PERKIN 2

Study on host–guest complexation of anions based on tri-podal naphthylthiourea derivatives

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A new host tris[*N*′-naphthyl-*N*-(2-aminoethyl)thiourea]amine (**3**) and the reference compounds bis[*N*′-naphthyl-*N*-(2-aminoethyl)thiourea]amine (**2**) and *N*′-naphthyl-*N*-*n*-amylthiourea (**1**) were synthesized and used for the recognition of anionic species. Considerable changes in UV/Vis absorption of host **3** induced by complexation with $H_2PO_4^-$ (or HSO_4^-) were observed. UV/Vis spectroscopy titration experiments and ^{1}H-NMR results both indicated the formation of 1 : 1 stable complexes between **3** and $H_2PO_4^-$ (or HSO_4^-). The stability constants of the complexes were determined in DMF. The results demonstrate that optically changeable receptors for anions may be constructed by appropriate design of host molecules.

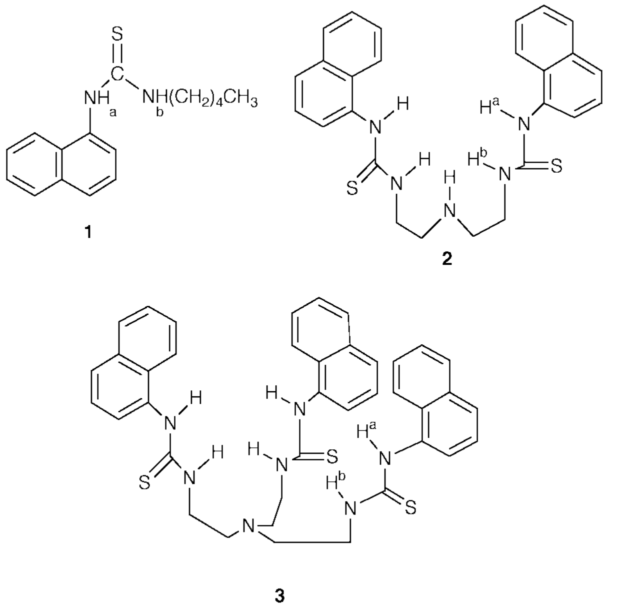
Introduction

In nature phosphate and sulfate binding proteins are very important receptors for active transport systems in cells and specific binding takes place exclusively through hydrogen bonding.[1] Currently, molecular recognition of anions by synthetic receptors is an expanding field of research.[2] Synthetic receptors for anions have to date typically employed various combinations of macrocyclic polyammoniums/guanidiniums,[3] pyrrols,[4] Lewis acids,[5] calix[*n*]arenes,[6] amides[7,6a] and urea/thioureas.[8] Electroneutral receptors which contain multiple hydrogen bonding sites generally have the advantage since their use gives less nonspecific binding thereby improving the selectivity for anions.[2a,9] Furthermore, receptors with flexible multi-podal structures have strong affinity for oxo-anions because the geometry and orientation of the host molecules favors formation of a stable host–guest complex.[7a,8]

Interaction between hosts and anionic guests has been generally studied by ^{1}H-NMR methods. However, this method suffers from low sensitivity reaulting from the high association and the relatively high concentrations in both host and guest required to obtain appreciable NMR signals (10^{-2}–10^{-3} M or more).[6,7a,8] Moreover, the ^{1}H-NMR signal of the active hydrogen (generally NH) measured becomes very broad upon the complexation of anions, thereby making it somewhat more difficult to determine the stability constant of the complexes by this method.[10]

It is interesting to develop other kinds of hosts that could use chromogenic signaling to show anion binding. However, the near-absence of chromophores which are responsive to small anions is an embarrassing fact. Until now, the number of optically responsive receptors has been very low.[11–13] The first example of a fluorescent chemosensor, utilizing a photo-induced electron transfer (PET) process, was described by Czarnik and co-workers.[12] Another example of anion indicators, reported by Teramae *et al.*,[11] works on the basis of controlling the intramolecular exciplex formation.

