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Relationship between ligand conformations and complexation properties in ditopic biphenyl thioureas

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Abstract—Four new homoditopic biphenyl thiourea derivatives have been prepared to be used in carboxylate sensing. Experiments carried out with these ligands have demonstrated that the conformation of the free ligand has a strong influence on both complex stoichiometry and geometry. High equilibrium constants were obtained in DMSO.

1. Introduction

The development of selective and sensitive chemosensors for anions, especially carboxylates and dicarboxylates, is a topic that is currently of interest.[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. However, few heteroditopic ligands have been described to recognize this type of anions.[4] Despite the many efforts made to understand the complexation mechanism with these binding motifs, mainly to distinguish real complexation processes from proton transfer reactions,[5] less interest has been directed towards clearly establishing the geometry of the formed complexes. It is, in general, assumed that thioureas bind to carboxylates through a double hydrogen bond, which involves both N–H fragments of the thiourea and both carboxylate oxygens in a Y-type bidentated complex (Chart 1).[1b,2d,3b,6] In most cases, geometries for thioureas and carboxylate complexes are proposed on the sole basis of this postulate.[1a–c] Our group has been interested in the geometry of the complexes formed between aliphatic and aromatic mono-carboxylates with mono-thioureas derived from biphenyl and we have recently reported that the Y-type geometry for these complexes should not be proposed as general and that other factors such as conformational equilibria, or dimerization processes or even steric hindrances should be considered.[7]

Following this topic, we report herein the synthesis of homo- and heteroditopic neutral carboxylate receptors **1**–**4** (Chart 2) based on bis-thioureas and macrolactones attached to a biphenyl system. Due to the presence of two anion binding points in these receptors our interest has been directed towards α,ω-dicarboxylates. These target anions were chosen in order to evaluate the influence that the length of the aliphatic chain could have in complexation stoichiometry. Thus, 1:1 complexes could be expected with the longer dicarboxylates whereas we expected that a 1:2 stoichiometry should be more favourable with the dicarboxylates presenting shorter chains. This possible different behaviour could give rise to same selectivity in base on the length of the aliphatic chain in the studied dicarboxylates. In addition, some control experiments with acetate were carried out. Finally, influence showed by the crown moiety could be explored by using different contra-ions (TMA, NH_4^+, Na^+).

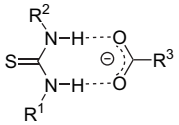

Chart 1.

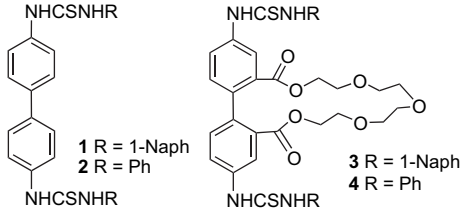

Chart 2.

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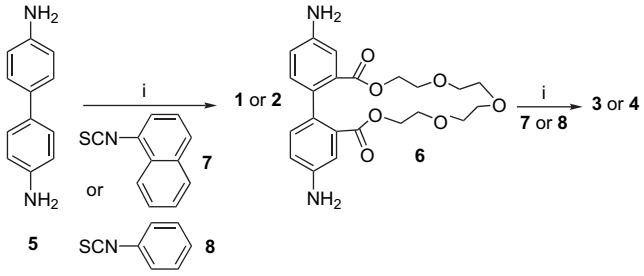
2. Results and discussion

2.1. Synthesis and conformational studies of receptors 1–4

Biphenyl thiourea derivatives were prepared from 4,4′-diaminobiphenyl (**5**) or the macrolactone **6**[8] and the corresponding isothiocyanates (**7** and **8**) in refluxing THF. All compounds were characterized by NMR and MS (Scheme 1).



Scheme 1. Synthesis of receptors **1**–**4**. (i) Et_3N, THF, reflux.

Thiourea derivatives in solution can adopt three different conformations (*E*–*Z*, *Z*–*E* or *Z*–*Z*), all of them of a similar energy, with the size of the substituents in the thiourea group being responsible for the main conformation in each case.[6c,9] ^{1}H NMR studies carried out with ligands **1**–**4** in DMSO have demonstrated that the interchange among the different conformations is slow in the NMR time scale and that there is a main conformation for each ligand. Thus, only one set of resonance is observed in the ^{1}H NMR spectra in DMSO-d_6 for ligand **1**, indicating that there is only one predominant thiourea rotamer in solution (Fig. 1a). The behaviour of ligand **2** was similar, even though a very small amount of a second conformation was detected (Fig. 1b). Finally, the ^{1}H NMR spectra in DMSO-d_6 of ligands **3** and **4**, with the macrolactone attached to the biphenyl system, are more complicated (Fig. 1c for ligand **3**, and Fig. 1d for ligand **4**), showing at least two sets of signals for each ligand. These results indicate that two different conformations of the thioureas are present in solution. Additional NMR experiments were carried out to know which conformations were present in solution in each case. Thus, NOESY experiments showed that the *Z*,*Z* rotamer of thiourea **1** is mainly present in DMSO solutions. In addition, weak NOE intermolecular correlations also suggest that some degree of aggregation in solution occurs under the experimental conditions as it has been observed in related compounds.[10]

