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N-Biphenyl thioureas as carboxylate receptors. Effect of the ligand substituents on the geometry of the complexes

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Abstract—Six new biphenyl thiourea derivatives have been prepared to be used in carboxylate sensing. Experiments carried out with these ligands have demonstrated that the type of interaction with TBA carboxylates is strongly dependent on the substituents in the thiourea moiety. These interactions go from the formation of 1:1 hydrogen-bonded complexes to acid–base reactions. In addition, different geometries have been observed for the complexes being dependent on the conformations of the free ligands in solution.

1. Introduction

There is currently a great interest in the development of sensors for carboxylate anions due to their presence in a variety of biomolecules and particularly in amino acids.[1] Many of the carboxylate binding sites in these systems contain either one[2] or two[3] urea or thiourea subunits as hydrogen-bond donor groups. There has been much discussion about the thiourea (urea)–carboxylate bonding motif. In general it is assumed that thioureas bind to carboxylates through a double hydrogen bond involving both N–H fragments of the thiourea and both carboxylate oxygens in a Y-type bidentated complex (Chart 1).[3b,4] However this geometry should not be proposed in general because other factors such as conformational equilibria[4e,5] or dimerization processes[6] should also be considered.

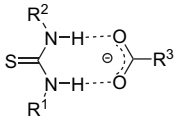

Chart 1.

In our group we have been interested in the use of 4,4′-disubstituted biphenyls as signalling units in cation and anion sensing[7] and of thioureas as binding sites for anion recognition.[8] We report herein the synthesis of neutral carboxylate receptors **1**–**4** based on thioureas bearing a 4′-nitrobiphenyl group attached to one N atom, as well as receptors **5** and **6** with a biphenyl substituent on the thiourea moiety. These receptors have been tested with various aromatic carboxylates with different basicities as well as with fluoride and acetate anions. Our experiments allow us to affirm that the complexes formed between thiourea receptors and carboxylate anions do not always show a Y-type geometry. By contrary, with several ligands the carboxylate group is only bound to one NH group of the thiourea as it has been previously described for amide-based ligands.[9] In addition, in some cases the process is not a real complexation but an acid–base reaction.[10]

2. Results and discussion

2.1. Synthesis and conformational studies of receptors 1–6

The structures of the new receptors **1**–**6** are shown in Scheme 1. Biphenyl thiourea derivatives were prepared from 4-amino-4′-nitrobiphenyl (**7**)[11] or 4-aminobiphenyl (**8**) and the corresponding isothiocyanates (**9**–**12**) in refluxing THF. 4-Amino-4′-nitrobiphenyl (**7**) was prepared by nitration of 4-nitrobiphenyl with nitric acid, followed by partial reduction to the *p*-aminonitro compound by reaction with aqueous sodium hydrogen sulfide.[12] 4-Aminobiphenyl (**8**) was obtained by reduction of 4-nitrobiphenyl with aqueous NaHS.

All compounds were characterized by NMR and MS. For ligands **1**, **3**, **4** and **6**, only one resonance is observed for each proton in the ^{1}H NMR spectra in DMSO-d_6, indicating that there is only one predominant thiourea rotamer in solution, or a fast equilibrium between different conformations

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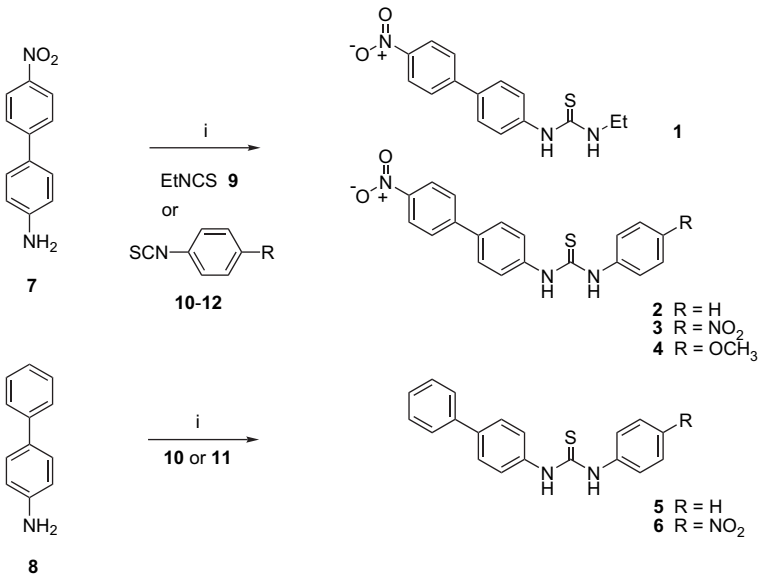

Scheme 1. Synthesis of receptors **1**–**6**. (i) Et_3N, THF, reflux.