Herein, we report the synthesis and binding properties of polyamine naphthyl thiourea derivatives **1**, **2** and **3**, functionalized with one, two or three thiourea moieties, respectively (Scheme 1). We show that tri-podal compound **3** can be used as a neutral host for anions, and that anion binding occurs through hydrogen bonding. The recognition can easily be monitored by anion-complexation induced changes in absorption spectra. The interaction between hosts and anions is confirmed by ^{1}H-NMR.



Scheme 1

Results and discussion

Absorption spectra of host compounds

The absorption spectra of the host compounds **1**–**3** in DMF were measured. Their absorption bands are of similar shape (peak wavelength all at 294 nm), assigned to the naphthyl $\pi\pi^*$ transition. The absorbances at 294 nm of these compounds are all linear as a function of the their concentration in DMF and the molar extinction coefficients, ε_H of **1**, **2** and **3** at peak wavelength were 13092, 18300 and 24003 M^{-1} cm^{-1}, respectively.

Anion-induced change in absorption spectra

The changes in the UV/Vis absorption spectra of host **3** upon the addition of anionic guests are shown in Fig. 1. Addition of HSO_4^- (Fig. 1(a)) or $H_2PO_4^-$ (Fig. 1(b)) to a solution of **3** in DMF results in an appreciable decrease of peak absorbance (at 294 nm) and a gradual increase of absorbance at around 340 nm. At the same time, a clear isosbestic point (at around 322 nm) is observed, indicating the formation of host–guest complexes between **3** and $H_2PO_4^-$ (or HSO_4^-). Addition of Br^-, I^- or CH_3COO^- to a solution of **3** does not induce any change in the absorption spectra of **3** even in the presence of high concentration of guests. This indicates that the host **3** exhibits highly selective complexation of tetrahedral oxoanions, especially $H_2PO_4^-$, whereas it does not bind well with spherical halide anions such as Br^- and I^- and the planar CH_3COO^-. In order to further investigate whether protonation of the tertiary amine group in **3** would have an effect on its UV/Vis absorption properties, CF_3COOH was also added to a solution of **3** in DMF. The results show that even in the presence of a large excess of CF_3COOH, the absorption spectra of **3** did not change.

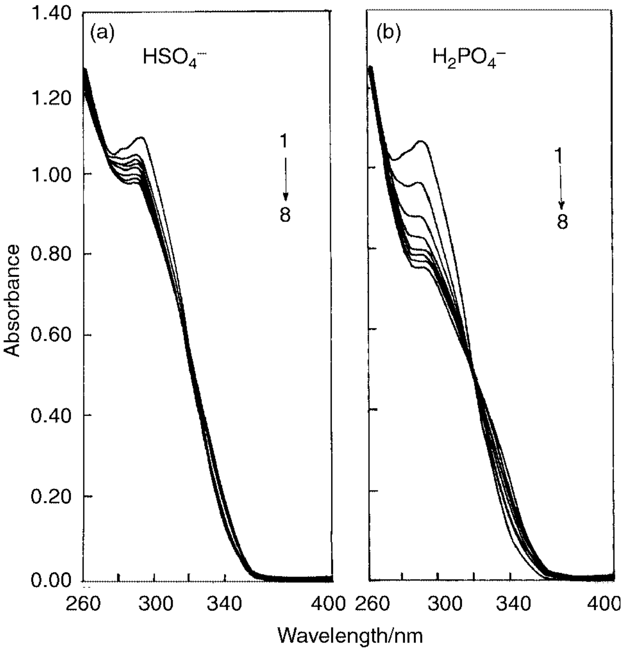


Fig. 1 The absorption spectra of compound **3** (0.05 mM) upon the addition of (a) HSO_4^- or (b) $H_2PO_4^-$ (as tetrabutylammonium salts) in DMF at 20 °C; the concentrations of HSO_4^- or $H_2PO_4^-$ added are: 1: 0; 2: 0.02; 3: 0.04; 4: 0.06; 5: 0.10; 6: 0.20; 7: 0.30; 8: 0.40 mM.

