Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

Crystallographic and Solution Anion Binding Studies of Bis-amidofurans and Thiophenes

Simon J. Coles[a]; Philip A. Gale[a]; Michael B. Hursthouse[a]; Mark E. Light[a]; Colin N. Warriner[a]
[a] School of Chemistry, University of Southampton, Southampton, UK

To cite this Article Coles, Simon J. , Gale, Philip A. , Hursthouse, Michael B. , Light, Mark E. and Warriner, Colin N.(2004) 'Crystallographic and Solution Anion Binding Studies of Bis-amidofurans and Thiophenes', Supramolecular Chemistry, 16: 7, 469 — 486
To link to this Article: DOI: 10.1080/10610270410001713303
URL: http://dx.doi.org/10.1080/10610270410001713303

Supramolecular Chemistry, October–November 2004, Vol. 16 (7), pp. 469–486

Taylor & Francis
Taylor & Francis Group

Crystallographic and Solution Anion Binding Studies of Bis-amidofurans and Thiophenes

SIMON J. COLES, PHILIP A. GALE*, MICHAEL B. HURSTHOUSE, MARK E. LIGHT and COLIN N. WARRINER

School of Chemistry, University of Southampton, Southampton SO17 1BJ, UK

Received (in Austin, USA) 3 March 2004; Accepted 12 April 2004

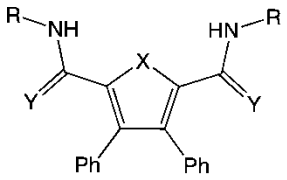
A variety of furan and thiophene amide and thioamide cleft type anion receptors have been synthesised and crystallographically characterised. Unlike 2,5-diamidopyrrole anions, analogous 2,5-diamidofurans and thiophenes do not interlock in the solid state. The anion binding properties of these receptors have been investigated in DMSO/0.5% water solution using ^{1}H NMR titration techniques. Solution studies and solid-state evidence suggests that the thiophene receptors may utilise a thiophene CH hydrogen atom for hydrogen bond formation to anions with a 2,4-diamidothiophene showing similar anion binding affinities to a 2,5-diamidopyrrole.

Keywords: Anion receptors; Amides; Thiophene; Furan; Hydrogen bonds

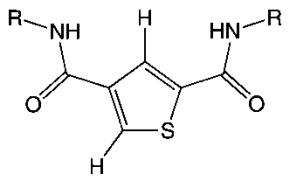
In 1997, Crabtree and co-workers reported the strong and selective binding of the smaller halides in organic solution, by very simple isophthalamide based anion receptors [1]. Since this first report, the isophthalamide hydrogen bond donor unit has been incorporated into a variety of anion [2] and ion-pair [3,4] receptors, while more recently this chemistry has extended to the formation of anion-directed molecular architectures [5–7]. In 1999, Crabtree and co-workers reported that an analogous diamidopyridine derivative displayed an increased selectivity for fluoride over the original generation of receptors [8]. Similarly, this hydrogen bond donor unit has been incorporated into macrocyclic anion receptors from the laboratories of Jurczak [9] and Bowman-James [2]. The thioamide functional group has been shown to form stronger hydrogen bonds than its amide counterpart [10] and is also a poorer hydrogen bond acceptor [10]. There have been a number of previous reports of the use of thioamides as anion binding groups [11,12]. We have recently reported the anion binding properties of 2,5-diamidopyrroles [13–19]. In cases where electron withdrawing groups were attached to the amide groups or to the 3- and 4-positions of the pyrrole ring, these species were found to deprotonate in the presence of base forming a pyrrole anion which, due to its self-complementary nature, forms an interlocked 'orthogonally' hydrogen bonded dimer in the solid state. We wished to see whether the 2,5-diamidofurans or thiophenes would interlock in the same 'orthogonal' manner as the 2,5-diamidopyrrole anions and also to ascertain the effect of 'replacing' the NH group in these receptors with O, S and CH on their affinities for anions. We have therefore synthesised a variety of linear 2,5- and 2,4-diamido and dithioamido heterocyclic receptors containing furan and thiophene groups (compounds **1**–**11** and model mono-amide **12**). X-ray crystallography has been used to study the hydrogen bonding networks formed by the receptors in the crystalline state. The anion binding properties of these receptors were investigated using ^{1}H NMR titration techniques. It was difficult to obtain crystals of anion complexes of these receptors, however in one case, the structure of a thiophene bis-amide with tetrabutylammonium fluoride has been determined showing thiophene CH···F hydrogen bonds in the crystalline state. Some preliminary aspects of this work have been published previously [20,21].

