respectively (**1** and **2**, Scheme 1), and studied their behaviour toward different anions in acetonitrile.



Scheme 1. Synthesis of receptors **1** and **2**.

2. Results and Discussions

2.1. Synthesis

1,9-Diaminophenothiazine derivative **3**²² was reacted with phenyl isocyanate and phenyl isothiocyanate in pyridine to give urea derivative **1** and thiourea derivative **2**, respectively (Scheme 1).

The crystal structure of receptor **1** was determined by X-ray crystallography. Crystals obtained from a solution of receptor **1** in a methanol–acetone mixture contained receptor **1** without solvent molecules. Receptor **1** formed chains held together by intermolecular N–H···O type hydrogen bonds between the urea NH and the carbonyl groups (Fig. S5, see Supplementary data). Crystals obtained from a solution of receptor **1** in DMSO-*d*₆ contained receptor **1** with three solvent molecules. One of them could not be identified in the electron density map (a disordered DMSO-*d*₆ molecule), which was removed using SQUEEZE program.²³ The other two solvent molecules were bound to the receptor by N–H···O type hydrogen bonds formed between the urea or phenothiazine NH groups and the sulfinyl groups (Fig. S6, see Supplementary data).

2.2. Anion recognition studies

The anion recognition ability of receptors **1** and **2** was studied in acetonitrile toward the tetrabutylammonium salts of fluoride, chloride, bromide, iodide, nitrate, hydrogen sulfate, sulfate, dihydrogen phosphate and acetate using UV–vis spectroscopy.

Both receptor molecules formed complexes of 1:1 stoichiometry with chloride, bromide, hydrogen sulfate, sulfate and dihydrogen phosphate, while complexation with nitrate took place only in the case of receptor **1** (spectral changes characteristic to complexation are shown in Fig. S8 and S9, see Supplementary data). Iodide had no effect on the absorption spectra of any of the receptors. In general, complexes of receptor **1** had more than one order of magnitude higher stability constants than those of receptor **2** (Table 1).

Table 1. Stability constants of complexes of **1**, **2**, deprotonated **1** and deprotonated **2** with different anions^a

1		2	
log <i>K</i> ₁	log <i>K</i> ₂	log <i>K</i> ₁	log <i>K</i> ₂

F ⁻	>8	>8	b	b
Cl ⁻	5.99	—	4.45	—
Br ⁻	4.60	—	3.28	—
I ⁻	—	—	—	—
NO ₃ ⁻	3.23	—	—	—
HSO ₄ ⁻	4.51	—	3.26	—
SO ₄ ²⁻	6.72	—	6.28	—
H ₂ PO ₄ ²⁻	7.51	—	6.17	—
CH ₃ COO ⁻	7.57	5.61	6.44	3.87

$${}^a K_1 = [\text{RHX}^-]/([\text{RH}][\text{X}^-]), K_2 = [\text{RX}^{2-}]/([\text{R}^-][\text{X}^-])$$

^bThe titration series of spectra could not be fitted satisfactorily

X-ray crystallographic analysis of a single crystal grown from a solution of receptor **1** and tetrabutylammonium chloride in a methanol–acetone mixture showed the formation of a 2:2 complex held together by urea N–H···Cl type hydrogen bonds (Fig. 1 and Fig. S7, see Supplementary data).

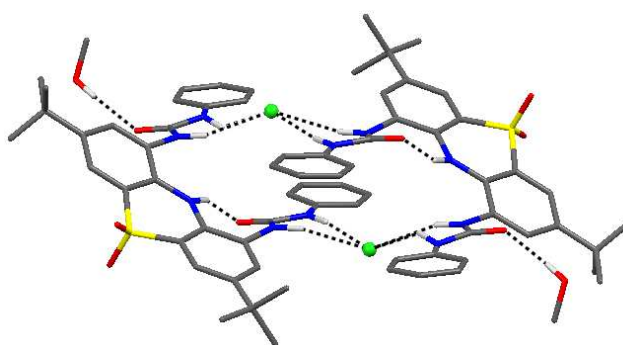


Figure 1. Hydrogen bonds in the crystal structure of the centrosymmetric 2:2 **1**–Cl⁻ complex (non-acidic hydrogens and tetrabutylammonium counterions are omitted for clarity).