Table 1 Variation in absorbances of compounds **1**, **2** and **3** in the absence or presence of various anions[a]

	A/A_0[b]		
Guest	**1**	**2**	**3**
None	1.000	1.000	1.000
$H_2PO_4^-$	0.967	0.987	0.748
HSO_4^-	1.000	0.992	0.938
Br^-	1.000	1.000	1.000
I^-	1.000	1.000	1.000
CH_3COO^-	1.000	1.000	1.000
CF_3COOH	1.000	1.000	1.000

[a] In DMF, at 20 °C, concentration of host 0.05 mM and concentrations of guests 0.1 mM, added as their tetrabutylammonium salts. [b] A_0,A are the absorbances of the host solution in the absence or presence of guests, respectively.

UV/Vis spectroscopy was also employed to study the interaction of compounds **1** and **2** with anionic guests. However, there was no change in the absorption spectra of **1** and **2** upon the addition of the above-mentioned anionic species (see Table 1). In the comparison between **3** and **1** and **2**, the results suggest that the shape, orientation and number of binding sites of the host are all factors in the recognition process for anions.

^{1}H-NMR spectra for the host–guest association

In order to provide further evidence that H-bonding is the main interaction binding host and anion guest together, the ^{1}H-NMR spectra of compounds **1**–**3** in the absence or presence of different anions were measured in d_6-DMSO solution at 20 °C and the results are given in Table 2. The ^{1}H-NMR spectra of host **3** shows a large downfield shift of the thiourea hydrogens upon the addition of $H_2PO_4^-$ and HSO_4^-, indicating the formation of hydrogen bonds to the oxoanion guests. In contrast, no shift was observed for **3** upon the addition of halide anions such as Br^- or I^-, suggesting that the interaction of **3** with halide guest is energetically unfavorable. In addition, the ^{1}H-NMR data also show that addition of $H_2PO_4^-$ (or HSO_4^-) to a solution of host **1** (or **2**) leads to a slight downfield shift of their thiourea hydrogens. This result indicates that a very weak interaction is likely to occur between **1** (or **2**) and $H_2PO_4^-$ (or HSO_4^-).

Stoichiometry and stability constants

UV/Vis spectroscopy was employed to determine the stoichiometry and stability constants for the complexes formed between host **3** and anionic guests. Fig. 2 shows the anion-induced change in absorbance at 294 nm for **3** in DMF as a function of the anionic concentration. Absorbances for **3** decreased with increasing concentration of $H_2PO_4^-$ (or HSO_4^-) and an approximate plateau is observed at a 1 : 1 molar ratio of host and anion guest, implying that the stoichiometry of the complexes in solution is 1 : 1. The stability constant of the complexes of **3** with anions can be determined by analysis of the spectral data using the eqn. (6) (see Appendix). A best fitting curve for **3**–$H_2PO_4^-$ was obtained by a nonlinear least-squares fitting procedure and the result is shown in Fig. 3. The stability constant, K_s, of **3**–$H_2PO_4^-$ is 1.076×10^5 M^{-1}. The same curve-fitting analysis was applied to HSO_4^- with good fitting (Fig. 4) giving K_s of **3**–HSO_4^- as 8.620×10^3 M^{-1}, implies **3** has a higher affinity for $H_2PO_4^-$ than for HSO_4^-.

Table 2 ^{1}H-NMR chemical shifts (δ/ppm) of compounds **1**, **2** and **3** in the absence or presence of anion guests[a]

	1			**2**			**3**		
Guest	H_a	H_b	H_8	H_a	H_b	H_8	H_a	H_b	H_8
None	9.55	7.48	7.94	9.84	7.46	7.95	9.70	7.40	7.94
$H_2PO_4^-$	10.07	8.39	7.93	10.27	8.79	8.00	10.76	9.55	8.06
HSO_4^-	9.62	8.00	7.94	10.01	8.12	7.95	10.10	8.59	7.95
Br^-	9.54	7.48	7.95	9.85	7.47	7.94	9.80	7.44	7.95
I^-	9.54	7.48	7.94	9.84	7.46	7.94	9.80	7.44	7.95

[a] In d_6-DMSO, at 20 °C; concentration of hosts and guests are all 2 mM. Guests are added as their tetrabutylammonium salts.

