ANION COMPLEXATION PROPERTIES OF THIOPHENE-2,4- AND -2,5-BISCARBOXAMIDES

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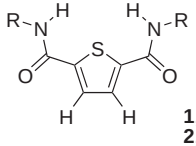
Dedicated to Professor Ivan Stibor on the occasion of his 60th birthday.

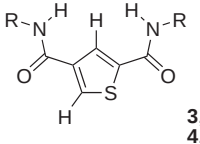
Thiophene-2,4- and -2,5-biscarboxamides have been synthesised and shown to act as anion receptors in DMSO-d_6/water solution. The crystal structure of the fluoride complex of a *N*,*N*′-diphenylthiophene-2,5-biscarboxamide derivative has been solved and reveals the involvement of the thiophene CH protons in anion complexation in the solid state.
Keywords: Amides; Thiophenes; Anion complexation; X-ray crystallography; Fluoride; Anion receptors.

In 1997, Crabtree and co-workers reported that very simple isophthalamide-based anion receptors form remarkably strong complexes with the smaller halides in organic solution[1]. This discovery has led to the incorporation of this hydrogen-bond donor unit in a variety of receptors for anions[2] and ion-pairs[3]. Recently, this chemistry was extended to the formation of anion-directed molecular architectures[4,5]. Our interest in pyrrole chemistry led us to synthesise analogous systems containing a central pyrrole ring in order to introduce an additional hydrogen bond donor group[6]. These systems showed enhanced anion complexation properties when compared with analogous isophthalamide systems[7]. We extended this chemistry to furan-2,5-biscarboxamides and found these receptors to be selective for fluoride in DMSO-d_6/0.5% water solution[8]. We therefore wished to explore the anion complexation properties of other bis-carboxamides of five-membered ring heterocycles. In this communication, we report the first anion complexation studies on thiophenebiscarboxamides. These receptors show unusual titration profiles with fluoride, behaviour that may indicate multiple equilibria in solution.

Compounds **1** and **2** were synthesised in 76 and 77% respective yields by conversion of commercially available thiophene-2,5-dicarboxylic acid to the bis-acid chloride with thionyl chloride and subsequent reaction with aniline or *n*-butylamine in the presence of triethylamine and a catalytic quantity of DMAP. Compounds **3** and **4** were synthesised in 59 and 46% respective yields in an analogous manner from thiophene-2,4-dicarboxylic acid[9].



1, R = Ph
2, R = *n*-Bu



3, R = Ph
4, R = *n*-Bu

Crystals of compound **1** were obtained from a DMSO solution of the receptor. The structure (shown in Fig. 1a) shows two molecules of DMSO hydrogen bonded to the receptor which adopts an "anti–anti" conformation. Crystals of compound **2** were obtained from a methanol solution of the receptor by slow evaporation. In this case the receptor adopts a similar conformation but crystallised without bound solvent (Fig. 1b).

Stability constants were obtained for compounds **1**–**4** with a variety of putative anionic guests by ^{1}H NMR titration methods employing the EQNMR computer program[10]. The results of these studies are summarised in Table I. The data presented in Table I were obtained by fitting the shifts

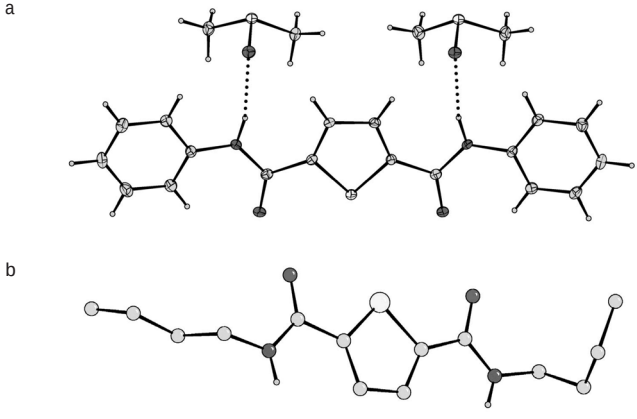


FIG. 1
The crystal structure of the DMSO solvate of compound **1** (a) and the crystal structure of compound **2** (b)

of the amide NH protons to 1:1 receptor:anion binding models. In the case of fluoride, the amide NH protons broadened considerably and a fit could not be obtained. It was found that bromide and hydrogensulfate bind very weakly, if at all to compounds **1**–**4** under these conditions.