(Fig. 1a). By contrast, the ^{1}H NMR spectra in DMSO-d_6 of ligands **2** and **5**, with a phenyl group attached to one nitrogen atom of the thiourea moiety are more complicated (Fig. 1b), showing at least two sets of signals for each ligand. These results indicate that two different conformations of the thioureas are present in solution, with slow *E*–*Z* rotameric interconversion rates on the NMR time-scale. In order to know which are the conformations present in solution in each case additional NMR experiments were carried out. Thus NOE experiments showed that thiourea **2** exists in DMSO solution as a mixture of *E*,*Z* and *Z*,*E* rotamers **2a** and **2b** (Chart 2).

Similar studies carried out with ligand **3** suggest that some degree of aggregation in solution occurs under the experimental conditions in contrast with that observed in ureas.[13] This self-association seems to situate the aromatic rings in

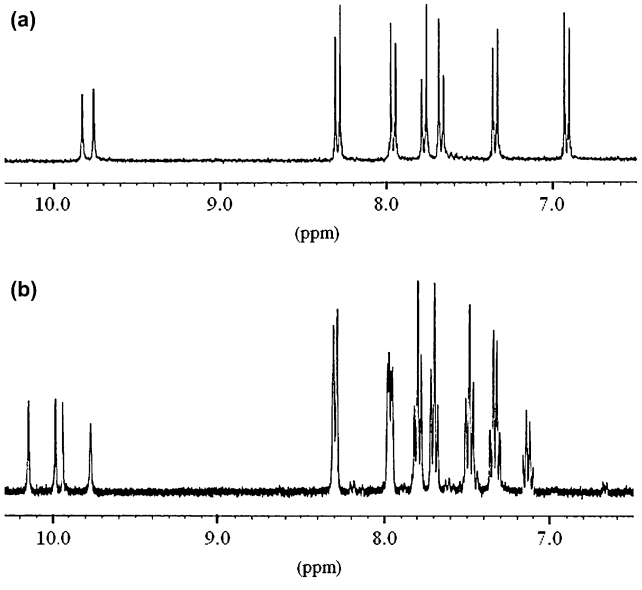

Figure 1. N–H and aromatic ^{1}H NMR signals of: (a) **4** and (b) **2** in DMSO-d_6.

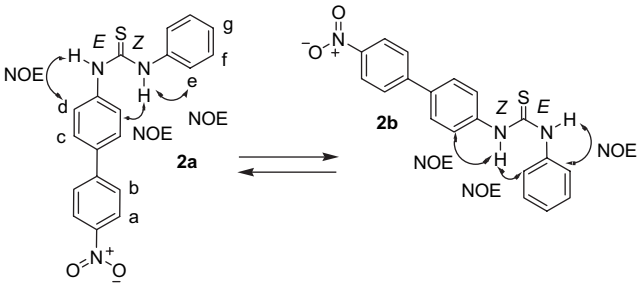

Chart 2. Main conformations of **2** in DMSO-d_6 solution.

the way shown in Chart 3 according to the NOE signals observed in the NMR experiments. In addition, when solvent was changed from DMSO-d_6 to the less polar acetone-d_6 a much more complex ^{1}H NMR spectrum was obtained reflecting the presence of a main conformation in addition to several rotamers and/or aggregates. This self-association through hydrogen-bonding is probably inhibited in the two rotamers of **2**.

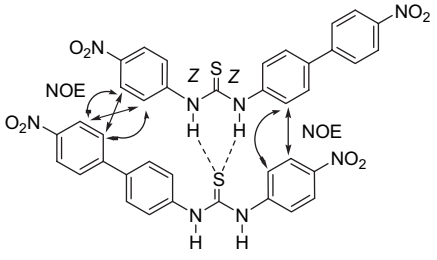

Chart 3. Proposed self-assembled dimer of **3** in DMSO-d_6 solution.

