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Tetrahedron
Tetrahedron 61 (2005) 4081–4089

Thioamides versus amides in anion binding

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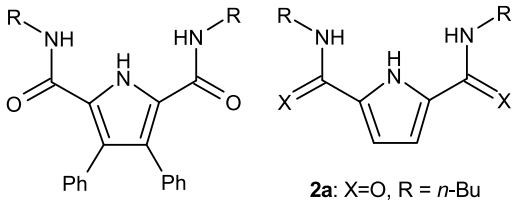
Received 24 November 2004; revised 24 January 2005; accepted 10 February 2005

Abstract—Amide and thioamide derivatives of the 1*H*-pyrrole-2,5-dicarboxylic acid have been synthesised. Properties of these simple anion receptors and their behaviour in the presence of anions have been studied both in solution and in the solid state. The results allowed to compare anion complexation properties of thioamides versus their amide analogues.

1. Introduction

Among various areas of supramolecular chemistry, coordination of anions has been recently a subject of intensive exploration.[1] Neutral anion receptors play an important role in Nature. For this reason, artificial neutral receptors became an attractive target for studies. These studies have been focused on development of receptors having an increased selectivity and/or binding affinities, and also succeeded in practical application, namely in catalysis,[2] transport through membranes,[3] or anion detection by electrochemical,[4] colorimetric[5] and fluorometric[6] techniques. However, a growing interest in the efficiency and application of neutral receptors has one drawback—a lack of basic, fundamental papers. Without such background it is hard to generalise and consolidate information discussed by various authors. For example, the diversity of titration techniques and solvents used for studies of successive generation of ligands, makes it difficult to analyse a structural influence on anion affinity. Basic studies of simple models[7] provide reference points for more sophisticated systems. In the course of fundamental studies, our group investigated macrocyclic effects,[8] size complementarity[9] and introduced new building blocks.[10] In this paper, we compare the properties of simple amide and thioamide ligands, shown in Scheme 1.

Amide groups are extensively used in neutral anion receptors as hydrogen bond donors.[11] However, they can also act as hydrogen bond acceptors and by participation in intramolecular hydrogen bonds decrease receptor affinity toward anions. Thioamides are readily accessible from amides,[12] and are known to be weaker hydrogen-bond acceptors and stronger acids than amides.[13] For these reasons, thioamides are attractive groups for the construction of anion hosts. Thioamide groups were recently successfully introduced into macrocyclic systems by the research teams of Yamamoto[14] and Bowman-James.[15] During preparation of this manuscript, Gale et al.[16] reported synthesis and complexation properties of furane and thiophene derivatives containing thioamide groups.



1a: R = *n*-Bu
1b: R = Ph

2a: X=O, R = *n*-Bu
2b: X=O, R = Ph
2c: X=O, R = Me
3a: X=S, R = *n*-Bu
3b: X=S, R = Ph
3c: X=S, R = Me

Scheme 1.

For our studies, we decided to take into account simple compounds, a kind of scaffold for the amide and thioamide groups. The model compounds should be able to bind anions strongly enough for determination of binding constants by usual techniques, and, on the other hand, to have simple enough structures for easy data interpretation and computer modelling. Appreciating the important role of the pyrrole moiety in complexation of anions[17] and impressed by the binding constants for diaamidopyrroles **1a** and **1b** found by Gale,[18] we chose pyrrole as a scaffold. In order to minimise

Keywords: Anion binding; Thioamides; Hydrogen bond; Neutral anion receptor.
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doi:10.1016/j.tet.2005.02.029

the disruptive influence of other factors on the comparison of amides versus thioamides, we used 3,4-unsubstituted pyrrole derivatives of type **2** and **3** (Scheme 1). Moreover, our model compounds resemble the known building blocks for neutral anion receptors, i.e. diamides derived from isophthalic acid and 2,6-pyridinedicarboxylic acid.[7d,f]

2. Results and discussion

2.1. Preparation of the model compounds

1*H*-Pyrrole-2,5-dicarboxylic acid **8** was synthesised via previously described procedures starting from pyrrole **4** (Scheme 2). Pyrrole **4** was reacted with phosgene trimer and, subsequently, with methanol leading to ester **5**[19] which was then formylated under Vilsmeier reaction conditions[20] yielding ester **6**. After oxidation of **6**[21] and subsequent hydrolysis of intermediate **7**, the acid **8** was obtained in good yield. This compound was then converted into the acid chloride **9**, which was immediately subjected to reaction with the corresponding amines to afford amides **2a** (72%) and **2b** (92%).

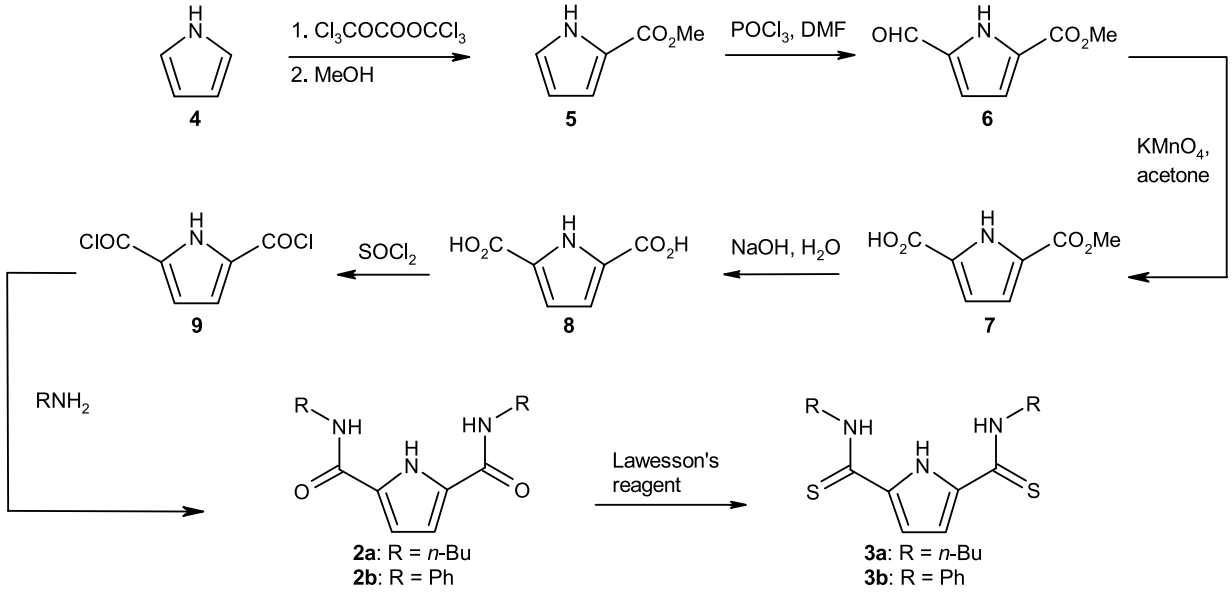
In order to prepare the thioamides, we reacted the amides with the Lawesson's reagent in boiling THF.[12] After easy workup, we got thioamides **3a** and **3b** in good yields (90 and 80%, respectively) as yellow crystals. The thioamides immediately showed their first advantage over amides, they were better soluble in organic solvents (THF, CH_3CN, CH_2Cl_2) then their amide analogues.