*Corresponding author. E-mail: philip.gale@soton.ac.uk

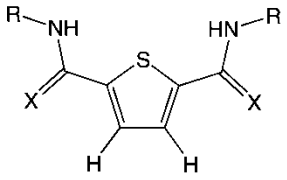
ISSN 1061-0278 print/ISSN 1029-0478 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/10610270410001713303



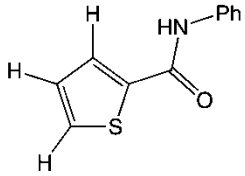
1 X = O, Y = O, R = n-Bu
2 X = O, Y = O, R = Ph
3 X = O, Y = S, R = n-Bu
4 X = O, Y = S, R = Ph
5 X = S, Y = O, R = Ph



10 R = n-Bu
11 R = Ph



6 X = O, R = n-Bu
7 X = O, R = Ph
8 X = S, R = n-Bu
9 X = S, R = Ph



12

EXPERIMENTAL

3,4-Diphenyl-furan-2,5-dicarboxylic Acid Dibutyl-amide (1)

3,4-Diphenyl-furan-2,5-dicarboxylic acid [22] (2.0 g, 4.8 mmol) was suspended in freshly distilled thionyl chloride (50 mL) and heated at reflux overnight. The excess thionyl chloride was removed *in vacuo* and the resulting solid dried under high vacuum for 2 h. The resulting 3,4-diphenyl-furan-2,5-dicarbonyl dichloride was dissolved in dry dichloromethane (80 mL). Triethylamine (2.0 g, 19.8 mmol), DMAP (catalytic quantity) and *n*-butylamine (1.00 g, 13.6 mmol) were added whilst the solution was stirred under a nitrogen atmosphere. The reaction mixture was stirred overnight and the organic solution was then washed with water (4 × 100 mL), dried with magnesium sulphate and the dichloromethane removed *in vacuo*. The yellow oily residue was purified by column chromatography on silica eluting with dichloromethane-2% methanol giving the desired compound (1.07 g, 53%). The product was crystallised from diethyl-ether (200 mL) and also from a solution of diethyl-ether:acetonitrile:dimethyl sulfoxide (2:2:1) giving polymorphic structures. ^{1}H NMR ($CDCl_3$, 300 MHz) 0.88 (t, $J = 7.29$ Hz, 6H, CH_3), 1.24 (m, 4H, CH_2), 1.43 (m, 4H, CH_2), 3.32 (m, 4H, CH_2), 6.28 (t, 2H, $J = 5.49$ Hz, NH), 7.18–7.30 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.76, 20.09, 31.47, 39.14, 128.39, 128.46, 130.25, 130.35, 131.09, 142.52, 158.26. MS (ES^+) 520 ($M + Et_3NH^+$), 837 ($2M + H^+$). HRMS (ES^+) 859 ($2M + Na^+$), $\Delta = 0.4$ ppm. Anal. calcd. for $C_{26}H_{30}N_2O_3$ + 0.33 MeOH: C, 73.69; H, 7.36; N, 6.53. Found: C, 73.79; H, 7.16; N, 6.51. Mp: 144°C.

3,4-Diphenyl-furan-2,5-dicarboxylic Acid Diphenyl-amide (2)

3,4-Diphenyl-furan-2,5-dicarboxylic acid [22] (2.0 g, 4.8 mmol) was suspended in freshly distilled thionyl chloride and heated at reflux overnight. The excess thionyl chloride was removed *in vacuo* and the resulting solid dried under high vacuum for 2 h. The resulting 3,4-diphenyl-furan-2,5-dicarbonyl dichloride was dissolved in dry dichloromethane (80 mL). Triethylamine (2.0 g, 19.8 mmol), DMAP (catalytic quantity) and aniline (1.27 g, 13.6 mmol) were added whilst the solution was stirred under a nitrogen atmosphere. The reaction mixture was stirred overnight and the organic solution was then washed with water (4 × 100 mL), dried with magnesium sulphate and the dichloromethane removed *in vacuo*. The product was recrystallised from acetonitrile (200 ml) affording the final product in yield as a white powder (1.77 g, 80%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.13–7.72 (m, 20H, Ar), 10.38 (s, 2H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 120.83, 124.34, 127.49, 127.68, 128.79, 130.02, 130.29, 132.21, 137.84, 141.45, 155.67. MS (ES^+) 560 ($M + Et_3NH^+$), 917 ($2M + H^+$). HRMS (ES^+) 939 ($2M + Na^+$), $\Delta = 2.8$ ppm. Anal. calcd. for $C_{30}H_{22}N_2O_3 + H_2O$ requires C, 75.61; H, 5.08; N, 5.88. Found: C, 75.82; H, 5.11; N, 5.69. Mp: 278°C.