By contrast, ligand **2** in solution presents the *Z*,*E* conformation shown in Chart 3, which is likely due to the smaller size of the phenyl group, which gives rise to lower steric hindrances. Finally, the main conformation shown by ligands **3** and **4** is the *E*,*Z* conformation (Chart 3). Apparently, the possibility of hydrogen bonding interactions with the thiourea NH places the crown moiety in between both aryl (phenyl or naphthyl) groups. Furthermore, there is also another conformation present under these conditions (*Z*,*E* for ligand **3** and *Z*,*Z* for ligand **4**).

2.2. Complexation studies

The ability of ligands **1**–**4** for complexing α,ω-dicarboxylates was studied by UV titrations. The complexes' stoichiometries as well as the complexation constant values for oxalate, succinate and adipate were determined. They are summarized in Table 1. These α,ω-dicarboxylates were prepared as their tetramethylammonium (TMA) salts from the corresponding carboxylic acids and TMA hydroxide in DMSO.

As seen in Table 1 the number of methylene groups in the aliphatic chain of the α,ω-dicarboxylate has a slight influence on the complexation constants. These results agree with complexes' structures where only one carboxylate is involved in complexation as proposed above.

2.2.1. Complexation studies with ligands 1 and 2. The anion binding ability of receptors **1** and **2** was evaluated by the UV–vis titration of each receptor with the appropriate anion in DMSO solution. These experiments showed that ligands **1** and **2** display different behaviours upon the addition of dicarboxylates (Fig. 2). After the addition of TMA succinate to a solution of ligand **1** (Fig. 2a; for oxalate and adipate, see the Supplementary data), the band at 315 nm, typical of the biphenyl chromophore undergoes a red shift. A plot of molar absorbance at 334 nm indicates only the formation of a 1:1 complex, even in the presence of a large excess of anion (10 equiv). As geometric reasons preclude both

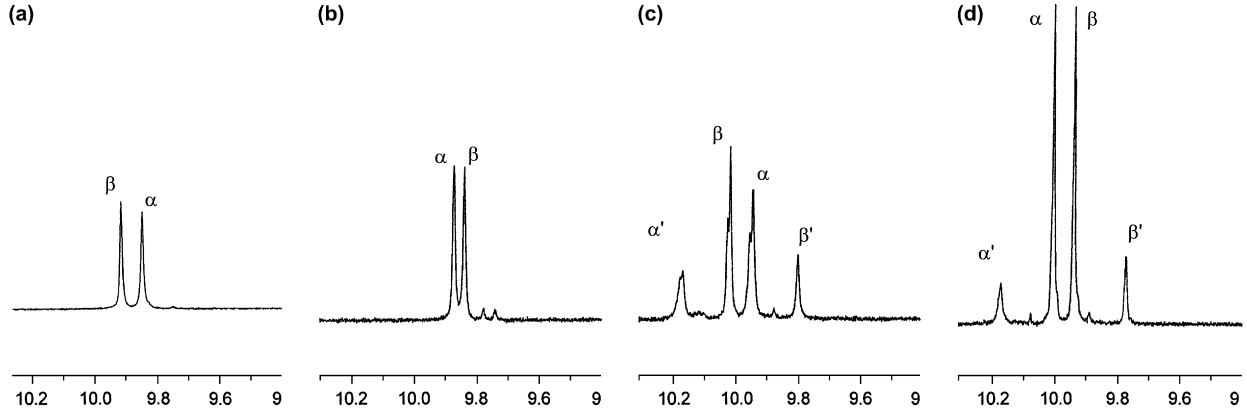


Figure 1. H–N ^{1}H NMR signals of **1** (a), **2** (b), **3** (c) and **4** (d) in DMSO-d_6.