2.2. Anion binding by the model compounds

Having prepared our model compounds, we started to investigate their anion binding properties using the ^{1}H NMR titration technique. Upon addition of tetrabutylammonium salts into the solution of ligands type **2** in DMSO-d_6+0.5% H_2O, we observed a downfield shift of the amide protons that allowed us to determine binding constants by applying non-linear curve fitting (Table 1).

Surprisingly, the model amides **2a** and **2b** interact with anions much more weakly than Gale's derivatives of type **1**. For example, the binding constant is 560 M^{-1} for **1b** with benzoate whereas it is only 80 M^{-1} for compound **2b**. Looking for rationalisation of such results, we suspected that maybe inaccuracies in experimental technique (e.g., presence of water in DMSO or processing of the curve fitting) were responsible for such differences. To check this suspicion, we obtained ligand **1b** and carried out ^{1}H NMR titration. The measured stability constants matched the literature data.[18] The ^{1}H NMR amide proton signal of our receptors are shifted downfield relative to phenyl substituted analogues (e.g., 10.12 ppm for **2b** and 9.37 ppm for **1b**), whereas pyrrole N*H* signals are shifted upfield (12.26 ppm for **2b** and 12.67 ppm for **1b**),[18b] so the differences in the binding constants of two families of compounds cannot be interpreted in terms of receptor acidity. It is immediately apparent that phenyl substituents in the pyrrole ring are crucial for effective anion binding. However, currently we are unable to explain this phenomenon.

Despite the fact that our model compounds bind anions more weakly than receptors of type **1**, they show the same selectivity. We observed typical ligand preferences for



Scheme 2.

Table 1. Binding constants (M^{-1}) for the formation of 1:1 complexes of **2a**, **2b**, **3a** and **3b** with various anions in DMSO-d_6+0.5% H_2O at 296 K[a], determined by ^{1}H NMR titration technique

	$PhCOO^-$	$H_2PO_4^-$	Cl^-	Br^-
2a	49	150	1.7	—[b]
2b	80	203	3.8	—[b]
3a	109	139	4.6	—[b]
3b	—[b]	—[b]	11.1	—[b]

[a] Errors are estimated to be <10%. Tetrabutylammonium salts were used as anion sources.
[b] Curve fitting failed (see the text for comments).

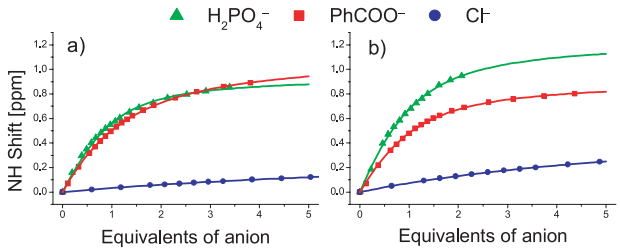


Figure 1. Curves of ^{1}H NMR titration with chloride, benzoate and dihydrogen phosphate in DMSO-d_6+0.5% H_2O: (a) compound **2a**; (b) compound **3a**.

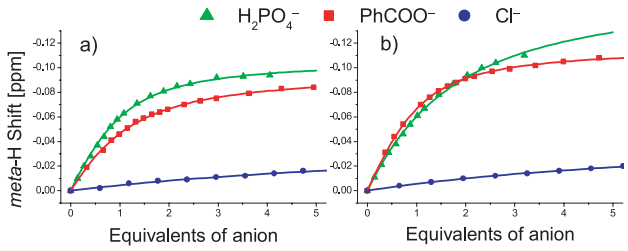


Figure 2. Phenyl meta-H chemical shift during ^{1}H NMR titration with chloride, benzoate and dihydrogen phosphate in DMSO-d_6+0.5% H_2O: (a) compound **2b**; (b) compound **3b**.

anions: dihydrogen phosphate, benzoate over chloride and bromide. Although there is a convention of presenting small association constants as '<5', we decided to report exact values calculated for the chloride anion. These results were obtained with small errors and allowed a comparison with the thioamides. Unfortunately, because of weak interactions with the bromide ion, we were unable to determine the stability constants in this case.

During the ^{1}H NMR titration of compound **3a**, we observed not only a downfield shift of thioamide protons but also severe broadening of the signal. When 2 equiv of dihydrogen phosphate were used, the signal was very wide and concealed in the baseline such that we could not assign its chemical shift. For this reason, we stopped the titration at the molar ratio of the anion to the ligand equal to 2 (Fig. 1). The broadening of the thioamide signal may be a manifestation of several phenomena, such as deprotonation by a basic anion, slow rates of complexation and decomplexation or averaging of thioamide and pyrrole N*H*'s. Unfortunately, we have no experimental data to support any of these hypotheses, however, the signal broadening is usually interpreted as an effect of deprotonation.[16]

Thioamide **3a** has a stronger affinity towards benzoate and chloride than its amide analogue **2a** (Table 1). These anions are bound more than two times stronger by **3a** than by **2a** (Table 2). On the contrary, dihydrogen phosphate seems to be stronger complexed by the amide than by the thioamide. In the case of **3a** titration with bromide, we obtained appropriate data for curve fitting, however, the calculated binding constant was about 1.