3,4-Diphenyl-furan-2,5-dicarboxylic Acid Dibutyl-thioamide (3)

3,4-Diphenyl-furan-2,5-dicarboxylic acid dibutyl-amide [20] **(1)** (0.7 g, 1.7 mmol) was suspended in freshly distilled tetrahydrofuran (100 mL), Lawessons reagent [23] (1.75 g, 4.3 mmol) was added and the solution heated at reflux for 24 h. The solvent was removed *in vacuo* and the resulting solid suspended in dichloromethane (50 mL). The organic layer was washed with water (3 × 20 mL), dried with magnesium sulphate and the dichloromethane removed *in vacuo*. The resultant solid was purified using column chromatography on silica gel eluting with dichloromethane–2% methanol solution. The product was crystallised from acetonitrile as yellow needles (0.60 g, 80%). ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 0.86 (t, 6H, $J =$ 7.00 Hz, CH_3), 1.18 (m, 4H, CH_2), 1.44 (m, 4H, CH_2), 3.53 (m, 4H, CH_2), 7.17–7.31 (m, 10H, Ar), 7.60

(s, 2H, NH). ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 14.20, 20.80, 30.53, 45.71, 129.14, 129.28, 130.04, 130.91, 131.69, 146.49, 183.49. MS (ES^+) 451 ($M + H^+$), 473 ($M + Na^+$) 923 ($2M + Na^+$). HRMS (ES^+) 473 ($M + Na^+$), $\Delta = 2.5$ ppm. Anal. calcd. for $C_{26}H_{30}N_2OS_2$: C, 69.29; H, 6.71; N, 6.22. Found: C, 68.93, H, 6.67, N, 6.23. Mp: 184–185°C.

3,4-Diphenyl-furan-2,5-dicarboxylic Acid Diphenyl-thioamide (4)

3,4-Diphenyl-furan-2,5-dicarboxylic acid diphenyl-amide [20] **(2)** (0.77 g, 1.7 mmol) was suspended in freshly distilled tetrahydrofuran (100 mL), Lawessons reagent [23] (1.75 g, 4.3 mmol) was added and the solution heated at reflux for 24 h. The solvent was removed *in vacuo* and the resulting solid suspended in dichloromethane (50 mL). The organic layer was washed with water (3 × 20 mL), dried with magnesium sulphate and the dichloromethane removed *in vacuo*. The resultant solid was purified using column chromatography on silica gel eluting with dichloromethane–2% methanol solution. The product was crystallised from acetonitrile as red prisms and needles (0.64 g, 78%). ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.25–7.55 (m, 20H, Ar), 9.37 (s, 2H, NH). ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 124.05, 127.54, 129.37, 129.41, 129.53, 131.02, 131.49, 138.89, 142.85, 147.16, 181.57. MS (ES^+) 491 ($M + H^+$), 1002 ($2M + Na^+$). HRMS (ES^+) 513 ($M + Na^+$), $\Delta = 2.3$ ppm. Anal. calcd. for $C_{30}H_{22}N_2OS_2$ +MeCN: C, 72.29; H, 4.74; N, 7.90. Found: C, 71.91 H, 4.58, N, 7.84. Mp: 204–206°C.

3,4-Diphenyl-thiophene-2,5-dicarboxylic Acid Diphenyl-amide (5)

3,4-Diphenyl-thiophene-2,5-dicarboxylic acid [22] (2.5 g, 7.7 mmol) was suspended in freshly distilled thionyl chloride and refluxed overnight. The excess thionyl chloride was removed *in vacuo* and the resulting solid dried under high vacuum for a couple of hours. The 3,4-diphenyl-thiophene-2,5-dicarbonyl dichloride was dissolved in dry dichloromethane (120 mL) under a nitrogen atmosphere. To this solution, triethylamine (1.5 g, 15 mmol), DMAP (catalytic quantity) and aniline (0.93 g, 10 mmol) were added and stirred overnight. The organic solution was washed with brine (4 × 50 mL) dried with magnesium sulfate and the dichloromethane solvent removed *in vacuo*. Acetonitrile (60 mL) was added leaving an undissolved solid that was collected by filtration and washed with cold acetonitrile (2 × 20 mL) affording the final product as a beige powder. Further purification was achieved by crystallisation from hot acetonitrile (2.14 g, 58%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.04–7.39 (m, 20H, Ar), 9.70 (s, 2H, NH). ^{13}C NMR (DMSO-d_6,100 MHz) δ 119.66, 124.10, 127.85, 128.05, 128.73, 129.88, 134.00, 135.40, 138.10, 142.01, 160.09. MS (ES^-) 509 ($M + Cl^-$), 587 ($M + TFA^-$). HRMS (ES^+) 475 ($M + H^+$), $\Delta = 1.3$ ppm. Anal. calcd. for $C_{30}H_{22}N_2O_2S$ +0.03 MeCN: C, 75.88; H, 4.68; N, 5.98. Found: C, 75.42; H, 4.53; N, 5.89. Mp: 234–236°C.