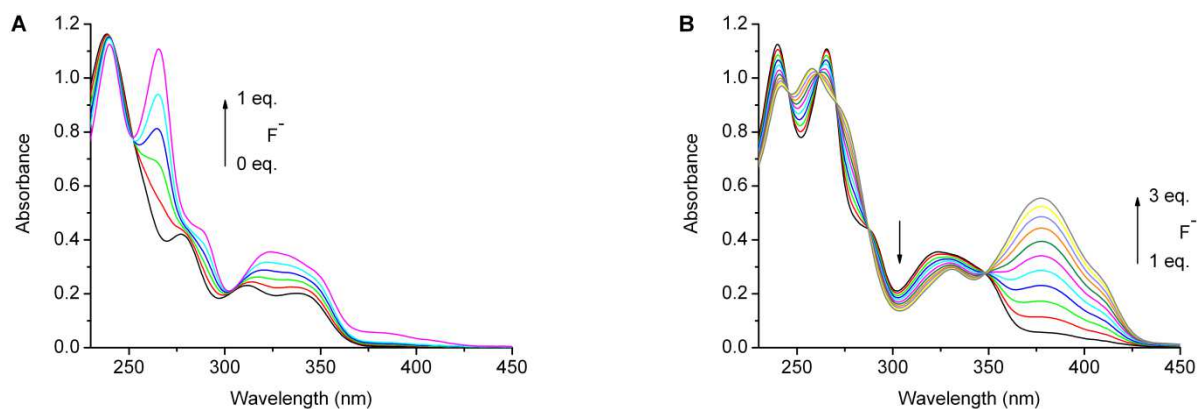


Figure 2. Series of absorption spectra upon titration of **1** (20 μM) with F^- (A: 0–1 equiv., B: 1–3 equiv.) in MeCN.

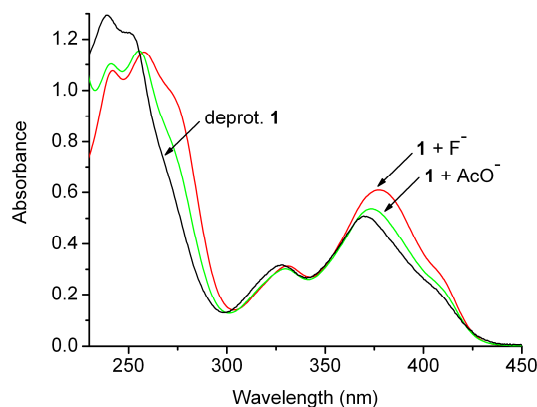


Figure 3. Absorption spectrum of deprotonated **1** (20 μM) and the endpoint spectra of titrations of **1** (20 μM) with F^- and AcO^- in MeCN.

Upon addition of one equivalent of fluoride or acetate to the solution of either receptor molecule, complexation induced changes could be observed in the absorption spectra (Fig. 2A and S10A, see Supplementary data). Further addition of these anions caused spectral changes characteristic to deprotonation (Fig. 2B and S10B, see Supplementary data), however, these spectra were different from those of deprotonated receptors **1** and **2** (Fig. 3 and S11, see Supplementary data). These results assumed that deprotonated receptor–anion complexes had been formed. This assumption was confirmed as follows. In the case of fluoride, after complexation not only further one (unlike the examples in the literature^{19,20,22}), but further two equivalents of the anion were needed for the deprotonation with the formation of the stable $[\text{HF}_2]^-$. The separation of the two near quantitative processes (complexation: 0–1 equiv. and deprotonation: 1–3 equiv.) clearly appeared on the titration curve showing a breaking point at one equivalent (Fig. 4A). ^1H NMR titration of receptor **1** with fluoride was also performed. The changes in the chemical shifts of the phenyl hydrogens also showed the complexation (0–1 equiv.) and deprotonation (1–3 equiv.) processes (Fig. 4B). The signals of the aromatic protons broadened (those of the phenothiazine unit practically disappeared) during the deprotonation process because of the equilibrium between the deprotonated and protonated complexes (Fig. S12, see Supplementary data). X-ray crystallographic analysis of a single crystal grown from a solution of receptor **1** and three equivalents of tetrabutylammonium

fluoride in an acetonitrile–hexane mixture confirmed that the deprotonated receptor complexed a fluoride anion by urea N–H···F type hydrogen bonds (Fig. 5).