These results show that dihydrogenphosphate is bound more strongly than chloride, bromide, hydrogensulfate, benzoate in DMSO-d_6/0.5% water with compound **3** showing the highest anion affinity. Whilst the NH protons broadened upon addition of fluoride, the thiophene CH protons remained sharp and their shifts could be followed upon addition of aliquots of fluoride. The NMR titration curves for compounds **1** and **3** are shown in Fig. 2. In these cases, the curves are indicative of multiple equilibria occur-

TABLE I

Stability constants (M^{-1}) for compounds **1** to **4** (calculated from amide NH resonances by ^{1}H NMR titration techniques) in DMSO-d_6/0.5% water at 298 K. Anions added as tetrabutylammonium salts. All errors are estimated to be less than 15%

Compound	Fluoride	Chloride	Benzoate	Dihydrogenphosphate
1	br.	<10	23	48
2	br.	<10	<10	13
3[a]	br.	<10	173	1508
3[b]	br.	<10	169	1625
4[a]	br.	<10	36	156
4[b]	br.	<10	37	159

[a] Calculated from most upfield amide NH resonance. [b] Calculated from most downfield amide NH resonance.

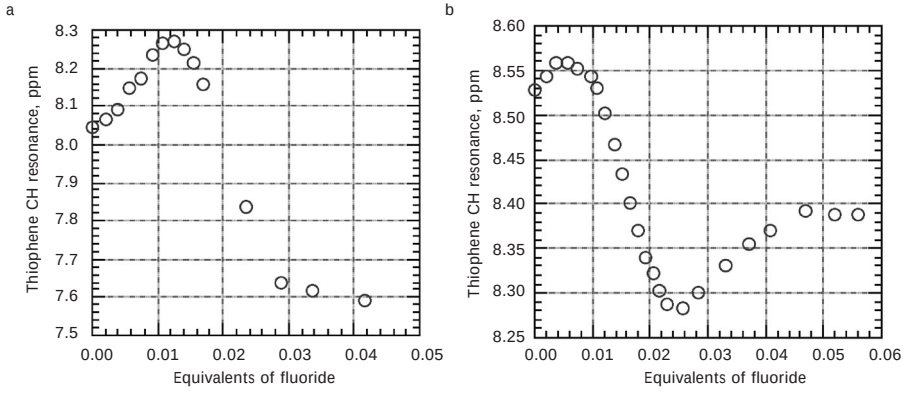


FIG. 2

^{1}H NMR titration curves of compounds **1** (a) and **3** (b) with tetrabutylammonium fluoride in DMSO-d_6/0.5% water following thiophene CH protons

ring in solution with initial downfield shifts followed by an upfield shift (compound **1**) and in the case of compound **3** a further downfield shift at higher equivalents of fluoride. It is likely that the compounds are forming both 1:1 and 2:1 fluoride:receptor complexes in solution; however, we have as yet not been able to obtain an adequate fit of the data using standard NMR fitting procedures. This may be due to the presence of other equilibria in the solution not accounted for in the simple 1:1 and 2:1 binding model[1,5]. In contradistinction to these results, the *n*-butyl-functionalised derivatives **2** and **4** showed typical 1:1 receptor:anion titration curves, and stability constants of 82 and 205 M^{-1} could be calculated by following the thiophene CH resonances.

Colour changes have been observed previously when basic anions are added to aromatic compounds containing hydrogen bond donor groups[11]. This is also true in this case; the addition of fluoride to compounds **1** and **3** is accompanied by a dramatic colourless to yellow colour change (see Fig. 3 for compound **1**). A much weaker yellow colour is observed upon addition of benzoate or dihydrogenphosphate.