Table 2. Ratio between binding constants for thioamides and amides determined by the ^{1}H NMR titration in DMSO-d_6+0.5% H_2O

Ratio of K_a	$PhCOO^-$	$H_2PO_4^-$	Cl^-
3a/2a	2.2	0.9	2.7
3b/2b	2.0[a]	0.4[a]	2.9

[a] Ratio of K_a calculated for *meta* H in phenyl ring; see text for comments.

The above-mentioned broadening of the thioamide proton signal for **3a** was even more pronounced for thioamide **3b**. In experiments with dihydrogen phosphate and benzoate, we could only record a few initial points, insufficient for calculation of K_a. Fortunately, we observed that *meta*-protons in the phenyl ring in aromatic amides gave good response to the presence of anions (Fig. 2). The values of the *meta*-proton chemical shifts in **2b** and **3b** were used for calculations of the binding constants and allowed us to compare thioamide and amide receptors (Table 2). These results are consistent with those described previously for the butyl derivatives **2a** and **3a**.

Although we changed solvent from DMSO to acetonitrile, we still observed broadening of the thioamide proton signals in the presence of anions. We hoped that another approach—UV/Vis titration would allow us more direct comparison of binding abilities of **2b** and **3b**. The estimated binding constants in the DMSO by ^{1}H NMR titration were to small to be measured using UV/Vis technique. For this reason we used the solvent of choice for UV/Vis studies—acetonitrile, in which binding constants are much higher than in DMSO, which is a more competitive medium.

Preliminary experiments revealed interesting feature of the thioamides; in the case of amides **2a** and **2b**, addition of anions into the ligand solutions caused only decreasing of the absorbance, whereas complexation with thioamides **3a** and **3b** resulted in a bathochromic shift (Fig. 3). This observation suggests that maybe some of thioamides can be used as optical sensors for anions.

Results of our UV/Vis studies, carried out in CH_3CN, are summarised in Table 3. Amides and thioamides have approximately the same affinity for the anions. However, it has to be stressed that there was no clear isosbestic point during thioamide titration, which could indicate occurrence of higher order equilibria than 1:1 (Fig. 3e and f). Job plots could not disclose their nature, so we assumed a strong one-to-one complexation and performed curve fitting for the 1:1 model.

Values of binding constants in acetonitrile lead to the question: 'what has happened to the stronger hydrogen bond donor abilities of thioamides?'. Some insight into the problem came from the isothermal titration calorimetry (ITC). Inspection of Table 4 reveals that thioamides indeed interact more strongly with benzoate than amides (more negative ΔH°). However, the binding constants are similar owing to enthalpy/entropy compensation. The values of K_a obtained from UV/Vis and ITC are slightly different but such inconsistency between methods has been observed.[22]

2.3. Structural studies

Structure analysis can reveal important facts about supramolecular systems. For example, investigation of a receptor and its complex structure can confirm proposed binding mode, clarify observed selectivity in terms of geometric fit,

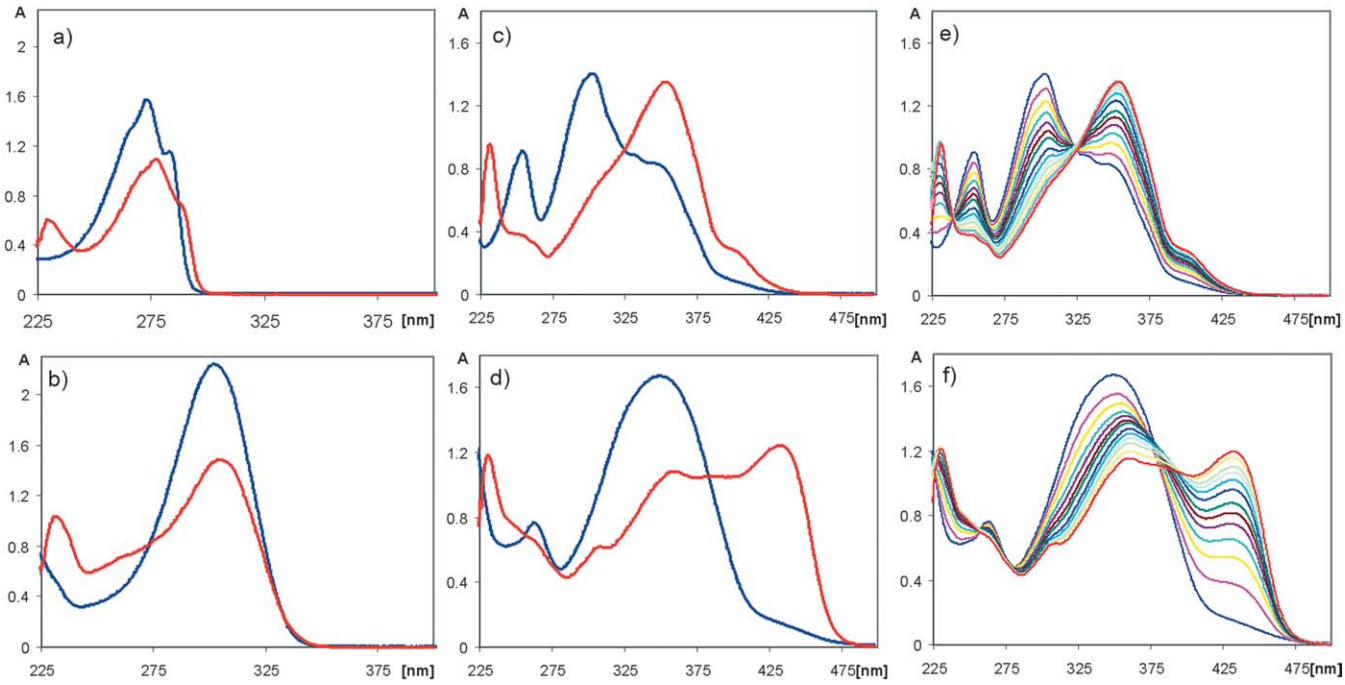


Figure 3. UV/Vis spectra of free ligand (blue) and in the presence of 5 equiv of benzoate (red) for compounds: **2a** (a), **2b** (b), **3a** (c) and **3b** (d). UV/Vis titration experiments in acetonitrile with benzoate for compounds **3a** (e) and **3b** (f).