2.2. Complexation studies

To study the ability of these ligands to act as sensors for carboxylates, a series of aromatic carboxylates (benzoate, *p*-methylbenzoate, *o*- and *p*-nitrobenzoate and *o*- and *p*-methoxybenzoate, all as their tetrabutylammonium (TBA)

salts) was studied, in order to evaluate the effect of the different substituents on the aromatic ring in the complexation constants. We also decided to test acetate and fluoride anions.

Aromatic carboxylates were prepared from the corresponding carboxylic acids and TBA hydroxide in DMSO. Benzoate, acetate and fluoride TBA salts were commercially available.

2.2.1. UV–vis studies. The anion binding ability of receptors **1**–**6** was evaluated by UV–vis titration of each receptor with the appropriate anion in DMSO solution. Changes in the UV spectra agree with the expected results. Thus, in the presence of the same anion, larger changes were observed with thioureas containing two aromatic substituents (**2**–**6**) than with thiourea derivative **1** (Fig. 2).

The presence of an electron withdrawing nitro group at the *para* position of the phenyl ring makes ligand **3** acid enough to experiment deprotonation reactions under some experimental conditions.[10] The deprotonation was characterized by the presence of a new band in the UV spectrum at 464 nm. As it was expected this band does not appear in the presence of both *p*-nitrobenzoate and *o*-nitrobenzoate

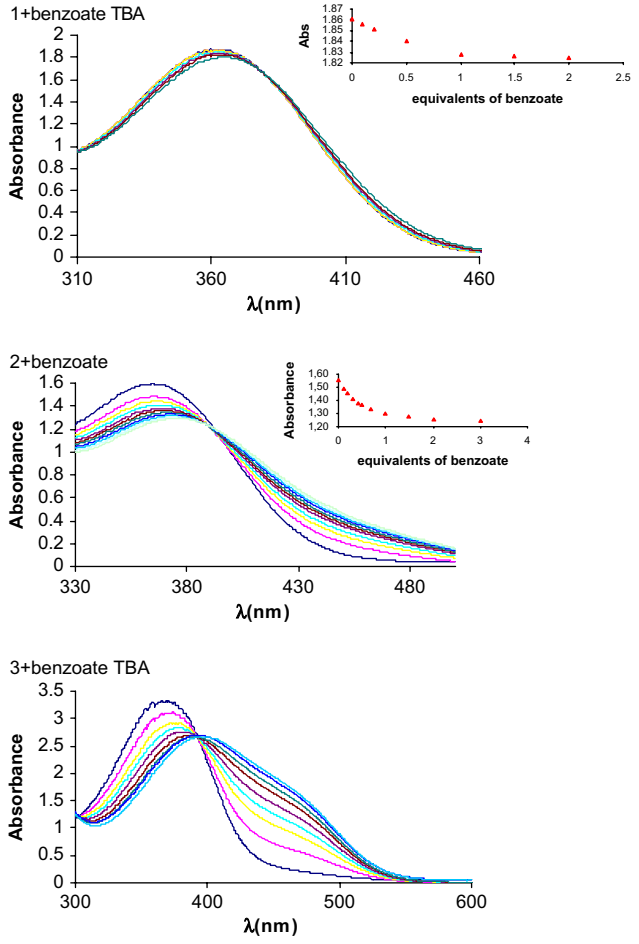

Figure 2. UV–vis absorption spectrophotometric titration of ligands **1**, **2** and **3** with TBA benzoate in DMSO at 25 °C. Inset: stoichiometry determination for **1**+TBA benzoate at 360.5 nm and **2**+TBA benzoate at 360 nm.

because of their lower basicity. Complexation constants evaluated in these experiments are shown in Table 1. These experiments in addition to other carried out by using ^{1}H NMR in DMSO-d_6 demonstrated that all the complexes have a 1:1 stoichiometry (Fig. 2).

If we try to correlate the observed binding constants with the basicity of the aromatic carboxylates, two different behaviours are observed, depending on the thiourea receptor. With ligands **1** and **4** a linear correlation is observed between the acid strengths of the *para* substituted benzoic acids and the binding constants of the corresponding complexes, following a Hammet-type behaviour (see Fig. 3). Thus, for ligand **1** the highest binding constant is observed with the more basic *p*-methoxybenzoate anion (log K 4.5) whereas the lowest binding constant is observed for *p*-nitrobenzoate (log K 3.1). In anion complexation generally for higher anion basicity, stronger complexation constants are observed.[14] This relationship indicates that the complexation of the anions to the receptor **1** is free from steric effects due to the substituent on the phenyl ring, and only electronic factors should be taken into account.