The conformational behaviour of compound **1** in the solid state in the presence of fluoride was investigated by single-crystal X-ray diffraction. Crystals of the tetrabutylammonium salt of **1** were obtained by slow evaporation of a dichloromethane solution of the ligand in the presence of excess

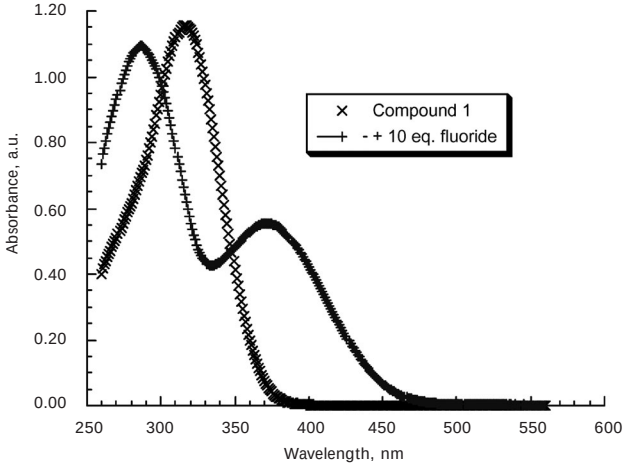


FIG. 3
UV/VIS spectra of 0.05 mM compound **1** in DMSO in the absence (×) and presence (+) of 10 equivalents of tetrabutylammonium fluoride trihydrate

tetrabutylammonium fluoride. The structure (shown in Fig. 4) reveals the presence of both NH···F^- (with N···F distances of 2.5903(16) and 2.6187(16) Å and N–H···F^- angles of 157.3 and 168.4°, respectively) and CH···F^- (C···F distance of 3.13(4) Å and C–H···F angle of 140.6(6)°) hydrogen bonds in the solid state in a 2:2 cyclic receptor:fluoride complex.

CONCLUSIONS

We have shown that bis-amidothiophenes function as anion receptors both in DMSO-d_6/0.5% water solution and in the solid state. Compounds **3** and **4** show a higher affinity for anions than compounds **1** and **2**, presumably due to the absence of the sulfur atom directly between the amide groups. Compound **3** is a particularly selective dihydrogenphosphate receptor amongst the anions studied. We are continuing to investigate the solution behaviour of compounds **1** and **3** with fluoride anions. The results of these studies will be reported in due course.

EXPERIMENTAL

N^2,N^4-Dibutylthiophene-2,4-dicarboxamide (**1**)

Thiophene-2,5-dicarboxylic acid (3 g, 0.017 mol) was suspended in freshly distilled thionyl chloride (100 ml) and refluxed overnight. Excess thionyl chloride was removed by rotary evaporation and the resulting solid dried under high vacuum. The resultant thiophene-2,5-dicarbonyl dichloride was dissolved in dry dichloromethane (100 ml). The solution was

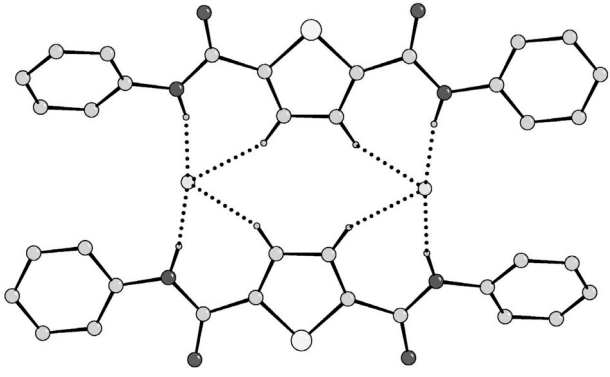


FIG. 4
The crystal structure of the fluoride complex of compound **1**. Tetrabutylammonium counter cations and non-acidic hydrogen atoms have been omitted for clarity

stirred under a nitrogen atmosphere and triethylamine (5.48 g, 0.0542 mol), DMAP (catalytic quantity) and aniline (3.44 g, 0.0369 mol) were added. The reaction mixture was further stirred overnight under a nitrogen atmosphere. A white solid was collected by filtration and washed with water (3 × 30 ml) then with dichloromethane (2 × 15 ml) affording the final product in 76% yield (4.3 g). X-ray quality crystals were formed by crystallisation from dimethyl sulfoxide. M.p. > 300 °C (decomp.). ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm): 7.13 (t, J = 7.26, 2 H, Ar); 7.38 (t, J = 7.29, 4 H, Ar); 7.74 (d, J = 7.29, 4 H, Ar); 8.05 (s, 2 H, CH); 10.40 (s, 2 H, NH). ^{13}C NMR (DMSO-d_6, 400 MHz), δ (ppm): 120.52, 124.13, 128.77, 129.29, 138.41, 143.92, 159.36. ES$^+$ MS, m/z: 323 (M + H$^+$), 501 (M + 2 DMSO + Na$^+$). HRES MS: $C_{36}H_{28}N_4NaO_4S_2$, calculated: 667.1444; found: 667.1447. Δ = 0.4 ppm.