Table 3. Binding constants (log K_a) in CH_3CN for complexes of **2a**, **2b**, **3a** and **3b** with various anions at 296 K[a], determined by UV/Vis titration technique

	$PhCOO^-$	$H_2PO_4^-$	Cl^-
2a	4.25	4.34	2.94
2b	4.40	3.90	2.77
3a	4.34	3.80	2.90
3b	4.55	3.70	—[b]

[a] Errors are estimated to be $<10\%$. Tetrabutylammonium salts were used as anion sources.
[b] Curve fitting failed.

Table 4. Thermodynamic parameters of binding of benzoate by ligands **2a**, **2b**, **3a**, **3b** in CH_3CN at 296 K, as determined by ITC

	log K_a	ΔH (kJ/mol)	$T\Delta S$ (kJ/mol)
2a	4.25	−11.43	12.66
2b	4.34	−14.71	9.90
3a	4.35	−13.67	10.98
3b	4.40	−16.40	8.54

or indicate existing intramolecular interactions that decrease ligand affinity towards guest. Hence, structure analysis is essential for contemporary studies of host–guest systems.

Amides **1a**, **1b** and their complexes were studied by X-ray diffraction method by Gale et al.[18] Structure analysis showed that free ligands exist in the *anti–anti* conformation. However, interaction with a guest results in rotation of an amide group to *syn* conformation, which allows simultaneous binding of the guest by pyrrole N*H* and amide N*H*. It was interesting to check if such behaviour is characteristic for all diamidopyrrole systems.

2.4. Structural analysis of amides

We succeeded in the preparation of diffraction-grade single crystals of amide **2a** by slow evaporation of its ethanol–acetone solution, and subjected them to X-ray analysis. Receptor molecules form an intermolecular net of hydrogen bonds and create a coordination polymer in the solid state (Fig. 4). The independent part consists of three ligand molecules (Fig. 5).

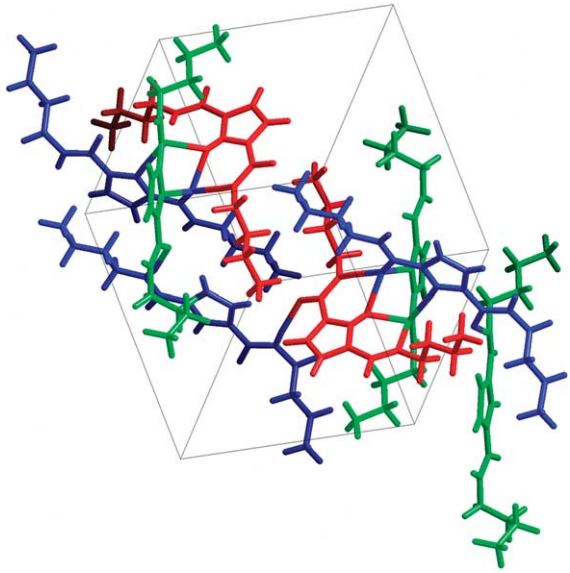


Figure 4. The X-ray crystal structure of **2a** showing the three inequivalent molecules in different colours.

There are two pyrrole moieties in the *anti–anti* conformation bound by the ligand possessing *syn–syn* conformation. This beautiful structure shows those two important

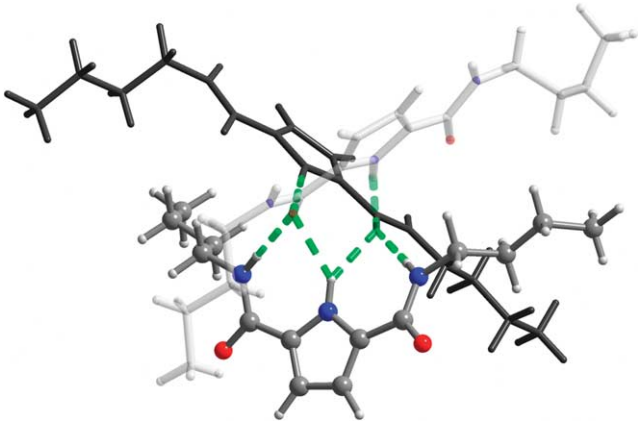


Figure 5. Crystal structure of **2a**.

aspects of diamidopyrrole receptors: they prefer *anti–anti* conformation; in the *syn–syn* conformation they can bind a guest by the convergent hydrogen bonds created by both amide and pyrrole N*H*. Amide protons participate in shorter hydrogen bonds (N–O from 2.81 to 2.87 Å) than pyrrole ones (N–O from 2.90 to 2.95 Å). It may suggest that the pyrrole hydrogen bond is weaker than that involving the amide group.

In order to investigate the conformation of **2a** in solution we carried out 2D NOESY spectra in DMSO-d_6. We found an NOE effect between amide N*H* protons and both pyrrole C*H* and N*H* protons (Fig. 6), which means that the amide groups in solution have both *anti* and *syn* relationship. During a dilution experiment we did not notice any significant changes in ^{1}H NMR spectra which discards possibility of trimer formation (similar to that in the solid phase).