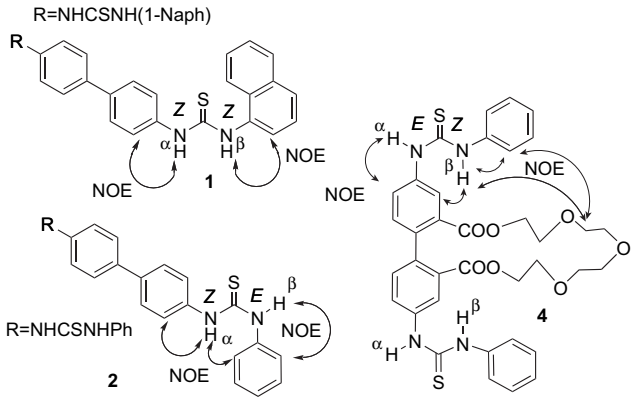


Chart 3. Main conformations of **1**, **2** and **4** in DMSO-d_6 solution.

thiourea groups to be simultaneously involved in a 1:1 complex, one thiourea moiety will remain uncomplexed. Control experiments were carried out with TBA acetate to confirm that the effect is due only to the ligand and not to the studied dicarboxylates. Once more, only the 1:1 complex was formed even with a large excess of anion (see Supplementary data). This behaviour can only be explained if the aggregation shown by this ligand in DMSO was so strong that only one thiourea was free to form complexes with the anions.

Under the same conditions ligand **2** shows a different behaviour (Fig. 2b). The UV spectrum of the free ligand showed a main band at λ=317 nm (corresponding to the biphenyl moiety) and a shoulder at 298 nm (corresponding to the phenyl moiety). Upon TMA succinate addition, the band at 298 nm remained unchanged, but the band at 317 nm clearly underwent a red shift. In addition, the complex stoichiometry was 2:1 (L_2A) in this case, even though a new species seems to appear at higher anion concentrations. Control experiments with TBA acetate also showed the expected red shift of the band at 317 nm (see Supplementary data). Also with this anion the complex stoichiometry was 2:1 (L_2A) and in this case, a new complex was formed under addition of increasing amounts of anion with a 1:2 stoichiometry.

Table 1. Stoichiometries and log β values for receptors **1**–**4** with dicarboxylates, in DMSO at 25 °C[a]

Anion[b]		Receptor			
		1	**2**	**3**	**4**
$^{-}$OOC–COO^{-}	L:A	1:1	2:1	2:1	2:1
	log β	5.6±0.2	9.4±0.2	9.4±0.3	8.5±0.2
$^{-}$OOC–$(CH_2)_2$–COO^{-}	L:A	1:1	2:1	2:1	2:1
	log β	6.2±0.3	9.0±0.2	9.5±0.3	8.1±0.2
$^{-}$OOC–$(CH_2)_4$–COO^{-}	L:A	1:1	2:1	2:1	2:1
	log β	5.8±0.4	10.3±0.3	9.8±0.2	8.9±0.2

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

The different complexation behaviours observed with ligands **1** and **2** could be related to the different conformations shown by these ligands and also to the aggregation shown by ligand **1**. Thus, whereas ligand **1** is able to form the classical Y-type complex with the carboxylate (Chart 1), at least two ligand molecules are required with ligand **2**, due to its *Z*,*E* conformation, to contribute with the two NH groups that seem to be essential to form a stable complex. Both thiourea groups in each molecule could be involved in complexation in the presence of higher amounts of the anion giving rise to L_2A_3 or LA_2 complexes, respectively, depending on the anion used.

^{1}H NMR studies were undertaken to obtain additional information about the structure of the different complexes in solution.

^{1}H NMR studies carried out with ligand **1** showed that changes in the spectrum were observed upon the addition of 2 equiv of TMA succinate (Fig. 3). Signals arising from both the biphenyl and the naphthyl protons show strong shifts. This coincides with a Y-type complex where both NH are involved in complexation. In addition, intermolecular NOEs between the biphenyl and naphthyl protons suggest that the aggregation of two ligands is maintained in the complex. These observations, along with the fact that stoichiometry and complexation constants are almost insensitive to the chain length of the dicarboxylate, suggest that only one carboxylate is involved, and leads us to propose the geometry depicted in Figure 4. The control ^{1}H NMR experiments carried out with TBA acetate showed a completely