Thiophene-2,5-dicarboxylic Acid Dibutyl-amide (6)

Thiophene-2,5-dicarboxylic acid (3 g, 17 mmol) was suspended in freshly distilled thionyl chloride (100 mL) and heated at reflux overnight. The excess thionyl chloride was removed *in vacuo* and the resulting solid dried under high vacuum for 2 h. The 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, 54.2 mmol), DMAP (catalytic quantity) and n-butylamine (2.7 g, 36.9 mmol) were added. Upon addition of *n*-butylamine the solution was effervescent forming a solid, however the reaction was left stirring overnight. The solid was collected by filtration and washed with water (3 × 30 mL) then with dichloromethane (2 × 15 mL). A white material resulted affording the final product (3.8 g, 77%). Further purification was achieved by crystallisation from methanol. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.89 (t, 6H, $J = 7.29$ Hz, CH_3), 1.31 (m, 4H, CH_2), 1.48 (m, 4H, CH_2), 3.21 (m, 4H, CH_2), 7.68 (s, 2H, CH), 8.56 (t, 2H, $J = 5.46$ Hz, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 13.66, 19.60, 31.16, 38.81, 127.82, 143.17, 160.54. MS (ES^+) 283 ($M + H^+$), 461($M + 2DMSO + Na^+$). HRMS (ES^+) 587 ($2M + Na^+$), $\Delta = 0.4$ ppm. Anal. calcd. for $C_{14}H_{22}N_2O_2S$: C, 59.54; H, 7.85; N, 9.92. Found: C, 59.69; H, 8.01; N, 9.59. Mp: decomp >225°C.

Thiophene-2,5-dicarboxylic Acid Diphenyl-amide (7)

Thiophene-2,5-dicarboxylic acid (3 g, 17 mmol) was suspended in freshly distilled thionyl chloride (100 mL) and heated at reflux overnight. The excess thionyl chloride was removed *in vacuo* and the resulting solid dried under high vacuum for 2 h. The 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, 54.2 mmol), DMAP (catalytic quantity) and aniline (3.44 g, 36.9 mmol) were added. Upon addition of aniline the solution was effervescent forming a solid, however the reaction was left stirring overnight. The solid was collected by filtration and washed with water (3 × 30 mL) then with dichloromethane (2 × 15 mL) affording the final product as a white powder (4.3 g, 76%). Further purification was achieved by crystallisation from dimethyl sulfoxide. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.13 (t, 2H, $J = 7.26$ Hz, Ar), 7.38 (t, 4H, $J = 7.29$ Hz, Ar), 7.74 (d, 4H, $J = 7.29$ Hz, Ar), 8.05 (s, 2H, CH), 10.40 (s, 2H, NH). ^{13}C NMR

(DMSO-d_6, 100 MHz) δ 120.52, 124.13, 128.77, 129.29, 138.41, 143.92, 159.36. MS (ES^+) 323 ($M + H^+$), 501($M + 2DMSO + Na^+$). HRMS (ES^+) 667 ($2M + Na^+$), $\Delta = 0.4$ ppm. Anal. calcd. for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.15; H, 4.58; N, 8.51. Mp: decomp >300°C.

Thiophene-2,5-dicarboxylic Acid Dibutyl-thioamide (8)

Thiophene-2,5-dicarboxylic acid dibutyl-amide [21] **(6)** (1 g, 3.5 mmol) was suspended in freshly distilled tetrahydrofuran (200 mL), Lawessons reagent (3.68 g, 9.1 mmol) was added and the solution heated at reflux for 24 h. The solvent was removed *in vacuo* and the resulting solid suspended in dichloromethane (100 mL). The organic layer was washed with water (3 × 20 mL) dried with magnesium sulphate and the dichloromethane removed *in vacuo*. The product was obtained as a yellow solid, further purification was achieved by crystallisation of yellow needles from a dichloromethane solution. (0.93 g, 84%) ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.91 (t, 6H, $J = 7.04$ Hz, CH_3), 1.35 (m, 4H, CH_2), 1.64 (m, 4H, CH_2), 3.66 (m, 4H, CH_2), 7.62 (s, 2H, CH), 10.21 (t, 2H, $J = 5.00$ Hz, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 13.67, 19.72, 29.37, 45.55, 124.34, 151.30, 185.87. MS (ES^+) 315 ($M + H^+$), 337 ($M + Na^+$), 651 ($2M + Na^+$). HRMS (ES^+) 315 ($M + H^+$), $\Delta = 1.8$ ppm. Anal. calcd. for $C_{14}H_{22}N_2S_3$: C, 53.46, H, 7.05, N, 8.90. Found: C, 53.24, H, 7.03, N, 8.64. Mp: 166–168°C.