In contrast, with ligands **2** and **5**, there is no apparent relationship between basicities and binding constants. As we observe in Table 1 for receptor **2**, similar association constants are observed for *p*-nitro and *p*-methoxybenzoate (log K 3.4 and 3.6), whereas the highest log K is observed for benzoate anion (5.0), with no substituent on the phenyl ring. One explanation to this behaviour can be found in the previously described conformational equilibrium shown by these ligands. Thus, the determined values correspond not only to the complexation process but to the overall equilibrium between both conformations of the free ligand and their corresponding complexes.

Finally, ligands **3** and **6** experiment deprotonation reactions (except in the presence of *p*- and *o*-nitrobenzoate) and the values obtained with the more basic carboxylates are related to this acid–base process and for this reason has a very similar value for each ligand.

These receptors were also tested against acetate and fluoride anions, which are more basic than the previous aromatic carboxylate anions (Table 2). A 'naked-eye' colour change was observed during most of these titrations.[15] The strongest colour changes were observed for F^- anion, which is the strongest base under these conditions (see Fig. 4).

The results indicate that an acid–base reaction is taking place, resulting in deprotonation of the receptor. In fact, when 3 equiv of fluoride was added to ligand **3** in DMSO-d_6 both a broad signal in the ^{1}H NMR spectrum at 15.7 ppm and a peak at −145.5 ppm in the ^{19}F NMR appear, which can be assigned to the HF_2^- species.[7a] In addition, the band at 464 nm observed in the UV spectrum also confirms the deprotonation reaction with these more basic anions (Fig. 5). This deprotonation process was confirmed by additional experiments with ligand **3** and TBA hydroxide. An instantaneous orange colour was observed upon addition of base, and the UV–vis spectra were very similar to those obtained in the presence of fluorides or acetate anions (see Supplementary data). As it was expected the effect was stronger

Table 1. Log *K* values for receptors **1–6** with aromatic carboxylates, in DMSO at 25 °C[a]

Anion[b]	Receptor					
	1	**2**	**3**	**4**	**5**	**6**
$C_6H_5COO^-$	3.8±0.1	5.0±0.2	5.2±0.4	4.4±0.4	4.0±0.3	5.8±0.5
p-$NO_2C_6H_4COO^-$	3.1±0.2	3.4±0.2	3.2±0.2	3.1±0.3	4.4±0.2	3.5±0.1
p-$MeC_6H_4COO^-$	4.1±0.3	4.4±0.2	5.3±0.4	4.8±0.3	4.1±0.4	5.9±0.6
p-$MeOC_6H_4COO^-$	4.5±0.3	3.6±0.3	5.2±0.4	5.8±0.4	3.7±0.1	5.8±0.3
o-$NO_2C_6H_4COO^-$	3.6±0.2	3.2±0.2	4.1±0.4	3.4±0.2	3.5±0.1	3.5±0.1
o-$MeOC_6H_4COO^-$	5.2±0.4	4.5±0.3	5.3±0.4	5.0±0.4	2.7±0.4	5.6±0.4

[a] The results were calculated by UV–vis titration.
[b] All anions were used as their TBA salts.

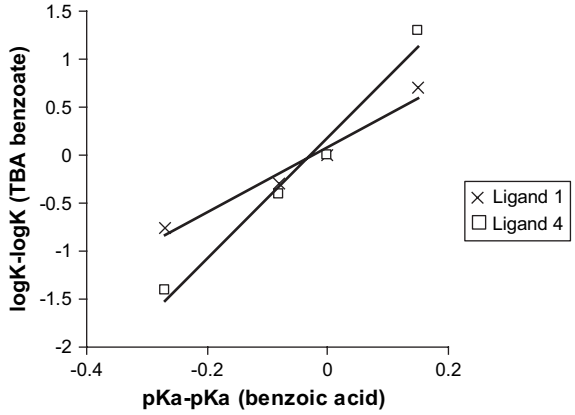

Figure 3. Correlation of the acid dissociation constants of benzoic acids with the binding constants between benzoate anions and receptors **1** and **4**.