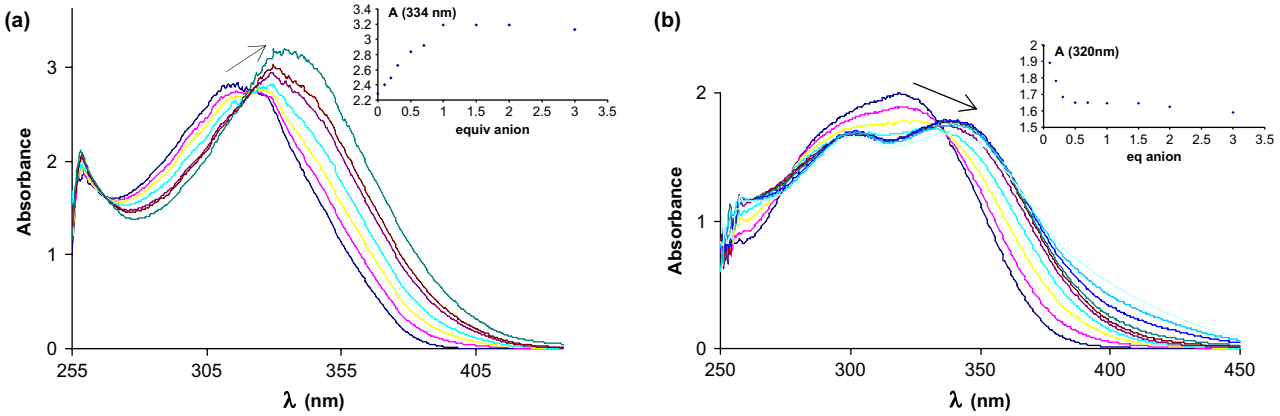


Figure 2. UV–vis absorption spectrophotometric titration of ligands **1** and **2** with TMA succinate in DMSO at 25 °C. Inset: stoichiometry determination for **1**·**TMA** succinate at 320 nm, **2**·**TMA** succinate at 334 nm.

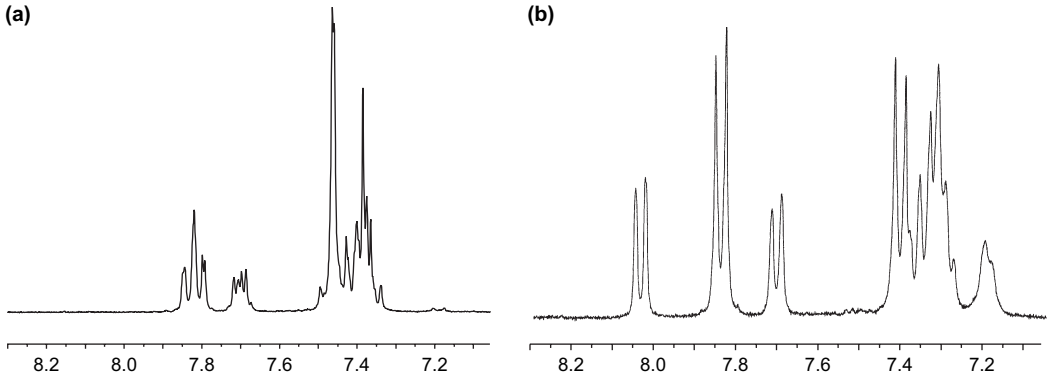


Figure 3. Aromatic zone of the ^{1}H NMR spectra (DMSO-d_6) of ligand **1**: (a) free, (b) upon addition of an excess of TMA succinate.

similar pattern to that showed by the studied dicarboxylates indicating that also with this anion the association of the ligand is present and Y-type complexes are formed by the free thiourea moieties.

Ligand **2** shows small upfield shifts for both the phenyl and the biphenyl hydrogen atoms upon addition of 0.5 equiv of all the studied anions (oxalate, succinate, adipate and acetate). However, the largest modifications were observed for the biphenyl moiety because those signals in the free ligand appear as two different doublets, yet they lead to a broad singlet on complexation (see Fig. 5 for succinate and Supplementary data for the other anions).

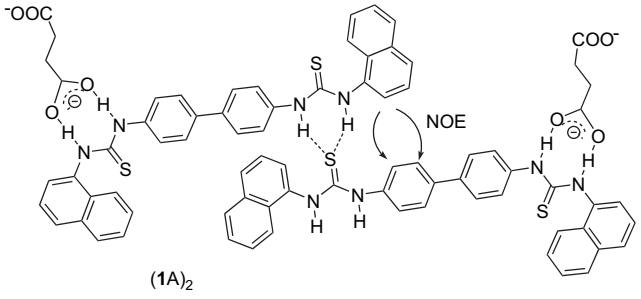


Figure 4. Structural proposal for the complexes between ligand **1** and excess of TMA succinate.

This would be in accordance with the structural proposal shown in Figure 6 where the rotation of the aromatic rings in the biphenyl systems might be hindered by the proximity of the second molecule involved in complexation. In addition, this geometry could also provide an explanation to the UV spectrum where only the band corresponding to the biphenyl moiety seems to be shifted.