Thiophene-2,5-dicarboxylic Acid Diphenyl-thioamide (9)

Thiophene-2,5-dicarboxylic acid diphenyl-amide [21] (7) (0.67 g, 2.1 mmol) was suspended in freshly distilled tetrahydrofuran (200 mL), Lawessons reagent (4.4 g, 18.2 mmol) was added and the solution refluxed for 72 h. The solvent was removed *in vacuo* and the resulting solid suspended in dichloromethane (100 mL). The organic layer was washed with water (3 × 20 mL) dried with magnesium sulfate and the dichloromethane removed *in vacuo*. The solid was purified by precipitation from hot acetonitrile (150 mL) the product was obtained as an orange solid (0.55 g, 74%). Further purification was achieved by crystallisation from a dimethyl sulfoxide solution. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.28–7.71 (m, 10H, Ar), 7.88 (s, 2H, CH), 11.70 (s, 2H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 124.98, 125.17, 126.68, 128.64, 139.26, 153.28, 186.01. MS (ES^-) 353 $(M - H)^-$, 707 $(2M - H)^-$. HRMS (ES^-) 353 $(M - H)^-$, $\Delta = 2.6$ ppm. Anal. calcd. for $C_{18}H_{14}N_2S_3$ requires C, 60.99, H, 3.98, N, 7.90. Found: C, 60.86, H, 3.99, N, 8.08. Mp: 357–359°C.

Thiophene-2,4-dicarboxylic Acid Dibutyl-amide (10)

Thiophene-2,4-dicarboxylic acid [24,25] (0.45 g, 2.6 mmol) was suspended in freshly distilled thionyl chloride (30 mL) and refluxed overnight. The excess thionyl chloride was removed *in vacuo* and the resulting solid dried under high vacuum for a couple of hours. The thiophene-2,4-dicarbonyl dichloride was dissolved in dry dichloromethane (20 mL) and stirred under a nitrogen atmosphere. To the solution triethylamine (0.81 g, 8 mmol), DMAP (catalytic quantity) and n-butylamine (0.41 g, 5.5 mmol) were added. After stirring overnight triethylammonium chloride was removed by filtration and the organic solution washed with brine (2 × 50 mL). The dichloromethane solvent was removed *in vacuo* leaving an oil. The oil was triturated in ether (50 ml) to precipitate a solid that was collected by filtration. The dark solid was dissolved in dichloromethane (20 mL), ether (100 mL) was added to precipitate the product as a beige solid (0.34 g, 46%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.89 (t, $J = 6.36$ Hz, 6H, CH_3), 1.32 (m, 4H, CH_2), 1.49 (m, 4H, CH_2), 3.21 (m, 4H, CH_2), 8.09 (s, 1H, CH), 8.24 (s, 1H, CH), 8.34 (t, $J = 6.39$ Hz, 1H, NH), 8.59 (t, $J = 5.46$ Hz, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 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. MS (ES^+) 283 ($M + H^+$), 565($2M + H^+$). HRMS (ES^+) 587 ($2M + Na^+$), $\Delta = 1.2$ ppm. Anal. calcd. for $C_{14}H_{22}N_2O_2S + 0.125$ CH_2Cl_2: C, 57.90; H, 7.65; N, 9.56. Found: C, 57.95; H, 7.55; N, 9.43. Mp: 113–115°C.

Thiophene-2,4-dicarboxylic Acid Diphenyl-amide (11)

Thiophene-2,4-dicarboxylic acid [24,25] (0.45 g, 2.6 mmol) was suspended in freshly distilled thionyl chloride (30 mL) and refluxed overnight. The excess thionyl chloride was removed *in vacuo* and the resulting solid dried under high vacuum for a couple of hours. The thiophene-2,4-dicarbonyl dichloride was dissolved in dry dichloromethane (20 mL) and stirred under a nitrogen atmosphere. To the solution triethylamine (0.81 g, 8 mmol), DMAP (catalytic quantity) and aniline (0.51 g, 5.5 mmol) were added. Although a white solid precipitated almost instantaneously upon addition of aniline the solution was stirred overnight. The solid was collected by filtration and washed with water (2 × 10 mL) then with dichloromethane (2 × 15 mL) affording the desired product as a white powder (0.49 g, 59%). Crystallisation was achieved by slow evaporation from a dimethyl sulfoxide solution. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.11 (m, 2H, Ar), 7.37 (m, 4H, Ar), 7.75 (m, 4H, Ar), 8.53 (s, 1H, CH), 8.63 (s, 1H, CH), 10.26 (s, 1H, NH), 10.46 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 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. MS (ES^-) 341 ($M + F^-$), 435 ($M + TFA^-$). HRMS (ES^+) 667 ($2M + Na^+$), $\Delta = 2.6$ ppm. Anal. calcd. for $C_{18}H_{14}N_2O_2S$ +0.05 CH_2Cl_2 requires C, 66.37; H, 4.35; N, 8.58. Found: C, 66.40; H, 4.27; N, 8.66. Mp: 233–235°C.