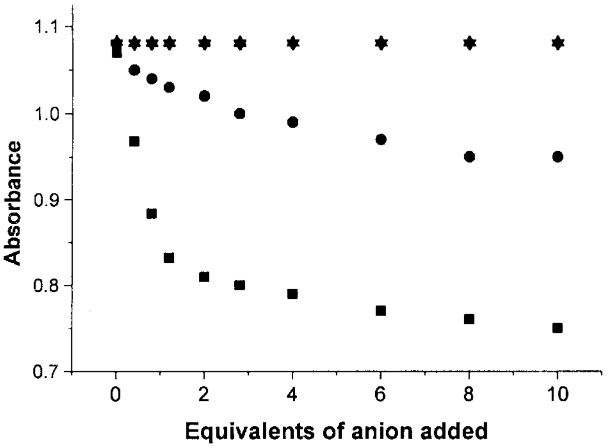


Fig. 2 UV/vis spectroscopy titrations of the host **3** in DMF (0.05 mM) at 294 nm with standard DMF solutions of $H_2PO_4^-$ (■); HSO_4^- (●); Br^- (▼); I^- (▲).

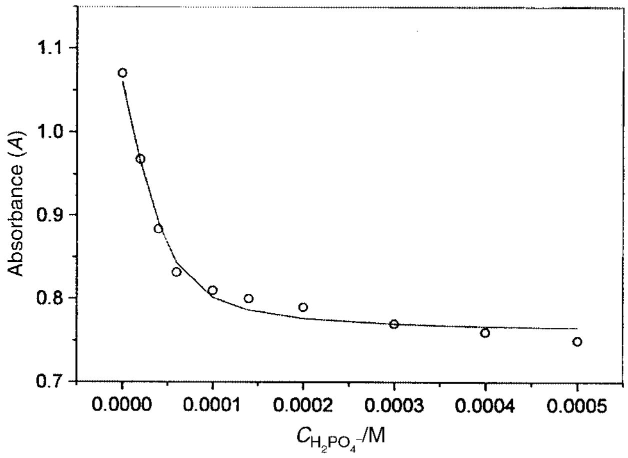


Fig. 3 Variation in absorbance of a solution of host **3** in DMF at 294 nm as a function of $H_2PO_4^-$ concentration (○). The concentration of host **3** is 5×10^{-5} M. The solid line represents the best fit corresponding to eqn. (6) by nonlinear least-squares fitting procedure.

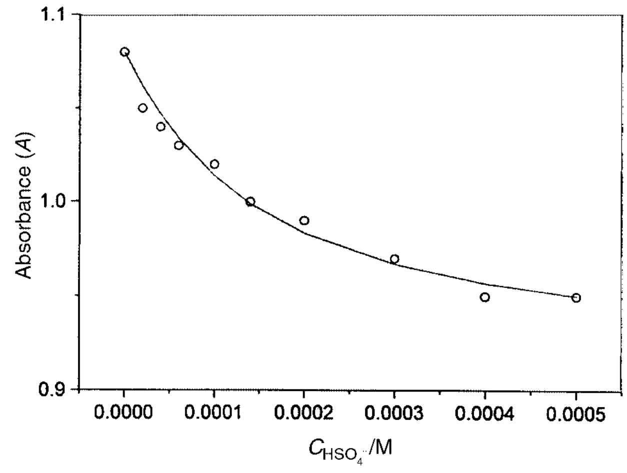
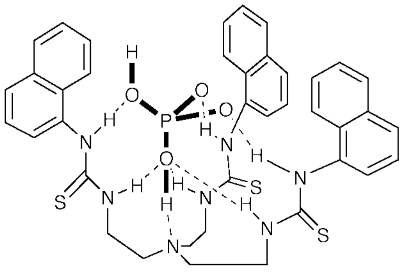


Fig. 4 Variation in absorbance of a solution of host **3** in DMF at 294 nm as a function of HSO_4^- concentration (○). The concentration of host **3** is 5×10^{-5} M. The solid line represents the best fit by nonlinear least-squares method.