Larger modifications were observed in the ^{1}H NMR spectrum when 2 equiv of TMA succinate is present. Then, the strong upfield shift also involves phenyl protons. When compared to the free ligand, global upfield shifts are $\Delta\delta$=0.33, 0.27, 0.23, 0.28 and 0.46 ppm for H_a, H_b, H_c, H_d and H_e, respectively (Fig. 5c). These strong modifications could be due to deprotonation processes what are in accordance with the results obtained with this ligand in the presence of TBAOH (see Supplementary data).

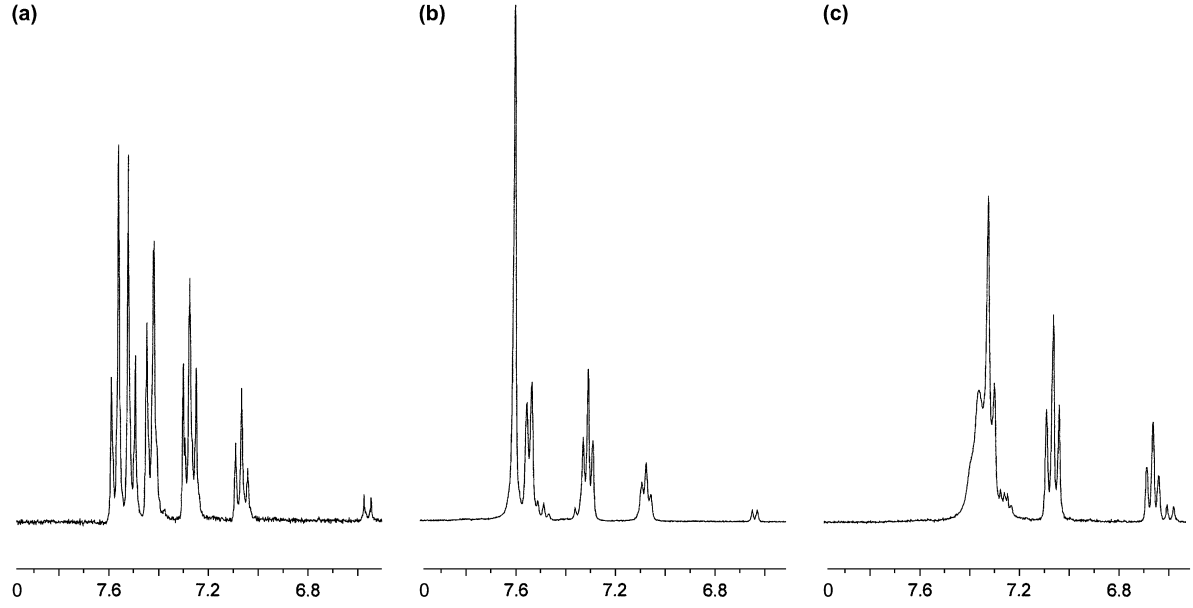


Figure 5. Aromatic zone of the ^{1}H NMR spectra (DMSO-d_6) of ligand **2**: (a) free, (b) upon addition of 0.5 equiv TMA succinate and (c) in the presence of 2 equiv of TMA succinate.

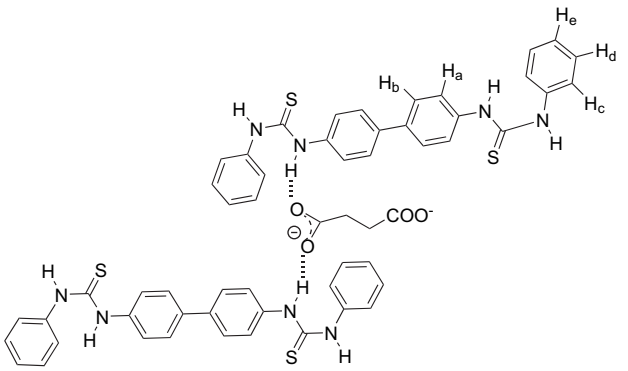


Figure 6. Structural proposal for the complexes between ligand **2** and 0.5 equiv of TMA succinate.

By contrast, the results obtained after the addition of 2 equiv of TBA acetate demonstrated that this anion is not basic enough to cause the deprotonation reaction. Thus, in this case, downfield shifts were observed ($\Delta\delta$=0.10 and 0.16 ppm for H_a, and H_c, respectively). These changes clearly support that, in the newly formed complex LA_2, both NH groups are involved in the complexation to the acetate, which implies a conformational change in the ligand (Fig. 7b).

Finally, fluorescence studies were carried out with these ligands and the studied anions. Nonetheless no modification in the emission spectra was induced in any case.

2.2.2. Complexation studies with ligands 3 and 4. Similar studies were carried out with ligands **3** and **4** to know the influence that the crown moiety has on the complexation with this type of ligands. Figure 8 shows the UV titration experiments with TMA succinate in DMSO at 25 °C.