Thiophene-2-carboxylic Acid Phenyl-amide (12)

Thiophene-2-carboxylic acid (3 g, 23 mmol) was suspended in freshly distilled thionyl chloride (50 mL) and refluxed overnight. The excess thionyl chloride was removed *in vacuo* and the resulting solid dried under high vacuum for 2 h. The thiophene-2-carbonyl chloride was dissolved in dry dichloromethane (50 mL). The solution was stirred under a nitrogen atmosphere and triethylamine (4 g, 40 mmol), DMAP (catalytic quantity) and aniline (2.79 g, 30 mmol) were added. Upon addition of aniline the solution was effervescent; however, the reaction was left stirring overnight. The solution was washed with water (2 × 50 mL). The organic layer was dried with magnesium sulphate and then filtered before removing the solvent *in vacuo* until a solid precipitated. To the slurry diethylether (40 mL) was added and the suspension filtered. The solid was washed with dichloromethane (2 × 10 mL) then with ether (2 × 10 mL). An off white material resulted affording the final product (3.02 g, 65%). Further purification was achieved by crystallisation from a dimethyl sulfoxide solution. ^1H NMR (MeCN-d_3, 400 MHz) δ 7.12–7.79 (m, 8H, Ar overlapping signals), 8.69 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 120.34, 124.78, 127.96, 128.60, 129.26, 130.86, 137.74, 139.42, 160.03. MS (ES^-) 238 ($M + Cl^-$), 316($M + TFA^-$). HRMS (ES^+) 204 ($M + H^+$), $\Delta = 0.4$ ppm. Anal. calcd. for $C_{11}H_9NOS$: C, 65.00; H, 4.46; N, 6.89. Found: C, 64.86; H, 4.41; N, 6.89. Mp: 131–133°C.

RESULTS AND DISCUSSION

Receptors **1** and **2** were synthesised by conversion of 3,4-diphenyl-furan-2,5-dicarboxylic acid [22] to the bis-acid chloride with thionyl chloride and subsequent reaction with *n*-butylamine and aniline in the presence of triethylamine and a catalytic quantity of DMAP. Thioamide analogues **3** and **4** were synthesised by converting the amide derivatives **1** and **2** using Lawessons reagent [23]. 3,4-Diphenyl-thiophene-2,5-dicarboxylic acid was synthesised using literature methods [22]. This material was converted to the acid chloride and then coupled to aniline in the presence of triethylamine and a catalytic quantity of DMAP to give compound **5**. Compounds **6** and **7** were synthesised 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 **8** and **9** were synthesised by converting bis-amides **6** and **7** to the corresponding bis-thioamides using Lawessons reagent. Thiophene-2,4-dicarboxylic acid was synthesised using literature methods [24,25]. This material was converted to the acid chloride and then coupled to *n*-butylamine or aniline in the presence of triethylamine and a catalytic quantity of DMAP to give compounds **10** and **11** respectively. Finally, model mono-amide **12** was synthesised by conversion of commercially available thiophene-2-carboxylic acid to the acid chloride with thionyl chloride and subsequent reaction with aniline in the presence of triethylamine and a catalytic quantity of DMAP.

X-ray data were collected on a Bruker Nonius Kappa CCD area detector diffractometer with a rotating anode generator following standard procedures. Full crystallographic data for the structure analyses have been deposited with the Cambridge Crystallographic Data Centre. Crystal data and CCDC deposition numbers for the furan and thiophene structures are shown in Tables I and II, respectively.

Polymorphic crystals of the butylamide derivative **1** were crystallised from different solvent systems. The first polymorph was obtained by slow evaporation of a diethyl ether (Fig. 1(a)) solution of the receptor whilst the second was obtained by evaporation of an ether:acetonitrile:dimethyl sulfoxide in a 2:2:1 ratio solution of **1** (Fig. 1(b)). Although both structures reveal the receptor assuming a cleft type conformation, the polymorph obtained from diethyl ether (Fig. 1(a)) reveals the amide moieties deviate from the furan plane by 23.4 and 22.5° with the amide groups orientated to opposite sides of the central furan ring. The structure of the other polymorph (Fig. 1(b)) reveals the amide groups pointing to the same side of the molecule with deviations of 19.2 and 17.9° from the furan plane. This variation between the structures has led to very different hydrogen bonding arrays in the extended crystal lattices (Fig. 2).

In the case of the crystal obtained from ether (Fig. 2(a)) the molecules form infinite chains along the *a*-axis via NH···O hydrogen bond linkages with N···O distances of 2.953(1) (N2—O2) and 2.956(2) Å (N1—O3), the adjacent furan rings adopt alternating orientations. The other structure (Fig. 2(b)) shows the receptor forming a helical chain along the *c*-axis, completing a rotational turn every 30.27 Å. Each molecule forms two NH···O hydrogen bonds (N···O distances of 3.108(4) (N1—O3) and 3.090(3) Å (N2—O3)) to only one of the two carbonyl groups present on the next molecule, the helix is formed by the molecules rotating about a central axis by 60° with every step along the chain.