N^2,N^5-Dibutylthiophene-2,5-dicarboxamide (**2**)

Thiophene-2,5-dicarboxylic acid (3 g, 0.017 mol) was suspended in freshly distilled thionyl chloride (100 ml) and heated at reflux overnight. Excess thionyl chloride was removed by rotary evaporation and the resulting solid dried under high vacuum. The resultant thiophene-2,5-dicarbonyl dichloride was dissolved in dry dichloromethane (100 ml). The solution was stirred under a nitrogen atmosphere and triethylamine (5.48 g, 0.0542 mol), DMAP (catalytic quantity) and butylamine (2.7 g, 0.0369 mol) were added. The reaction mixture was further stirred overnight under a nitrogen atmosphere. A white solid was collected by filtration and washed with water (3 × 30 ml) then with dichloromethane (2 × 15 ml) affording the final product in 77% yield (3.8 g). X-ray quality crystals were obtained by slow evaporation of a methanol solution of the receptor. M.p. > 225 °C (decomp.). ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm): 0.89 (t, J = 7.29, 6 H, CH_3); 1.31 (m, 4 H, CH_2); 1.48 (m, 4 H, CH_2); 3.21 (m, 4 H, CH_2); 7.68 (s, 2 H, CH); 8.56 (t, J = 5.46, 2 H, NH). ^{13}C NMR (DMSO-d_6, 400 MHz), δ (ppm): 13.66, 19.60, 31.16, 38.81, 127.82, 143.17, 160.54. ES$^+$ MS, m/z: 283 (M + H$^+$), 461 (M + 2 DMSO + Na$^+$). HRES MS: $C_{28}H_{44}N_4NaO_4S_2$, calculated: 587.2696; found: 587.2694. Δ = 0.4 ppm.

N^2,N^4-Diphenylthiophene-2,4-dicarboxamide (**3**)

Thiophene-2,4-dicarboxylic acid[9] (0.45 g, 0.0026 mol) was suspended in freshly distilled thionyl chloride (30 ml) and refluxed overnight. Excess thionyl chloride was removed in vacuo and the resulting solid dried under high vacuum. The resultant thiophene-2,4-dicarbonyl dichloride was dissolved in dry dichloromethane (20 ml). The solution was stirred under a nitrogen atmosphere and triethylamine (0.81 g, 0.008 mol), DMAP (catalytic quantity) and aniline (0.51 g, 0.0055 mol) were added. The reaction mixture was further stirred overnight under a nitrogen atmosphere. The product was collected by filtration and washed with water (2 × 10 ml) then with dichloromethane (2 × 15 ml) affording the bis-amide in 59% yield (0.49 g). M.p. 233–235 °C . ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm): 7.11 (m, 2 H, Ar); 7.37 (m, 4 H, Ar); 7.75 (m, 4 H, Ar); 8.53 (s, 1 H, CH); 8.63 (s, 1 H, CH); 10.26 (s, 1 H, NH); 10.46 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 400 MHz), δ (ppm): 120.27, 120.32, 123.74, 123.86, 128.67, 128.69, 129.13, 133.69, 138.22, 138.61, 138.81, 140.45, 159.45, 160.51. ES$^-$ MS, m/z: 341 (M + F$^-$), 435 (M + TFA$^-$). HRES MS: $C_{36}H_{28}N_4NaO_4S_2$, calculated: 667.1444; found: 667.1427. Δ = 2.6 ppm.