The UV spectrum of ligand **3** presents a main band at 315 nm with a fine structure, which corresponds to the naphthyl thiourea and a shoulder at 346 nm corresponding to the biphenyl moiety. After complexation, only the biphenyl band is modified, which agrees with a complex involving only this type of NH groups. Two ligand molecules should be involved to therefore achieve a stable complex given the observed L_2A stoichiometry. Ligand **4** displays a similar behaviour. In this case the UV spectrum shows a band at 285 nm corresponding to the thiourea phenyl part and a shoulder at 335 nm due to the biphenyl. Only the biphenyl moiety was modified after the carboxylate addition as observed with ligand **3**.

Complexes with a higher stoichiometry or deprotonated species were never observed with these ligands even in the presence of a high concentration of anion (10 equiv). This behaviour could be due to a hydrogen bond between NH^{β} and the crown moiety. This can stabilize a conformation similar to that described for the free ligand (Chart 3) that precludes the conformational change observed with ligand **2** and excess of some of the carboxylates.

In addition, UV experiments carried out with ligands **3** and **4** upon addition of ammonium and sodium acetates demonstrated that the presence of the lactone cavity has a slight influence on the complexation constants.

^{1}H NMR studies carried out with these ligands in the presence of the studied anions were not conclusive given the broadness of the signals in the spectra.

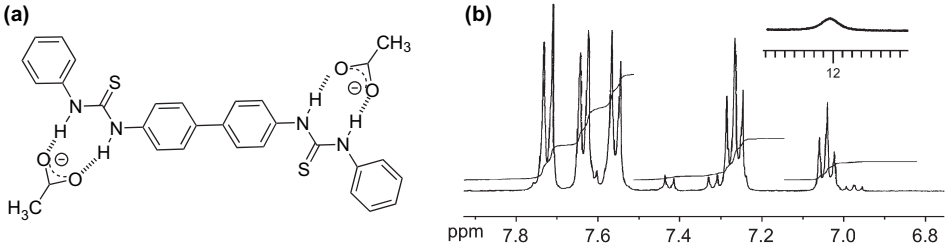


Figure 7. (a) Structural proposal for the complexes between ligand **2** and 2 equiv of TBA acetate. (b) Aromatic zone of the ^{1}H NMR spectra (DMSO-d_6) of ligand **2** upon addition of 2 equiv of TBA acetate.

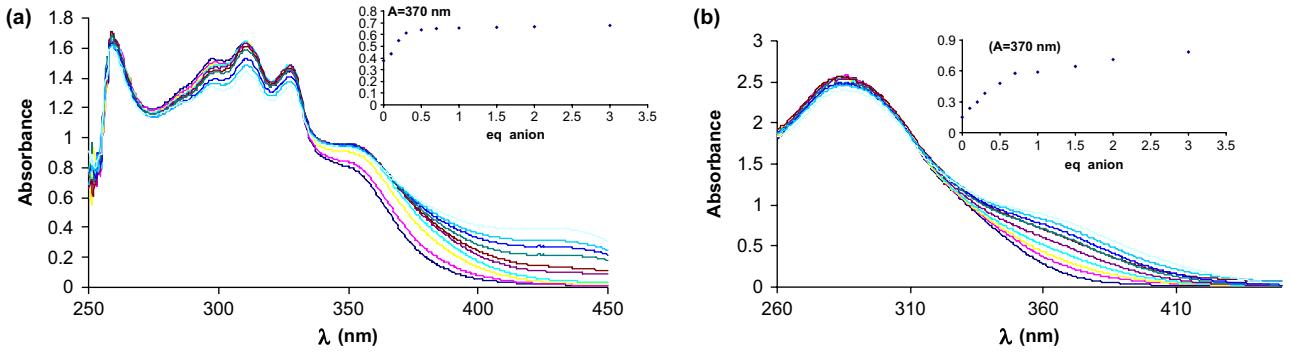


Figure 8. UV–vis absorption spectrophotometric titration of ligands (a) **3** and (b) **4** with TMA succinate in DMSO at 25 °C. Inset: stoichiometry determination for **3**·**TMA** succinate at 370 nm and **4**·**TMA** succinate at 370 nm.