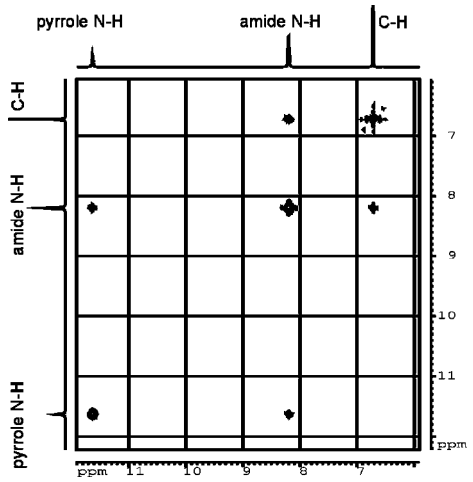


Figure 6. NOESY spectra of **2a** in DMSO-d_6 solution.

The X-ray crystal structure of amide **2b** consists of only one independent molecule in *anti–anti* conformation. In contrast to the Gale's phenylamide **1b**, compound **2b** does not form dimers but head-to-tail chains are formed (Fig. 7). The carbonyl groups of the next molecule accept hydrogen bonds from the amide group (N–O 3.07 Å) and from the aromatic ring (C–O 3.32 Å). In this structure, the pyrrole N*H* does not participate in any hydrogen bond.

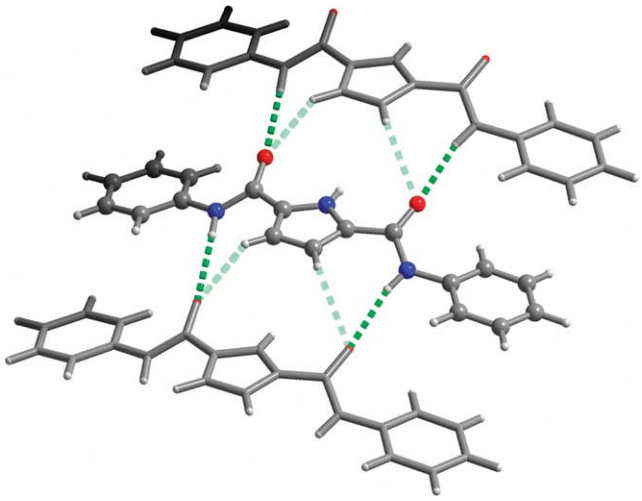


Figure 7. Crystal structure of **2b**. Symmetrically dependent molecules are presented by stick model.

2.5. Structural analysis of thioamides

Using the diffusion method ($C_2H_4Cl_2$/pentane), crystals of compound **3a** were obtained and subjected to X-ray analysis. Independent part of the structure consists of one ligand molecule with disorder in one of the butyl chains. Thioamide groups are in the *anti–anti* conformation and participate in hydrogen bonding (Fig. 8).

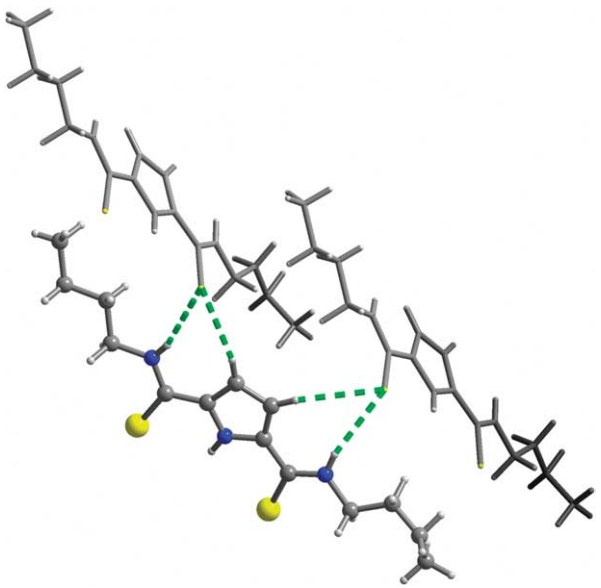


Figure 8. The X-ray crystal structure of **3a**. Part of disorder was removed for clarity.

Thioamide N*H* and pyrrole C*H* protons form hydrogen bonds with thiocarbonyl groups from neighbour molecules, in a similar way as in the case of **2b**. However, contrary to the structure of **2b**, each molecule of **3a** binds thiocarbonyl groups of two others. Inspection of hydrogen bond lengths reveals that the interactions are not equal (distances are: N–S, 3.55 Å; C–S, 3.68 Å and N–S, 3.66 Å; C–S, 3.84 Å, respectively). This structure shows that the thioamide groups act as hydrogen bond acceptors, at least in the solid state. However, comparison with average hydrogen

bond lengths and angles (with a thiocarbonyl group as acceptor)[13b] suggests that intermolecular interactions of **3a** are very weak. Crystals of **3a** have an interesting phase transition which will be discussed in the separate paper.

The 2D NOESY spectra of **3a** in DMSO-d_6 revealed close proximity between thioamide protons and pyrrole C*H* (Fig. 9) without NOE effect involving pyrrole N*H*. Therefore, ligand **3a** conformation in solution is *anti–anti* as was observed for the solid state.

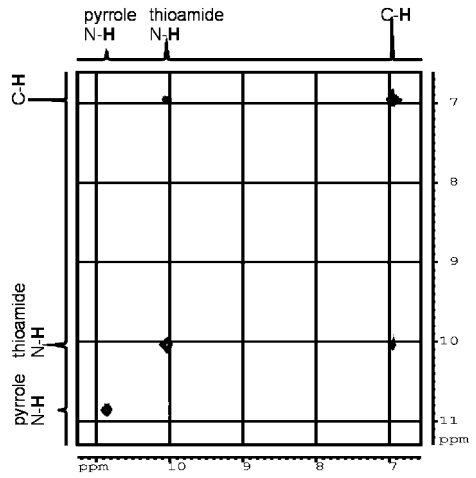


Figure 9. NOESY spectra of **3a** in DMSO-d_6 solution.