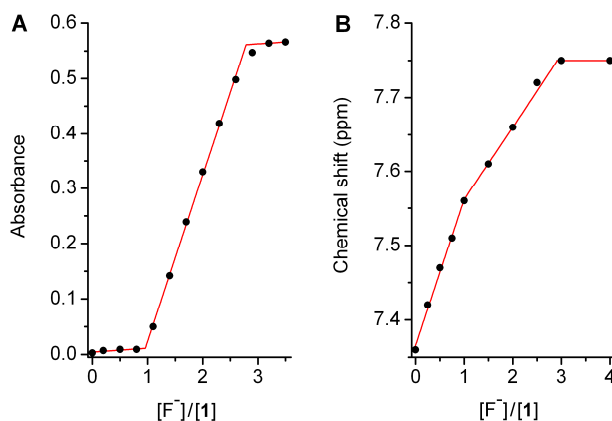


Figure 4. Titration curves of **1** with F⁻ (A: [1] = 100 μM, absorption changes in MeCN at 377 nm, B: changes of chemical shift of the *ortho* phenyl hydrogens in MeCN-*d*₃ at 300 MHz).

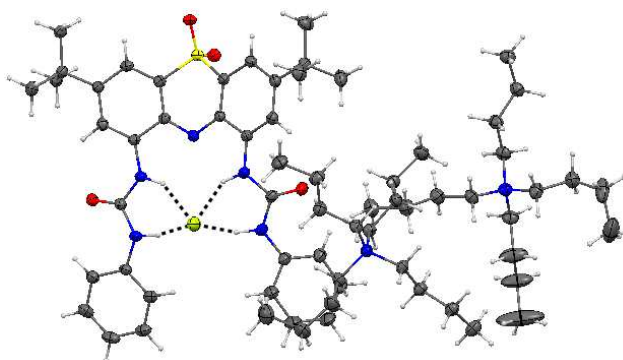


Figure 5. ORTEP style diagram of the asymmetric unit in the crystal of deprotonated **1**-F⁻ complex.

Similar results were found by Camiolo and co-workers between a dinitrophenyl-substituted pyrrole-2,5-diamide and fluoride, however, they reported a three-step process. Namely, the first equivalent of fluoride was complexed by the neutral receptor molecule, the second equivalent caused deprotonation with the formation of [HF₂]⁻, and the third equivalent was coordinated by the deprotonated receptor.²⁴

Since our latter results showed that in the cases of fluoride and acetate, deprotonated receptor–anion complexes were formed *via* deprotonation of the neutral receptor–anion complexes by an excess of the anion, we also examined whether the receptors deprotonated by an excess of a base

(DBU or tetrabutylammonium hydroxide) could form complexes with anions. As expected, fluoride was strongly complexed by the deprotonated receptors (Table 1, Fig. 6 and S13, see Supplementary data). The absorption spectra of these complexes showed good accordance with the spectra obtained by addition of three equivalents of fluoride to the neutral receptors. The deprotonated receptors showed similar, but weaker complexing ability toward acetate than fluoride (Table 1). Upon addition of bromide, iodide and nitrate to the solution of the deprotonated receptors, no spectral changes could be observed. Addition of acidic anions (hydrogen sulfate and dihydrogen phosphate) caused the protonation of the deprotonated receptors, and the resulted neutral receptor molecules formed complexes with the deprotonated anions (Fig. S14, see Supplementary data). Upon addition of chloride and sulfate to the deprotonated receptors, the deprotonation was suppressed, and the resulted neutral receptors formed complexes with the anions, because the equilibrium constants of the complexation and the deprotonation processes are probably comparable.