A plausible structure of the complexes

The proposed scheme for the structure of the complex of host **3** with $H_2PO_4^-$ guest (Scheme 2) is the simplest one that can account for the experimental data. Some general conclusions for interaction of host with anions have been advanced and confirmed.[2] There are three main factors affecting the stability of the host–anion complexes. Firstly, there are six H-bonding sites in the complex of host **3** with oxoanions, namely the six H-bond donor sites of host **3** (six NH). The accumulation of H-bond sites enables a strong binding affinity between host **3** and oxoanions, as has been reported in literatures.[8a] Secondly, the flexible, three-dimensional molecular structure of **3** allows the shape and preorganization of the receptor to guide the recognition process. This adds directionality to the system and renders it sensitive to the spatial arrangement and orientation of oxoanion guests, resulting in a higher affinity for **3** to oxoanions relative to **1** and **2**. Lastly, the fit size and shape of anionic species favor formation of a stable host–guest complex.



Scheme 2

Conclusion

The results illustrate the possibility of designing chromogenic receptors for quantitative determination of important biological anions by the principles of supramolecular chemistry. ^1H-NMR spectra reveal that the $H_2PO_4^-$ guest is bound tightly into the cavity of receptor **3** through hydrogen bonding interactions. In general, a host molecule used as the optical chemosensor includes an optical response portion and a guest-binding receptor portion. When an anionic species is bound in the receptor portion, the chromogenic portion gives a spectral response, thereby providing information on anion binding. On the other hand, for anions themselves, the size, shape and the number of interaction sites also should be considered when designing a specific binding agent for anions.

Experimental

General

^1H- and ^{13}C-NMR spectra were recorded on a Varian GEMANA-300 spectrometer. IR spectra were recorded on KBr film, using a BIORAD FTS-spectrometer. A Heiaeus CHN-Rapid instrument was used for elemental analyses. Absorption spectra were recorded with a Hitachi 300 spectrophotometer. Chloroform was distilled from anhydrous $CaSO_4$ and stored over molecular sieves (4 Å) prior to use. Tris(2-aminoethyl)amine, diethylenetriamine and *n*-amylamine (redistilled prior to use) were purchased from Aldrich Chemical Co. except for 1-naphthyl isothiocyanate (Acros Chemical Co.). Trifluoroacetic acid (99%) and tetrabutylammonium dihydrogen phosphate (97%), hydrogen sulfate (98%), bromide (99%), iodide (98%) and acetate (97%) were all purchased from Acros Chemical Co. DMF was dried over hot molecular sieves (4 Å) and then redistilled.

General procedure for the preparation of compounds 1–3

To a solution of *n*-amylamine (0.7 mL, 5.41 mmol for **1**), diethylenetriamine (0.25 mL, 2.45 mmol for **2**) or tris(2-aminoethyl)amine (0.25 mL, 1.67 mmol for **3**) in dried $CHCl_3$ (20 mL) was added 1-naphthyl isothiocyanate (1.0 g, 5.41 mmol). The reaction mixture was stirred at room temperature for 15 h and then water (40 mL) was added. The organic layer was separated and washed with brine (40 mL) and dried with anhydrous $MgSO_4$. Evaporation of the solvent yielded the crude product that was then purified as described below.

***N′*-Naphthyl-*N*-*n*-amylthiourea (1).** Yield 95%; mp 84–85 °C; ^{1}H-NMR (d_6-DMSO; 300 MHz): δ_H 9.55 (1H, s, NH_a), 7.94 (1H, m, ArH), 7.84 (2H, d, $J = 6.0$ Hz, ArH), 7.53 (4H, m, ArH), 7.48 (1H, s, NH_b), 3.41 (2H, t, NCH_2), 1.47 (2H, m, NCH-CH_2), 1.23 (4H, m, C-CH_2CH_2-C), 0.85 (3H, t, -CH_3); ^{13}C-NMR (d_6-DMSO; 300 MHz): δ_C 180.2 (S=C), 135.2, 133.7, 128.3, 127.8, 126.7, 126.1, 125.8, 125.5, 125.3 and 122.9 (ArC), 52.0 (NH_2C), 29.5 (-CH_2C), 28.8 (-CH_2CH_2C), 21.8 (CH_3C), 13.7 (H_3C); IR ν_{max}/cm^{-1}: 3182 (N-H).