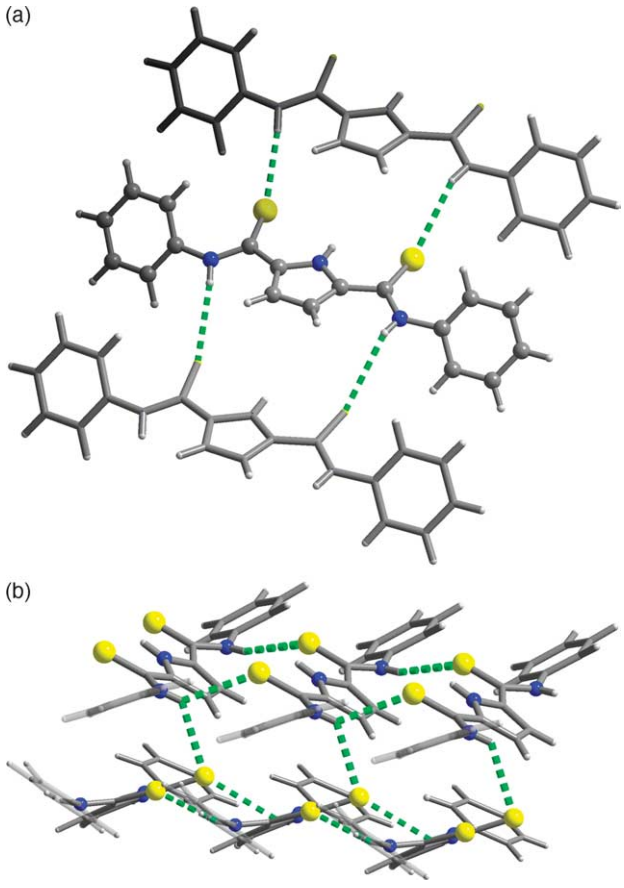


Figure 10. Crystal structure of **3b**. (a) Top view. (b) Side view.

Single crystal of compound **3b** were obtained from its solution in the mixture of acetonitrile and methanol (9:1 v/v) by slow evaporation of solvents. The X-ray crystal structure is very similar to that obtained for the amide analogue **2b** (cf. Figs. 7 and 10a). The ligand molecules have the *anti–anti* conformation and form head-to-tail chains via hydrogen bonds between thioamide groups. However, one of the thioamide groups is engaged in bifurcated hydrogen bond, which ties the chain below (Fig. 10b).

2.6. Structural analysis of anion complexes

The next diffusion experiment (**2b**, tetrabutylammonium chloride in $C_2H_4Cl_2$/pentane) led to diffraction-grade crystals of the chloride complex with **2b**. X-ray structure analysis revealed that the receptor adopts the *syn–syn* conformation and the chloride anion is bound by three hydrogen bonding interactions (Fig. 11). Each hydrogen bond has different length, the shortest being the pyrrole N*H* (N–Cl 3.07 Å) when distances of amide nitrogens to chloride are of 3.33 and 3.39 Å. Differences in amide hydrogen bond lengths may indicate that chloride anion cannot perfectly match the binding site of the receptor.

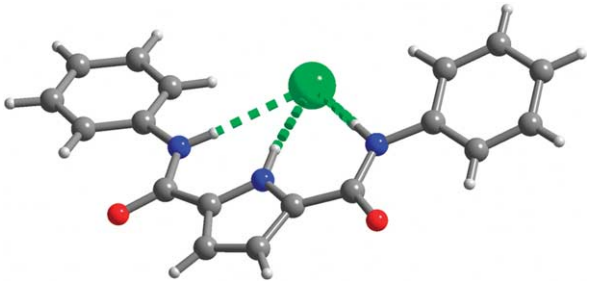


Figure 11. The crystal structure of the complex **2b**×TBACl.

Single crystals of chloride complex of thioamide **3b** were also obtained by diffusion of pentane into the solution of complex in dichloroethane. The X-ray structure analysis revealed that the ligand remained in the *anti–anti* conformation. Two chloride anions and two molecules of receptor **3b** form centrosymmetrical dimer in which anions are anchored by hydrogen bonding interactions involving amide N*H* and pyrrole C*H* (Fig. 12).

The ligand forms different contacts with chloride ions; one set consists of hydrogen bonds, which are shorter at one side

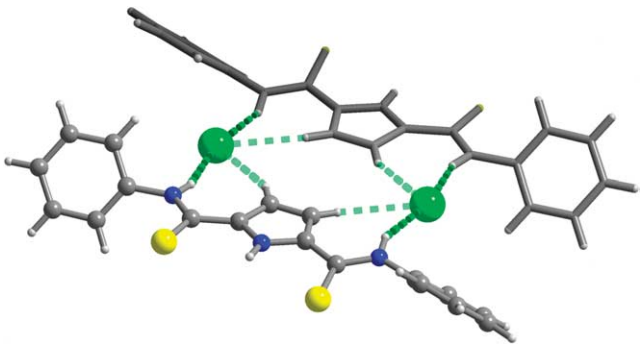


Figure 12. Crystal structure of complex **3b**×TBACl. The symmetrically dependent structure is shown in light grey.

(N–Cl 3.26 Å; C–Cl 3.55 Å, and N–Cl 3.30 Å; C–Cl 3.64 Å, respectively). In this complex, pyrrole N*H* is not engaged in any hydrogen interactions.

Similar structure was reported by Gale et al.[16] for the complex of thiophene-2,5-dicarboxylic acid diphenylamide with fluoride anion. Thiophene ligand in the *anti–anti* conformation forms a 2:2 complex with fluoride anion, which is bound by the amide N*H* and thiophene C*H*. The main difference between these two structures is that pyrrole rings of ligand **3b** and chloride anions lay in the same plane, whereas in the case of fluoride complex, the thiophene rings occupy parallel planes.

The results of the X-ray analysis of $[\mathbf{3b}\cdot\mathrm{Cl}]^-$ raised the question about the complex structure in solution. In complexes of these class of ligands, we expect the *syn–syn* conformation of the ligand, so the complex can benefit from convergent, three hydrogen bonds, impossible in the *anti–anti* conformation. We were unable to make a NOESY experiment and elucidate the complex structure in solution due to the N*H* proton signal broadening in the presence of tetrabutylammonium salts. However, during the ^{1}H NMR titration, we observed a downfield shift of the pyrrole N*H* proton signal (however, it lost intensity very fast) and curve fitting matched the 1:1 model. For these reasons, we believe, that binding mode observed in the solid state does not take place in solution, and that anions are bound by hydrogen bonds from thioamides and the pyrrole N*H* as observed for the amide analogues.