TABLE I Crystallographic data and CCDC deposition numbers of the furan receptors

Compound number	**1**	**1**	**2**	**3**	**4**
CCDC number	229151	229150	195420	229144	229149
Empirical formula	$C_{26}H_{30}N_2O_3$	$C_{26}H_{30}N_2O_3$	$C_{30}H_{22}N_2O_3{\cdot}CH_3CN$	$C_{26}H_{30}N_2OS_2$	$C_{32}H_{25}N_3OS_2$
Formula weight	418.52	418.52	499.55	450.64	531.67
Crystal system	Triclinic	Hexagonal	Monoclinic	Monoclinic	Triclinic
Space group	*P*-1	$P6_5$	$P2_1/n$	$P21/c$	*P*-1
a(Å)	8.5528(2)	11.4137(3)	8.8334(2)	8.6986(8)	10.1937(2)
b(Å)	11.6747(3)	11.4137(3)	15.6053(4)	14.1628(05)	11.9696(2)
c(Å)	11.9030(3)	30.2650(10)	19.0971(7)	19.4377(05)	13.4313(3)
α (°)	99.7980(10)	90	90	90	64.5590(10)
β (°)	96.3680(10)	90	102.4470(10)	91.566(5)	89.3040(10)
γ (°)	100.7530(10)	120	90	90	66.6820(10)
Z	2	6	4	4	2
Cell volume (Å^3)	1138.07(5)	3414.48(17)	2570.62(13)	2393.9(17)	1334.16(5)
μ (mm^{-1})	0.080	0.080	0.084	0.243	0.231
Crystal	Colourless rod	Colourless prism	Colourless block	Yellow rod	Orange prism
Crystal size (mm)	0.18 × 0.04 × 0.03	0.24 × 0.10 × 0.07	0.20 × 0.07 × 0.07	0.40 × 0.15 × 0.15	0.32 × 0.21 × 0.18
Reflections collected	20647	16128	8697	21486	24851
Independent reflections (R_{int})	5177 (0.0447)	4869 (0.0784)	4541 (0.0390)		6103 (0.0757)
Data/restraints/parameters	5177/0/291	4869/1/302	4541/0/344	21498/2/291	6103/0/353
Goodness-of-fit on F^2	1.026	0.979	0.965	1.057	1.013
Final *R* indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0453$, $wR2 = 0.1030$	$R1 = 0.0563$, $wR2 = 0.1122$	$R1 = 0.0435$, $wR2 = 0.0987$	$R1 = 0.0682$, $wR2 = 0.2055$	$R1 = 0.0383$, $wR2 = 0.0950$
R indices (all data)	$R1 = 0.0693$, $wR2 = 0.1131$	$R1 = 0.1302$, $wR2 = 0.1369$	$R1 = 0.0763$, $wR2 = 0.1127$	$R1 = 0.0804$, $wR\ 2 = 0.2201$	$R1 = 0.0530$, $wR2 = 0.1035$
Largest difference peak and hole (e Å^{-3})	0.302 and −0.219	0.224 and −0.198	0.209 and −0.256	0.479 and −0.493	0.282 and −0.318
Flack parameter	–	Not reliably determined	–	–	–

TABLE II Crystallographic data and CCDC deposition numbers of the furan receptors

Compound number	**5**	**6**	**7**	**7 + F^-**	**9**	**11**	**12**
CCDC number	229147	209227	209225	209226	229145	229148	229146
Empirical formula	$C_{30}H_{22}N_2O_2S$	$C_{14}H_{22}N_2O_2S$	$C_{22}H_{26}N_2O_4S_3$	$C_{34}H_{50}FN_3O_2S$	$C_{22}H_{26}N_2O_2S_5$	$C_{18}H_{14}N_2O_2S$	$C_{11}H_9NOS$
Formula weight	474.56	282.40	478.63	583.83	510.75	322.37	203.25
Crystal system	Triclinic	Triclinic	Monoclinic	Monoclinic	Triclinic	Orthorhombic	Orthorhombic
Space group	*P*-1	*P*1	$P2_1/n$	*P*21/*c*	*P*1	*Pbcm*	$Pna2_1$
a(Å)	9.47580(10)	9.7501(16)	8.5976(2)	9.5551(2)	5.1621(3)	5.1983(2)	9.9803(10)
b(Å)	9.74920(10)	9.9693(12)	28.2287(6)	17.7042(3)	9.5482(4)	7.8605(3)	16.7614(18)
c(Å)	26.1353(4)	15.583(3)	9.5512(2)	19.3409(5)	13.2970(73)	35.409(2)	5.6223(3)
α(°)	97.4930(10)	87.571(8)	90	90	70.293(2)	90	90
β(°)	90.7210(10)	87.548(4)	99.4300(10)	93.8900(10)	85.521(2)	90	90
γ(°)	92.9810(10)	84.241(8)	90	90	86.786(4)	90	90
Z	4 (2 molecules)	4 (4 molecules)	4	4	1	4	4
Cell volume (Å^3)	2390.10(5)	1504.5(12)	2286.74(9)	3264.27(12)	614.18(5)	1446.86(11)	940.52(15)
μ (mm^{-1})	0.167	0.216	0.356	0.138	0.493	0.236	0.305
Crystal	Colourless block	Colourless block	Colourless prism	Colourless block	Orange lath	Colourless plate	Colourless blade
Crystal size (mm)	0.20 × 0.15 × 0.08	0.15 × 0.10 × 0.06	0.20 × 0.10 × 0.06	0.40 × 0.30 × 0.10	0.60 × 0.15 × 0.03	0.30 × 0.16 × 0.04	0.60 × 0.15 × 0.10
Reflections collected	16236	11960	6736	11226	5652	4436	4765
Independent reflections (R_{int})	8365 (0.0359)	9238 (0.0680)	4003 (0.0283)	5740 (0.0289)	3891 (0.0371)	1451 (0.0565)	1553 (0.0533)
Data/restraints/parameters	8365/0/631	9238/3/693	4003/0/285	5740/0/375	3891/3/284	1541/7/111	1553/1/131
Goodness-of-fit on F^2	0.883	0.943	1.035	1.038	1.196	1.040	1.063
Final *R* indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0414$, $wR\,2 = 0.0983$	$R1 = 0.0864$, $wR2 = 0.2258$	$R1 = 0.0369$, $wR2 = 0.0841$	$R1 = 0.0398$, $wR2 = 0.1044$	$R1 = 0.0508$, $wR2 = 0.1338$	$R1 = 0.0544$, $wR2 = 0.1392$	$R1 = 0.0430$, $wR2 = 0.1065$
R indices (all data)	$R1 = 0.0546$, $wR\,2 = 0.1081$	$R1 = 0.1342$, $wR2 = 0.2544$	$R1 = 0.0591$, $wR2 = 0.0919$	$R1 = 0.0502$, $wR2 = 0.1106$	$R1 = 0.0533$, $wR2 = 0.1404$	$R1 = 0.0757$, $wR2 = 0.1535$	$R1 = 0.0535$, $wR2 = 0.1123$
Largest difference peak and hole (e Å^{-3})	0.202 and −0.274	0.560 and −0.381	0.243 and −0.343	0.201 and −0.271	1.773 and −0.497	0.404 and −0.505	0.418 and −0.294
Flack parameter	–	0.06(14)	–	–	−0.04(14)	–	−0.02(14)