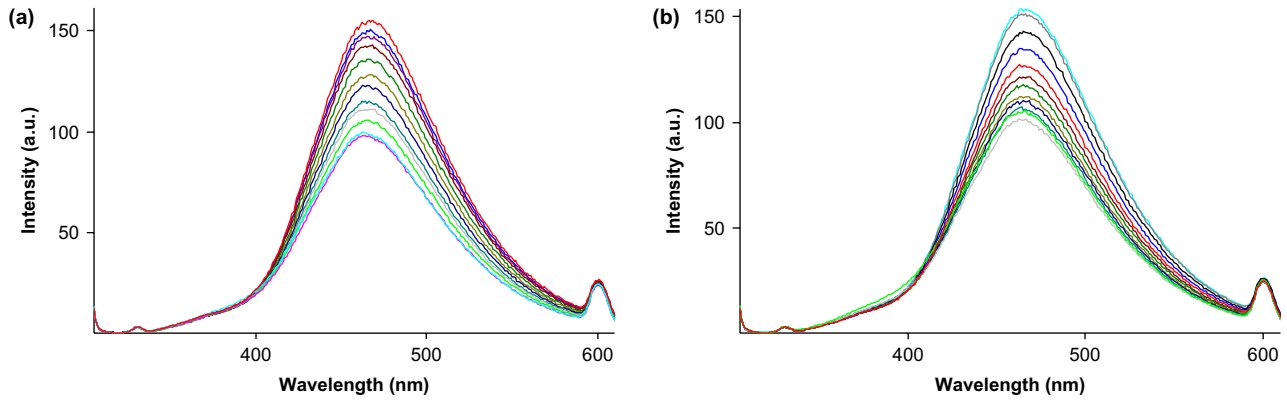


Figure 9. Fluorescence titration of ligand **3** in DMSO (a) with TMA oxalate and (b) with TMA adipate.

Finally, fluorescence studies carried out with ligands **3** and **4** showed that a quenching of the fluorescence was induced by the anions. However, this quenching was insensitive to the length of the chain in the α,ω-dicarboxylate (Fig. 9 for ligand **3**; for ligand **4** see Supplementary data).

3. Conclusion

A series of biphenyl dithioureas have been prepared. Their conformation in DMSO solutions has been studied by proton NMR and their ability to bind α,ω-dicarboxylates and acetate has been evaluated by UV–vis titration, fluorescence and NMR experiments. These studies allow us to establish that not only the geometry but also the stoichiometry of the complexes formed between these carboxylates and the thiourea receptors is strongly dependent on their conformational behaviour. Thus, when the ligand is mainly in a *Z*,*Z* conformation, a Y-type complex can be postulated. By contrast, the stoichiometry of the complex is 2:1 when other rotamers are present in the solution. In addition, deprotonation reaction has been observed in ligand **2** in the presence of an excess of α,ω-dicarboxylates whereas the less basic anion acetate did not give rise to this process and the corresponding 1:2 complex was observed. When strong aggregation is present in the ligand (ligand **1**) neither deprotonation reaction nor complexes with higher stoichiometries were observed. Our experiments allow us to affirm that both the substituent in the thiourea moiety and the presence of the macrolactone have a strong influence on complexation and on the properties of the prepared ligands. Finally, the three α,ω-dicarboxylates studied presented a similar spectroscopic behaviour which precludes ligands **1**–**4** to be used as selective sensors.

4. Experimental

4.1. General procedures and materials

Compound **6** was prepared as previously reported.[8] 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 F_{254} (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). Fluorescence spectra were carried out in a Varian Cary Eclipse Fluorimeter.

4.1.1. Syntheses.

4.1.1.1. 4,4′-Bis-(naphthylthiourea)biphenyl, 1. Benzidine (1.0 g, 5.4 mmol) in dry THF (30 mL) was heated till the reflux was achieved. Then, 1-naphthylisocyanate (2 equiv, 2.0 g, 10.8 mmol) was added. A white precipitate was appearing as the dithiourea was formed. After refluxing for 2 h the reaction was left to room temperature. The resulting white solid was filtered and 50 mL of hexane was added to the solution of THF, where the rest of the dithiourea precipitated. After filtration both solids were joined and dried in vacuum to yield **1** (2.64 g, 88%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.92 (br s, 2H, 2NH), 9.85 (br s, 2H, 2NH), 8.01–7.96 (m, 8H), 7.90–7.80 (m, 4H), 7.63–7.50 (m, 10H). ^{13}C NMR (DMSO-d_6, 100.5 MHz) δ (ppm): 181.2, 138.9, 135.7, 135.1, 134.0, 130.0, 128.2, 126.8, 126.3, 126.1, 126.0, 125.7, 125.4, 124.3, 123.2. HRMS (FAB^+): found 555.1675; $C_{34}H_{27}N_4S_2$ (MH^+) required 555.1677.