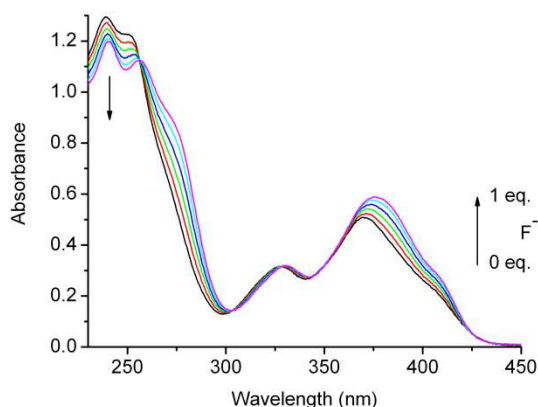


Figure 6. Series of absorption spectra upon titration of deprotonated **1** (20 μM) with F^- (0–1 equiv.) in MeCN.

3. Conclusion

In summary, we reported here the anion recognition studies of new 5,5-dioxophenothiazine bis(phenylurea) and bis(phenylthiourea) (**1** and **2**), which proved to be capable of complexing fluoride in the presence of bases. These results suggest that anion receptors of similar structures with more acidic properties could provide an opportunity for the development of selective sensor molecules toward fluoride in basic media.

4. Experimental

4.1. General

Reagents were purchased from Sigma–Aldrich Corporation unless otherwise noted. Silica gel 60 F₂₅₄ (Merck) plates were used for TLC. Ratios of solvents for the eluents are given in volumes (mL/mL). Solvents were dried and purified according to well established methods.²⁵

IR spectra were recorded on a Bruker Alpha-T FT-IR spectrometer. ¹H (500 MHz) NMR spectrum was obtained on a Bruker DRX-500 Avance spectrometer. ¹H (300 MHz) and ¹³C (75.5 MHz) NMR spectra were obtained on a Bruker 300 Avance spectrometer. Elemental analyses were performed on a Vario EL III instrument (Elementanalyze Corporation). Mass spectra were recorded on an Agilent-1200 Quadrupole LC/MS instrument using ESI method. Melting points were taken on a Boetius micro-melting point apparatus and were uncorrected. X-Ray crystallographic data were collected on a Rigaku R-AXIS-RAPID diffractometer (graphite monochromator). Suitable single crystals for X-ray analysis were obtained in the following way. **1**: A solution of receptor **1** was prepared in 1:1 acetone–methanol mixture at rt. The solvent was evaporated slowly, and few days later crystals appeared in the ampoule. **1**–DMSO-*d*₆: An almost saturated solution of receptor **1** was prepared in DMSO-*d*₆ at rt, and few days later crystals appeared on the surface of the solution. These crystals could only be measured in a capillary. **1**–Cl[−]: Single crystals of the **1**–Cl[−] complex were grown by slow evaporation of a solution of receptor **1** and an excess of tetrabutylammonium chloride in a methanol–acetone mixture. Deprotonated **1**–F[−]: Single crystals of the deprotonated **1**–F[−] complex were grown by slow evaporation of a solution of receptor **1** and three equivalents of tetrabutylammonium fluoride in an acetonitrile–hexane mixture.

UV–vis spectra were taken on a Unicam UV4-100 spectrophotometer. Quartz cuvettes with path length of 2, 10 and 40 mm were used. Tetrabutylammonium sulfate was prepared by adding 1 equiv. of tetrabutylammonium hydrogen sulfate to 1 equiv. of Bu₄NOH dissolved in MeOH. After evaporating MeOH the salt was dried under reduced pressure over P₂O₅. All of the other tetrabutylammonium salts of anions were purchased from Sigma–Aldrich Corporation. The stability constants of complexes were determined by global nonlinear regression analysis using SPECFIT/32TM program. The concentrations of the solutions of receptors **1** and **2** were 1.3, 3.2 and 20 μM during the UV–vis titrations. The concentrations of the solutions of receptor **1** during the

NMR titration were 0.77 mM, 1.77 mM, 2.58 mM, 3.37 mM and 12.5 mM in the cases of 0, 0.25, 0.5, 0.75 and 1–4 equiv. of F⁻, respectively (more dilute solutions were needed because of the lower solubility of the uncomplexed receptor).