Bis[*N′*-naphthyl-*N*-(2-aminoethyl)thiourea]amine (2). The crude product was purified by column chromatography (silica gel, THF–hexane, 1 : 1) followed by trituration with MeOH: yield 60%; mp 126–128 °C; ^{1}H-NMR (d_6-DMSO; 300 MHz): δ_H 9.84 (2H, s, NH_a), 7.95–7.88 (6H, m, ArH), 7.86–7.82 (2H, m, ArH, NH_b), 7.51 (8H, m, ArH), 3.48 (4H, t, NCH_2), 2.67 (4H, t, NCH_2); ^{13}C-NMR (d_6-DMSO; 300 MHz): δ_C 180.8 (S=C), 134.2, 133.6, 129.8, 127.5, 126.2, 126.0, 125.7, 125.5, 125.0 and 122.0 (ArC), 52.3 (H_2C), 42.1 (H_2C); IR ν_{max}/cm^{-1}: 3286, 3182 (N-H); Mass spectrum, *m*/*z* 473 (M^+).

Tris[*N′*-naphthyl-*N*-(2-aminoethyl)thiourea]amine (3). The crude product was purified by trituration with MeOH: yield 90%; mp 88–90 °C; ^{1}H-NMR (d_6-DMSO; 300 MHz): δ_H 9.67 (3H, s, NH_a), 7.95 (3H, t , $J = 3.3$ Hz, ArH), 7.85 (6H, d, $J = 6.7$ Hz, ArH), 7.53–7.50 (9H, m, ArH), 7.72–7.40 (6H, m, ArH), 7.53 (3H, m, ArH), 7.48 (3H, s, NH_b), 3.40 (6H, t, NCH_2), 2.66 (6H, t, NCH_2); ^{13}C-NMR (d_6-DMSO; 300 MHz): δ_C 181.8 (S=C), 134.3, 133.9, 129.8, 127.9, 126.6, 126.1, 125.8, 125.5, 125.0 and 122.8 (ArC), 52.2 (H_2C), 42.1 (H_2C); IR ν_{max}/cm^{-1}: 3182 (NH); Anal. Calcd. for $C_{39}H_{39}N_7O_3$: C, 71.65; H, 6.01; N, 15.00; Found: C, 71.69; H, 6.05; N, 14.94%.

Recording absorption spectra

Stock solutions of compounds **1**, **2** and **3** (0.05 mM) in DMF were prepared. Solution of the anions as their tetrabutylammonium salts were prepared at concentrations of 4.0 mM in DMF. The anion salt solutions were gradually added to 2 mL of each of the solutions of **1**–**3** with micropipets, keeping the concentrations of the host compounds constant.

Appendix: Methods of determination of K_s by UV/Vis spectroscopy

As reported in the literature,[14] the following equations were derived for the 1 : 1 stoichiometry of the host–guest complexes. The equilibrium $H + G \rightleftharpoons HG$ is characterized by the stability constant K_s of the complex of host (H) with anion guest (G) defined by eqn. (1).

$$K_s = \frac{[HG]}{[H][G]} \qquad (1)$$

The initial absorbance of the solution of the free host, A_0, at a given wavelength, is given by eqn. (2), where C_0 is the molar

$$A_0 = \varepsilon_H \, l C_0 \qquad (2)$$

concentration in host, ε_H, ε_{HG} are the molar extinction coefficients of the free host and the complexes, respectively and l is the optical path length (cm). After the addition of a given amount of anion, the absorbance is given by eqn. (3).

$$A = \varepsilon_H \, l[H] + \varepsilon_{HG} \, l[HG] \qquad (3)$$

At full complexation, we have eqn. (4).

$$A_{lim} = \varepsilon_{HG} \, l C_0 \qquad (4)$$

These relations, together with $C_0 = [H] + [HG]$ lead to eqn. (5).

$$A = \frac{A_0 + A_{lim} K_s [G]}{1 + K_s[G]} \qquad (5)$$

Considering the overall concentration of anion is $C_G = [G] + [HG]$, it is easy to derive a more general relation by combining eqns. (1)–(4) and to give eqn. (6).

$$A = A_0 + \frac{A_{lim} - A_0}{2C_0}\{C_0 + C_G + 1/K_s - [(C_0 + C_G + 1/K_s)^2 - 4C_0C_G]^{1/2}\} \qquad (6)$$

Using a nonlinear least-squares fitting procedure and eqn. (6), the stability constant K_s can be calculated by analysis of the spectral data.

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