Table 2. Log *K* values for the interaction of receptors **1–6** with fluoride and acetate anion, in DMSO at 25 °C[a]

Anion[b]	Receptor					
	1	**2**	**3**	**4**	**5**	**6**
CH_3COO^-	4.3±0.4	—	6.0±0.5	4.6±0.6	5.3±0.5	6.5±0.5
F^-	4.1±0.1	10.4±0.2	—	5.5±0.4	4.6±0.1	6.7±0.4

[a] The results were calculated by UV–vis titration.
[b] All anions were used as their TBA salts.

with ligand **3** than with ligand **6** due to the second nitro group present in ligand **3**, which makes the receptor more acidic.

Figure 4. Colour changes observed on addition of TBA salts (10 equiv) to a DMSO solution of receptor **3**. Left to right: no addition, fluoride, acetate, *o*-methoxybenzoate and *o*-nitrobenzoate.

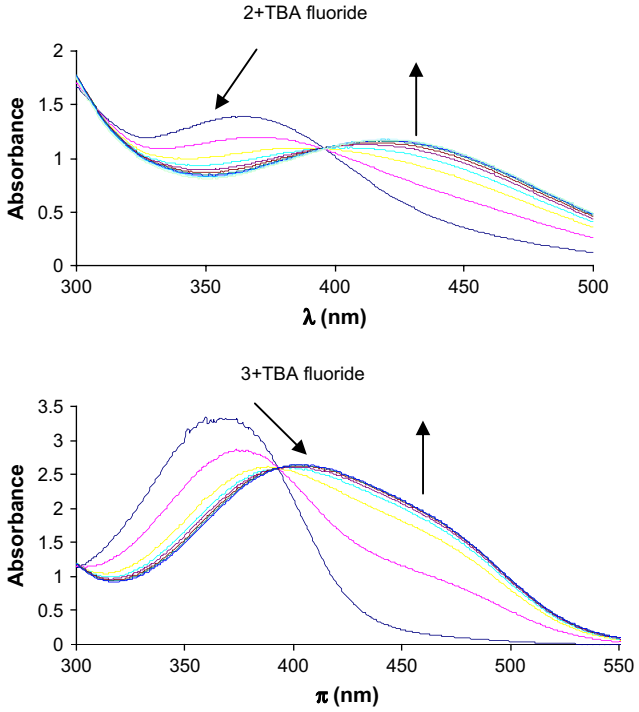

Figure 5. UV–vis absorption spectrophotometric titration of ligands **2** and **3** with TBA fluoride in DMSO at 25 °C.

2.2.2. ^{1}H NMR studies. In order to get some information about the structure of the complex in solution, ^{1}H NMR studies were undertaken. Figures. 6 and 7 show the ^{1}H NMR spectra in DMSO-d_6 of ligands **1** and **2** in the presence of 1 equiv of TBA benzoate. As it can be seen, the NH signals corresponding to ligand **1** are shifted downfield after the anion addition. The $\Delta\delta$ showed by both signals are very similar (2.43 ppm for H_α and 2.35 ppm for H_β) what agrees with a Y-type complex involving both thiourea hydrogens. Similar complexes can be proposed for ligand **4**. With ligands **3** and **6** the NH signals do not appear in the ^{1}H NMR spectrum, which is also coherent with the deprotonation previously proposed.[10]

Finally, ligands **2** and **5** showed a clearly different behaviour similar to what was observed with the free ligands. Addition of TBA *p*-methoxybenzoate to DMSO solutions of **2** or **5** gave rise in each case to two different 1:1 complexes, corresponding very likely to the two different thiourea rotamers originally present in solution. Thus, as it can be seen in Figure 7 in the case of ligand **2**, four signals are observed for the N–H hydrogen, these signals, as it was expected are