2.7. DFT energy calculations of conformers

The above-described structure $[\mathbf{3b}\cdot\mathrm{Cl}]^-$ prompted us to hypothesise that thioamides could have a greater tendency to stay in the *anti–anti* conformation than the corresponding amides. To confirm this assumption, we decided to perform an energy calculation for different conformers of 1*H*-pyrrole-2,5-dicarboxylic acid bis-methylamide **2c** and its thioamide analogue **3c**. We began by carrying out geometry optimisation using density functional method (DFT) with B3LYP functional and 6-31+G(d,p) basis set. We found three local minima (*anti–anti*, *syn–anti*, *syn–syn*) for both amide and thioamide. For each conformer, we performed single point energy calculations [B3LYP/6-311+G(3df,2pd)],[23] the results are presented in Table 5. For both amide and thioamide *anti–anti* conformer possess the lowest energy what is in agreement with our previous finding. The energy difference between *syn–syn* and *anti–anti* conformers for **2c** and **3c** are 38.8 and 41.9 kJ/mol, respectively. So, the thioamide indeed shows a larger preference for *anti–anti* conformation than the amide does (about 3 kJ/mol).

Table 5. DFT calculations of the relative energies (kJ/mol) for the conformers of amide **2c** and thioamide **3c**[a]

	Amide **2c**	Thioamide **3c**
$E_{anti-anti}$	0	0
$E_{syn-anti}$	14.0	12.3
$E_{syn-syn}$	38.8	41.9

[a] Calculations in the gas phase performed by using B3LYP method and 6-311+G(3df,2pd) basis set. Zero-point correction included.

Provided that this 3 kJ difference is compensated during complexation, we can consider what would happen if thioamides had the same energy levels of conformers as amides. It would result in decreasing ΔG of 3 kJ and hence the binding constant would be more than three times higher (Eqs. 1).

$$\Delta G_0 = -RT\ln K_0; \quad \Delta G = \Delta G_0 - 3$$

$$\ln K = -\frac{1}{RT}\Delta G; \quad \ln K = \frac{1}{RT}(\Delta G_0 - 3) \tag{1}$$

$$K = \mathrm{e}^{\frac{-\Delta G_0}{RT}}\mathrm{e}^{\frac{3}{RT}} = K_0\,\mathrm{e}^{\frac{3}{RT}} \quad K = 3.36K_0(T = 298\ \mathrm{K})$$

This is only an attempt to rationalise the quite disappointing binding properties of thioamides on the basis of the structural analysis. Therefore, we believe that thioamides would be better receptors in a preorganised system, in which conformation preferences would play a less significant role (as was shown for macrocyclic tetrathioamides[14]).

3. Conclusions

In this paper, we present results of our extensive studies on the complexation properties of the model amides and thioamides both in solution and in the solid phase. One simple transformation of an amide ligand can give a novel thioamide-based receptor. Thioamide ligands possess better physical properties (good solubility, absorbance in visible part of spectra), have a slightly modified selectivity and may have an increased affinity towards anions. However, thioamide receptors seem to require preorganisation to efficiently bind anion guests. We hope that these results encourage other researchers to make further investigations of thioamides as anions receptors.

4. Experimental

4.1. General remarks

Details concerning determination of binding constants are provided in the supplementary material. DFT calculations were done using Gaussian 03 software[24] and are briefly described in the supplementary material. The X-ray measurements were performed in the Crystallographic Unit of the Physical Chemistry Laboratory at the Chemistry Department of the Warsaw University; the crystal data are included in the supplementary material. Crystallographic data (excluding structure factors) for the structures discussed in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 256442, 256443, 256444, 256445, 256652 and 261402. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

If not stated otherwise, all reagents were obtained from commercial sources and used as received. The column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh), the thin-layer chromatography was carried out using Merck Kieselgel F_{254} plates.

4.1.1. 1*H*-Pyrrole-2,5-dicarboxylic acid (8). The acid **8** was prepared by hydrolysis of the 1*H*-pyrrole-2,5-dicarboxylic acid monomethyl ester **7**.[21] The ester (2.8 g) was stirred with a solution of NaOH (12 g) in water (100 ml) at 60 °C for 3 h, and the reaction mixture was acidified with concentrated HCl. The precipitated crystals were filtered off and washed with 2 M HCl to give pyrrole-2,5-dicarboxylic acid in 90%.

Colourless crystals, mp decomposition at 250 °C (lit. dc. at 250 °C);[25] ^{1}H NMR (200 MHz DMSO) δ=12.75 (bs, 2H, COO*H*), 12.20 (s, 1H, N*H*-pyrrole), 6.74 (d, 2H, J_1= 2.4 Hz, *H*-pyrrole).

4.1.2. 1*H*-Pyrrole-2,5-dicarboxylic acid bis-butylamide (2a). To the suspension of pyrrole-2,5-dicarboxylic acid **8** (1 g, 6.5 mmol) in dry CH_2Cl_2 (25 ml) thionyl chloride (4.7 ml, 64 mmol) was added, followed by two drops of DMF. The mixture was refluxed overnight to become a clear, yellow solution. The solvent and the excess of thionyl chloride were removed in vacuo. After dissolving the resulting acid chloride **9** in dichloromethane (15 ml) and cooling to 0 °C, a solution of butylamine (3.2 ml, 33 mmol) in 2 ml CH_2Cl_2 was added with intensive stirring. The reaction was stirred overnight, and then the solvent was removed in vacuo. The solid was washed with 2 M HCl, water and ether. The resulting crude product was recrystallised from ethyl acetate. Yield 72%.