4.1.1.2. 4,4′-Bis-(phenylthiourea)biphenyl, 2. Benzidine (1.0 g, 5.4 mmol) in dry THF (30 mL) was heated to reflux. Then, phenylisothiocyanate (1.3 mL, 12.5 mmol) was dropped during 1 h. A white solid appeared immediately. The reaction was heated for 3 h. When room temperature was achieved, the solution was poured over 40 mL of hexane, and kept in the fridge for 24 h. The white solid was filtered and dried in a vacuum pump to give **2** (1.28 g, 52%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.87 (s, 2H, 2NH), 9.84 (s, 2H, 2NH), 7.64 (d, J=8.8 Hz, 4H), 7.57 (d, J=8.8 Hz, 4H), 7.50 (d, J=8.7 Hz, 4H), 7.34 (t, J=7.9 Hz, 4H), 7.14 (t, J=7.2 Hz, 2H). ^{13}C NMR (DMSO-d_6, 100.5 MHz) δ (ppm): 179.8, 139.5, 138.7, 135.5, 128.4, 126.3, 124.4, 123.8, 123.6. HRMS (FAB^+): MH^+ found: 455.1357. $C_{26}H_{23}N_4S_2$ required 455.1364.

4.1.1.3. 4,4′-Bis-(naphthylthiourea)-2,2′-macrolactone-biphenyl, 3. In a round bottom flask under argon were

added, in this order, diamine **6** (280 mg, 0.65 mmol), dry THF (30 mL), dry triethylamine (180 mL, 1.3 mmol) and 1-naphthylisocyanate (121 mg, 0.65 mmol). The mixture was heated until reflux and was kept for two days. After the solution was cold, it was poured over hexane (100 mL) and kept in the fridge. The precipitate was filtered and dried to get **3** as a pale pink solid (338 mg, 65%). ^{1}H NMR (DMSO-d_6, 400 MHz) (mixture of conformers) δ (ppm): 10.17 and 9.80 (br s, NH), 10.01 and 9.94 (br s, NH), 8.07–7.90 (m, 6H), 7.88–7.83 (m, 4H), 7.69–7.55 (m, 8H), 7.16–7.11 (m, 2H), 4.12–4.02 (m, 4H), 3.55–3.32 (m, 12H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 182.1, 166.4, 138.7, 138.3, 134.8, 133.9, 129.9, 129.0, 128.1, 126.9, 126.2, 126.1, 125.9, 125.6, 125.3, 124.8, 123.0, 70.1, 69.8, 67.8, 63.5. HRMS (FAB$^+$): found 801.2475. $C_{44}H_{41}N_4O_7S_2$ (MH$^+$) required 801.2417.

4.1.1.4. 4,4′-Bis-(phenylthiourea)-2,2′-macrolactone-biphenyl, 4. In a similar way, from diamine **9** (260 mg, 0.6 mmol), dry triethylamine (173 μl, 1.2 mmol) in THF (45 mL) and phenylisocyanate (144 μl, 1.2 mmol), **4** was prepared as a yellow solid (240 mg, 57%). ^{1}H NMR (DMSO-d_6, 300 MHz) (mixture of conformers) δ (ppm): 10.22 and 9.80 (br s, NH), 10.04 and 9.97 (br s, NH), 8.09 (s, 2H), 7.81 (d, J=8.3 Hz, 2H), 7.52 (d, J=7.8 Hz, 4H), 7.36 (t, J=7.8 Hz, 4H), 7.17–7.13 (m, 4H), 4.10–3.98 (m, 4H), 3.54–3.35 (m, 12H). ^{13}C NMR (CD_3CN, 100 MHz) δ (ppm): 179.7, 165.9, 139.3, 138.6, 138.3, 130.3, 129.2, 128.6, 126.4, 124.4, 123.6, 70.1, 69.8, 67.8, 63.5. HRMS (FAB$^+$): found 700.2020. $C_{36}H_{36}N_4O_7S_2$ (MH$^+$) required 700.2025.

4.1.2. Binding studies. Binding constants of ligands **1**–**4** towards tetramethylammonium dicarboxylates were evaluated by UV–vis 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 dicarboxylates (as their TMA salts) in DMSO and registering the UV–vis spectrum after each addition. The value of log K_c was calculated by fitting all spectrophotometric titration curves with the SPECFIT program [SPECFIT/32 Global Analysis System v. 3.0, Spectrum Associates (Marlborough, MA, USA), www.bio-logic.info/rapid-kinetics/specfit.html].

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Supplementary data

^{1}H NMR of ligands **1**–**4** in DMSO-d_6; ^{13}C NMR of ligands **1** and **2** in DMSO-d_6; UV titrations of ligands **1**–**4** with TMA oxalate and adipate (from 0 to 3 equiv). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.05.082.

References and notes

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