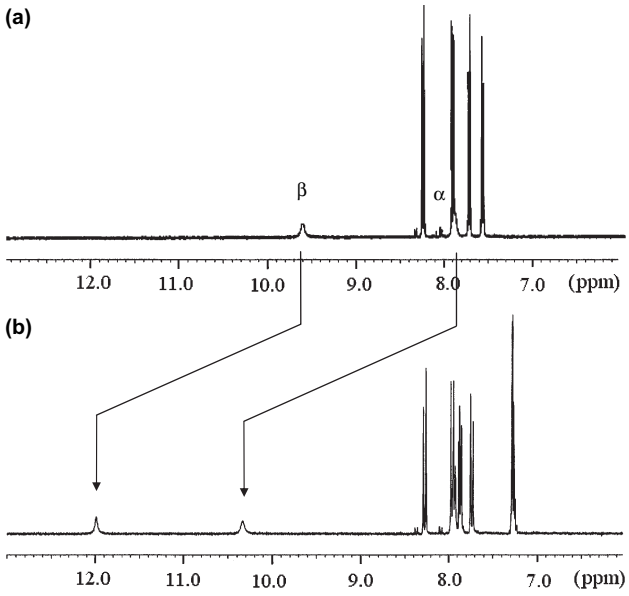

Figure 6. ^{1}H NMR aromatic and amide zone in DMSO-d_6 of: (a) ligand **1** and (b) ligand **1**+1 equiv of TBA benzoate.

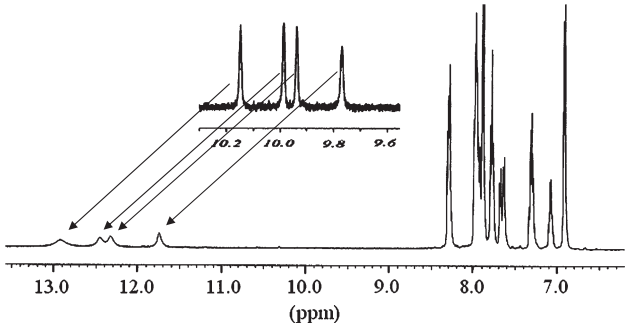

Figure 7. ^{1}H NMR aromatic and amide zone in DMSO-d_6 of ligand **2**+1 equiv of TBA *p*-methoxybenzoate. Inset: NH zone of the free ligand.

downfield shifted as a consequence of the complexation. In addition, NOE′s experiments suggest for one of the complexes the structure shown in Figure 8, which is also in accordance with the structure obtained by PCModel.[16] Of course the system is present in the solution in a dynamic equilibrium containing the four possible complexes. This is in good agreement with the strong shifting observed for the four NH signals in the NMR spectrum. Anyway, what is conclusive is that the two conformations observed in the ligand are also present in the complex. This fact excludes a Y-type complex in this case.

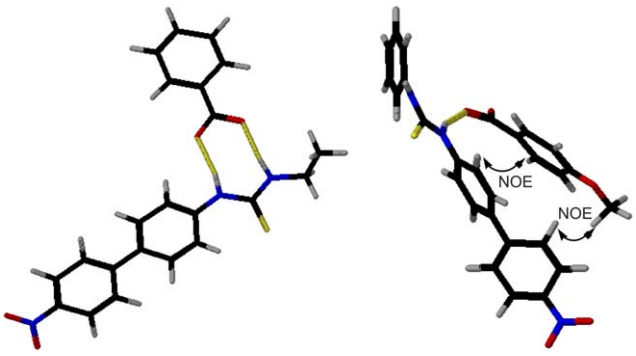

Figure 8. Structural proposal based on PC model 8.0[16] for the complexes between ligands **1** with benzoate (Y-type complex) and **2** with *p*-methoxybenzoate (open complex).

3. Conclusion

A series of biphenyl substituted thioureas have been prepared and their ability to bind aromatic carboxylates has been evaluated by UV–vis titration and NMR experiments. These studies allow us to establish that the geometry of the complexes formed between carboxylate and thiourea receptors is strongly dependent on the substituent in the thiourea group and on their conformational behaviour.[17] Thus, when the ligand is mainly in a *Z,Z* conformation, a Y-type complex can be postulated. By contrast, when other rotamers are present in the solution the geometry of the 1:1 complex can be different with the carboxylate group only bound by one oxygen atom to the more acidic NH atom. Finally, when the thiourea NH groups are acidic enough to give rise to acid–base reactions, strong colour changes are observed with the most basic anions.

4. Experimental

4.1. General procedures and materials

4-Amino-4′-nitrobiphenyl, **7**, was prepared as previously reported, by nitration of 4-nitrobiphenyl with nitric acid followed by partial reduction of the isolated product with sodium hydrogen sulfide.[12] All other reagents were commercially available, and were used without purification. Triethylamine was freshly distilled from CaH_2. THF was distilled from Na/benzophenone under Ar prior to use. Column chromatography was performed with silica gel 60 (230–400 mesh, Merck). Silica gel 60 F254 (Merck) plates were used for TLC. ^{1}H and ^{13}C NMR spectra were recorded with the deuterated solvent as the lock and residual solvent as the internal reference. High-resolution mass spectra (FAB) were recorded in the positive ion mode. UV–vis spectra were recorded using a 1 cm path length quartz cuvette. All measurements were carried out at 293 K (thermostatted).