Colourless crystals, mp 195–197 °C; ^{1}H NMR (200 MHz DMSO) δ=11.66 (s, 1H, N*H*-pyrrole), 8,22 (t, 2H, J_1= 5.4 Hz, CON*H*), 6.72 (d, 2H, J_1=2.2 Hz, *H*-pyrrole), 3.22 (dt, 4H, J_1=5.8 Hz, J_2=6.8 Hz, CH_2NH), 1.46 (m, 4H, CH_2), 1.32 (m, 4H, CH_2), 0.90 (t, 6H, J_1=7.2 Hz, CH_3); ^{13}C NMR (50 MHz DMSO) δ=160.2, 129.3, 111.8, 38.7, 31.7, 20.1, 14.2; HR ESI calcd for $C_{14}H_{23}N_3O_2Na$ $[M+Na]^+$: 288.1682 found: 288.1698; Anal. calcd for $C_{14}H_{23}N_3O_2$: C 63.37, H 8.74, N 15.84, found: C 63.55, H 8.40, N 15.81.

4.1.3. 1*H*-Pyrrole-2,5-dicarboxylic acid bis-phenylamide (2b). Acid chloride **9** was prepared as described for diamide **2a**, starting from 0.5 g (3.2 mmol) of acid **8**. After dissolving the acid chloride in dry dichloromethane (15 ml) and cooling it to 0 °C, the solution of aniline (1.4 ml, 16 mmol) in 2 ml CH_2Cl_2 was added with intensive stirring, and a precipitate appeared. The reaction was stirred overnight, and then the precipitate was filtered off and thoroughly washed with ether, 2 M HCl and water. The resulting amide **2b** was recrystallised from methanol/dichloromethane mixture. Yield 92%.

Colourless crystals, mp 248–286 °C; ^{1}H NMR (200 MHz DMSO) δ=12.26 (s, 1H, N*H*-pyrrole), 10,12 (s, 2H, CON*H*), 7.75 (d, 4H, J_1=7.6 Hz, *o*-Ph), 7.37 (dd, 4H, J_1=7.8 Hz, J_2=7.8 Hz, *m*-Ph), 7.13–7.07 (m, 4H, *p*-Ph+ *H*-pyrrole); ^{13}C NMR (50 MHz DMSO) δ=158.6, 139.4, 129.8, 129.2, 124.0, 120.5, 133.6; HR ESI calcd for $C_{18}H_{15}N_3O_2Na$ $[M+Na]^+$: 328.1056 found: 328.1074; Anal. calcd for $C_{18}H_{15}N_3O_2$: C 70.81, H 4.95, N 13.76, found: C 70.74, H 4.99, N 13.65.

4.1.4. 1*H*-Pyrrole-2,5-dicarbothioic acid bis-butylamide (3a). The 1*H*-pyrrole-2,5-dicarboxylic acid butylamide **2a** (265 mg, 1 mmol) and the Lawesson's reagent (0.8 g, 2 mmol) were suspended in dry THF (20 ml), and the mixture was refluxed for one day under argon. The solvent was evaporated in vacuo and the reaction product was purified by column chromatography on silica gel (CH_2Cl_2). The resulting crude product was recrystallised from $C_2H_4Cl_2$/pentane. Yield 90%.

Yellow crystals, mp 114–115 °C; ^{1}H NMR (200 MHz DMSO) δ=10.86 (s, 1H, N*H*-pyrrole), 10.07 (t, 2H, J_1= 5.6 Hz, CSN*H*), 6.96 (d, 2H, J_1=2.4 Hz, *H*-pyrrole), 3.68 (dt, 4H, J_1=7.0 Hz, J_2=5.6 Hz, CH_2NH), 1.64 (m, 4H, CH_2), 1.34 (m, 4H, CH_2), 0.91 (t, 6H, J_1=7.2 Hz, CH_3); ^{13}C NMR (50 MHz $CDCl_3$) δ=184.9, 134.6, 106.0, 45.5, 30.4, 20.2, 13.7; HR EI calcd for $C_{14}H_{23}N_3S_2$ M^+: 297.1333 found: 297.1332; Anal. calcd for $C_{14}H_{23}N_3S_2$: C 56.53, H 7.79, N 14.12, S 21.56, found: C 56.74, H 7.75, N 14.15, S 21.51.

4.1.5. 1*H*-Pyrrole-2,5-dicarbothioic acid bis-phenylamide (3b). The 1*H*-pyrrole-2,5-dicarboxylic acid bisphenylamide **2b** (305 mg, 1 mmol) and Lawesson's reagent (0.8 g, 2 mmol) were suspended in dry THF (50 ml), and the mixture was refluxed over night under argon. The solvent was evaporated in vacuo. The residue was washed with CH_2Cl_2 and filtered off. The solid was purified by flash chromatography on silica gel using the following eluents: hexane/CH_2Cl_2 1:1 (150 ml), CH_2Cl_2 (150 ml), CH_2Cl_2/THF 1:1 (100 ml). The CH_2Cl_2/THF fraction gave crude thioamide **3b** which was recrystallised from THF/hexane. Yield 80%.

Yellow crystals, mp 242–244 °C; ^{1}H NMR (200 MHz DMSO) δ=11.52 (s, 2H, CSN*H*), 11.13 (s, 1H, N*H*-pyrrole), 7.71 (d, 4H, J_1=7.6 Hz, *o*-Ph), 7.46 (dd, 4H, J_1= 7.9 Hz, J_2=7.9 Hz, *m*-Ph), 7.33–7.25 (m, 4H, *p*-Ph+*H*-pyrrole); ^{13}C NMR (50 MHz $CDCl_3$) δ=183.8, 139.6, 135.8, 129.0, 126.9, 125.5, 112.0; HR EI calcd for $C_{18}H_{15}N_3S_2$ M^+: 337.0707 found: 337.0702; Anal. calcd for $C_{18}H_{15}N_3S_2$: C 64.07, H 4.48, N 12.45, S 19.00, found: C 63.88, H 4.45, N 12.39, S 18.41.

Acknowledgements

Financial support from the State Committee for Scientific Research (Project # T09A 087 21) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.029.

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