N^2,N^4-Dibutylthiophene-2,4-dicarboxamide (**4**)

Thiophene-2,4-dicarboxylic acid[9] (0.45 g, 0.0026 mol) was suspended in freshly distilled thionyl chloride (30 ml) and refluxed overnight. Excess thionyl chloride was removed in vacuo and the resulting solid dried under high vacuum. The resultant thiophene-2,4-dicarbonyl dichloride was dissolved in dry dichloromethane (20 ml). The solution was stirred under a nitrogen atmosphere and triethylamine (0.81 g, 0.008 mol), DMAP (catalytic quantity) and butylamine (0.41 g, 0.0055 mol) were added. Upon addition of butylamine the solution was effervescent. Triethylammoniumhydrogen chloride was removed by filtration, then the organic solution washed with brine (2 × 50 ml). The organic solvent was removed in vacuo leaving an oil. The oil was triturated in ether (50 ml) affording a solid which was filtered. The solid was dissolved in dichloromethane (20 ml) and ether (100 ml) was added to precipitate the product as a beige solid in 46% yield (0.34 g). M.p. 113–115 °C. ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm): 0.89 (t, J = 6.36, 6 H, CH_3); 1.32 (m, 4 H, CH_2); 1.49 (m, 4 H, CH_2); 3.21 (m, 4 H, CH_2); 8.09 (s, 1 H, CH); 8.24 (s, 1 H, CH); 8.34 (t, J = 6.39, 1 H, NH); 8.59 (t, J = 5.46, 1 H, NH). ^{13}C NMR (DMSO-d_6, 400 MHz), δ (ppm): 13.63, 13.66, 19.54, 19.59, 31.08, 31.21, 38.53, 38.74, 127.65, 131.03, 138.31, 140.29, 160.62, 161.67. ES$^+$ MS, *m/z*: 283 (M + H$^+$), 565 (2 M + H$^+$). HRES MS: $C_{28}H_{44}N_4NaO_4S_2$, calculated: 587.2696; found: 587.2689. Δ = 1.2 ppm.

Crystal data for **1**·2DMSO: $C_{22}H_{26}N_2O_4S_3$, *Mm* = 478.63, *T* = 120(2) K, monoclinic, space group $P2_1/n$, *a* = 8.5976(2) Å, *b* = 28.2287(6) Å, *c* = 9.5512(2) Å, β = 99.4300(10)°, *V* = 2286.74(9) Å^3, ρ_{calc} = 1.390 g cm^{-3}, μ = 0.356 mm^{-1}, *Z* = 4; reflections collected 6736, independent reflections 4003 (R_{int} = 0.0283), final *R* indices [$I > 2\sigma I$]: *R*1 = 0.0369, *wR*2 = 0.0841, *R* indices (all data): *R*1 = 0.0591, *wR*2 = 0.0919.

Crystal data for **1**·TBAF: $C_{34}H_{50}FN_3O_2S$, *Mm* = 583.83, *T* = 120(2) K, monoclinic, space group $P2_1/c$, *a* = 9.5551(2) Å, *b* = 17.7042(3) Å, *c* = 19.3409(5) Å, β = 93.8900(10)°, *V* = 3264.27(12) Å^3, ρ_{calc} = 1.188 g cm^{-3}, μ = 0.138 mm^{-1}, *Z* = 4; reflections collected 11 226, independent reflections 5740 (R_{int} = 0.0289), final *R* indices [$I > 2\sigma I$]: *R*1 = 0.0398, *wR*2 = 0.1044, *R* indices (all data): *R*1 = 0.0502, *wR*2 = 0.1106.

Crystal data for **2**: $C_{14}H_{22}N_2O_2S$, *Mm* = 282.40, *T* = 120(2) K, triclinic, space group *P*1, *a* = 9.750(5) Å, *b* = 9.970(5) Å, *c* = 15.582(5) Å, α = 87.570(5)°, β = 87.549(5)°, γ = 84.233(5)°, *V* = 1504.5(12) Å^3, ρ_{calc} = 1.247 g cm^{-3}, μ = 0.216 mm^{-1}, *Z* = 4; reflections collected 11 960, independent reflections 9238 (R_{int} = 0.0680), final *R* indices [$I > 2\sigma I$]: *R*1 = 0.0864, *wR*2 = 0.2258, *R* indices (all data): *R*1 = 0.1342, *wR*2 = 0.2544.

CCDC 209225 (for **1**·2DMSO), 209226 (for **1**·TBAF) and 209227 (for **2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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