4.2. Syntheses

4.2.1. *N*-Ethyl-*N*′-(4′-nitro[1,1′-biphenyl]-4-yl)thiourea, 1. Ethylisothiocyanate, **9** (0.24 mL, 2.8 mmol) and dry Et_3N (0.2 mL, 1.4 mmol) were slowly added to a 60 °C solution of 4-amino-4′-nitrobiphenyl, **7** (0.30 g, 1.4 mmol) in THF (3 mL). The mixture was refluxed overnight and then was allowed to reach room temperature. The resulting yellow precipitate was filtered off and dried in vacuum, to give **1** (0.173 g, 42%) as a yellow powder. Mp: 214–216 °C. IR (KBr): 3370 (NHEt), 3145 (NHAr), 2986 (Ar), 1594 (C=C), 1510 (N=O), 1524 (N=O), 1344 (C=S), 850 (C–N) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.67 (br s, 1H, NH), 8.29 (d, J=8.9 Hz, 2H), 7.95 (br s, 1H, NH), 7.94 (d, J=8.9 Hz, 2H), 7.76 (d, J=8.6 Hz, 2H), 7.64 (d, J=8.6 Hz, 2H), 3.52 (q, J=7.0 Hz, 2H), 1.15 (t, J=7.0 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 180.0, 146.2, 146.1, 140.6, 132.6, 127.4, 127.2, 124.1, 122.7, 38.7, 14.1. Anal. calcd for $C_{15}H_{15}N_3SO_2$: C, 59.78%; H, 5.02%;

N, 13.94%; S, 10.62%. Found: C, 59.15%; H, 4.94%; N, 13.66%; S, 10.23%. HRMS (FAB): calcd for $C_{15}H_{15}N_3SO_2$: 301.116; found: 301.094.

4.2.2. *N*-(4′-Nitro[1,1′-biphenyl]-4-yl)-*N*′-phenylthiourea, 2. In a similar way, **2** was prepared from **7** (1.4 g, 6.09 mmol), phenylisothiocyanate, **10** (0.75 mL, 6.3 mmol) and Et_3N (0.9 mL, 6.3 mmol) in refluxing THF (12 mL) for 4 h. The yellow precipitate was filtered off and purified by column chromatography on silica gel (CH_2Cl_2) to yield **2** as a pale yellow solid (1.47 g, 70%). Mp 175–177 °C. IR: 3203 (NH), 1348 (C=S), 1594 (NO_2), 1513 (C=C), 830, 730. ^{1}H NMR (DMSO-d_6, 400 MHz): (mixture of conformers) δ 10.16, 10.00, 9.94, 9.78 (2NH), 8.30 (d, J=8 Hz, 2H), 7.98 (m, 2H), 7.80 (m, 2H), 7.70 (m, 2H), 7.49 (m, 2H), 7.34 (m, 2H), 7.14 (m, 1H). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 179.4, 146.3, 146.1, 140.6, 140.5, 139.4, 139.3, 133.3, 133.1, 128.5, 128.4, 127.4, 127.3, 124.5, 124.4, 124.1, 123.6, 123.5. HRMS (FAB) calcd for $C_{19}H_{15}N_3O_2S$: 349.406; found: 349.401.

4.2.3. *N*-(4′-Nitro[1,1′-biphenyl]-4-yl)-*N*′-(4-nitrophenyl)-thiourea, 3. This compound was prepared from **7** (1.5 g, 7.0 mmol), *p*-nitrophenylisothiocyanate, **11** (1.26 g, 7.0 mmol) and Et_3N (1.0 mL, 7.0 mmol) in THF (20 mL) as described above. The solvent was partially evaporated, giving rise to an orange precipitate, which was filtered off and dried in vacuum (1.49 g, 54%). Mp 217–219 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.50 (br d, 2H, 2NH), 8.30 (d, J=9.0 Hz, 2H), 8.22 (d, J=9.2 Hz, 2H), 7.97 (d, J=9.0 Hz, 2H), 7.87–7.80 (m, 4H), 7.69 (d, J=8.7 Hz, 2H). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 179.1, 146.4, 146.2, 146.0, 142.4, 140.0, 133.8, 127.5, 127.4, 124.4, 124.2, 123.7, 121.7. HRMS (FAB) calcd for $C_{19}H_{15}N_3O_2$: 394.400; found: 394.403.