4.2. General procedure for the synthesis of receptors 1 and 2

To a stirred solution of diamine **3**²² (300 mg, 0.80 mmol) in pyridine (3 mL) was added a solution of phenyl isocyanate (201 mg, 1.69 mmol) or phenyl isothiocyanate (326 mg, 2.41 mmol) in pyridine (2 mL) at rt. After the reaction was completed, the reaction mixture was poured into a water–ice mixture, and acidified to pH 2 using concentrated hydrochloric acid. The precipitate was filtered off, and triturated with hot butyl acetate to give **1** or **2** as white crystals.

4.2.1. *1,1'-(3,7-Di-tert-butyl-5,5-dioxo-5,10-dihydro-5λ⁶-phenothiazine-1,9-diyl)bis(3-phenylurea)* (**1**). Yield: 406 mg, 83%; Mp 238–240°C; R_f 0.48 (silica gel TLC, MeOH–CH₂Cl₂ 1:20); IR (KBr) ν_{max} 3404, 3286, 2960, 2906, 2870, 1650, 1610, 1574, 1510, 1444, 1364, 1296, 1250, 1227, 1142, 1103, 1055, 900, 883, 748, 730, 694, 611, 540 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.34 (s, 18H), 6.92 (t, *J*=8 Hz, 2H), 7.11 (t, *J*=8 Hz, 4H), 7.37 (d, *J*=8 Hz, 4H), 7.65 (d, *J*=2 Hz, 2H), 7.69 (d, *J*=2 Hz, 2H), 8.64 (s, 2H, NH), 8.84 (s, 2H, NH), 9.65 (s, 1H, NH); ¹H NMR (300 MHz, MeCN-*d*₃) 1.36 (s, 18H), 7.00 (t, *J*=8 Hz, 2H), 7.19 (t, *J*=8 Hz, 6H, phenyl H and NH), 7.36 (d, *J*=8 Hz, 4H), 7.58 (s, 2H, NH), 7.64 (d, *J*=2 Hz, 2H), 7.84 (d, *J*=2 Hz, 2H), 9.19 (s, 1H, NH); ¹³C NMR (75.5 MHz, DMSO-*d*₆) δ 30.88, 34.40, 114.20, 118.58, 121.48, 121.99, 126.66, 126.80, 128.60, 131.08, 139.25, 144.35, 153.71; MS calcd for C₃₄H₃₇N₅O₄S: 611.2. Found (M–H)⁻: 610.2. Anal. Calcd for C₃₄H₃₇N₅O₄S: C, 66.75; H, 6.10; N, 11.45; S, 5.24. Found: C, 66.51; H, 5.92; N, 11.18; S, 5.53.

4.2.2. *1,1'-(3,7-Di-tert-butyl-5,5-dioxo-5,10-dihydro-5λ⁶-phenothiazine-1,9-diyl)bis(3-phenylthiourea)* (**2**). Yield: 259 mg, 50%; Mp 208–210°C; R_f 0.32 (silica gel TLC, EtOAc–hexane 1:2); IR (KBr) ν_{max} 3354, 3280, 3163, 2962, 1609, 1592, 1542, 1527, 1489, 1290, 1278, 1231, 1130, 746, 695 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.32 (s, 18H), 7.11 (t, *J*=8 Hz, 2H), 7.25 (t, *J*=8 Hz, 4H), 7.48 (d, *J*=8 Hz, 4H), 7.60 (d, *J*=2 Hz, 2H), 7.74 (d, *J*=2 Hz, 2H), 8.45 (s, 1H, NH), 9.62 (s, 2H, NH), 10.12 (s, 2H, NH); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 30.84, 34.45, 115.96, 121.11, 124.22, 124.89, 127.14, 128.51, 130.23, 132.10, 138.79, 144.26, 180.98; MS calcd for C₃₄H₃₇N₅O₂S₃: 643.2. Found (M–H)⁻: 642.2. Anal. Calcd for C₃₄H₃₇N₅O₂S₃: C, 63.42; H, 5.79; N, 10.88; S, 14.94. Found: C, 63.15; H, 5.67; N, 10.58; S, 14.69.

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Supplementary data

¹H and ¹³C NMR spectra, NMR titration spectra, additional UV–vis titration spectra and crystallographic data. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 923802–923805. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.tet.xxxx.xx.xxx>.

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