4.2.4. *N*-(4′-Nitro[1,1′-biphenyl]-4-yl)-*N*′-(4-methoxyphenyl)thiourea, 4. *p*-Methoxy phenylisothiocyanate **12** (0.25 mL, 1.8 mmol), Et_3N (0.2 mL, 0.14 mmol) and TBAF (1 M in THF, 20 μL) were added to a refluxing solution of **7** (0.39 g, 1.8 mmol) in THF (15 mL). After 20 h of refluxing, another equivalent of **12** was added to the reaction mixture, and the reflux was maintained for another 20 h. The solvent was evaporated and the crude product was purified by column chromatography on silica gel (hexane–EtAcO) to give **4** as a yellow solid (0.27 g, 40%). Mp 178–182 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.83 (s, 1H, NH), 9.76 (s, 1H, NH), 8.29 (d, J=9.0 Hz, 2H), 7.96 (d, J=9.0 Hz, 2H), 7.78 (d, J=9.0 Hz, 2H), 7.68 (d, J=9.0 Hz, 2H), 7.35 (d, J=9.0 Hz, 2H), 6.92 (d, J=9.0 Hz, 2H), 3.75 (s, 3H). ^{13}C NMR (DMSO-d_6, 100.5 MHz): δ 179.7, 156.6, 146.3, 146.1, 140.7, 133.3, 133.0, 132.0, 127.3, 126.0, 124.1, 123.5, 113.7, 55.2. HRMS (FAB) calcd for $C_{20}H_{17}N_3O_3S$: 379.543; found: 379.547.

4.2.5. *N*-(1,1′-Biphenyl-4-yl)-*N*′-phenylthiourea, 5. Phenylisothiocyanate (0.22 mL, 1.77 mmol) and Et_3N (0.26 mL) were added dropwise to a 70 °C solution of **8** (0.30 g, 1.77 mmol) in THF (10 mL) and the mixture was refluxed for 48 h. The solvent was evaporated under reduced pressure, and the residue was treated with a 1:1 mixture of hexane–ether to give a white precipitate, which was filtered off and dried in vacuum to yield **5** as a white powder (0.39 g, 86%). Mp 158–160 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.91 and 9.87, 9.80 (3×s, 2H, 2NH), 7.70–7.10 (m, 14H). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 179.6, 139.7, 139.5, 139.4, 136.0, 129.3, 129.0, 128.4, 127.2, 126.6, 126.4, 124.4, 123.6. HRMS (FAB) calcd for $C_{19}H_{16}N_2S$: 304.103; found: 304.104.

4.2.6. *N*-(1,1′-Biphenyl-4-yl)-*N*′-(4-nitrophenyl)thiourea, 6. Reaction of **8** (0.30 g, 1.5 mmol), **11** (0.27 g, 1.5 mmol) and Et_3N (0.26 mL) in refluxing THF (6 mL) for 24 h, gave **6** (0.48 g, 91%) as a white powder. Mp 184–187 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.43 (br s, 2H, 2NH), 8.22 (d, J=9.0 Hz, 2H), 7.86 (d, J=9.0 Hz, 2H), 7.70–7.58 (m, 6H), 7.47 (t, J=7.9 Hz, 2H) and 7.35 (t, J=7.2 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 179.1, 142.3, 139.6, 138.4, 136.6, 129.0, 127.3, 126.8, 126.5, 126.4, 124.4, 123.9, 121.6. HRMS (FAB): calcd for $C_{19}H_{15}N_3O_2S$, 350.0963; found: 350.0970.

4.3. Binding studies

Binding constants of ligands **1**–**6** toward tetrabutylammonium carboxylates were evaluated by UV–visible titrations in DMSO. Typically, 10^{-4} M solutions of the receptors in DMSO (3 mL) were titrated by adding 2 μL aliquots of the envisaged carboxylates (as their TBA salts) in DMSO and registering the UV–visible spectrum after each addition. Log K_c was calculated by fitting all spectrophotometric titration curves with the SPECFIT program.[18]

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