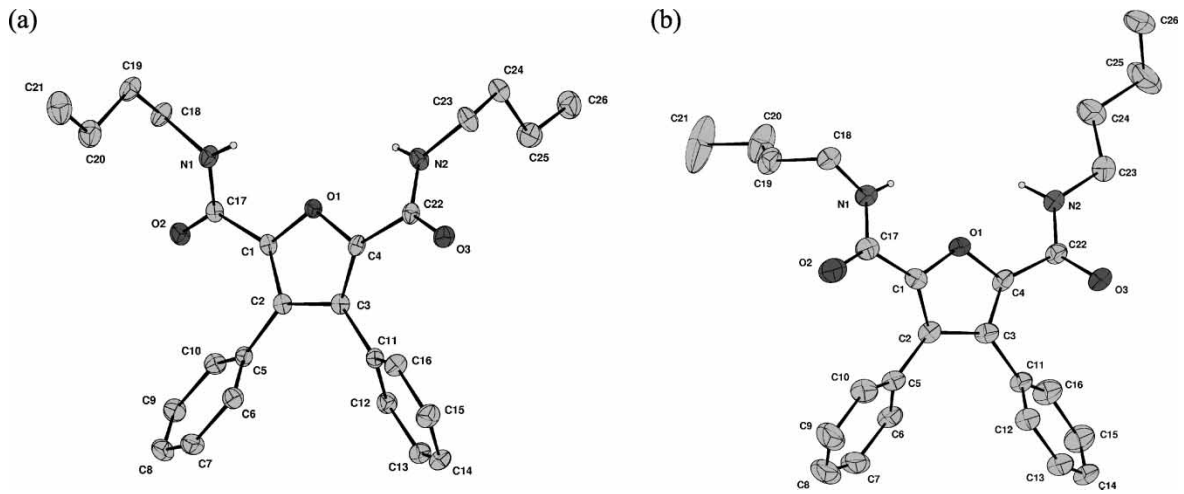


FIGURE 1 Thermal ellipsoid plots of the X-ray crystal structures of compound **1** obtained from diethylether (a) and ether:acetonitrile:dimethyl sulfoxide (2:2:1) (b) solutions. Non-acidic hydrogen atoms have been omitted for clarity.

Crystals of compound **2** suitable for single crystal X-ray diffraction analysis were obtained by slow evaporation of an acetonitrile solution of the receptor. As seen previously for the butyl derivative, the free receptor adopts a cleft conformation in the solid state (Fig. 3) the amide moieties point to opposite sides of the central furan ring, deviating from this ring plane by 26.8 and 20.6°. The hydrogen bond array (shown in Fig. 4) is similar to that seen with compound **1** when crystallised from diethylether (Fig. 2(a)). The molecules form chains along the *a*-axis via NH···O hydrogen bonds with the adjacent furan rings adopt alternating orientations. In this case there are two unique hydrogen bonds operating

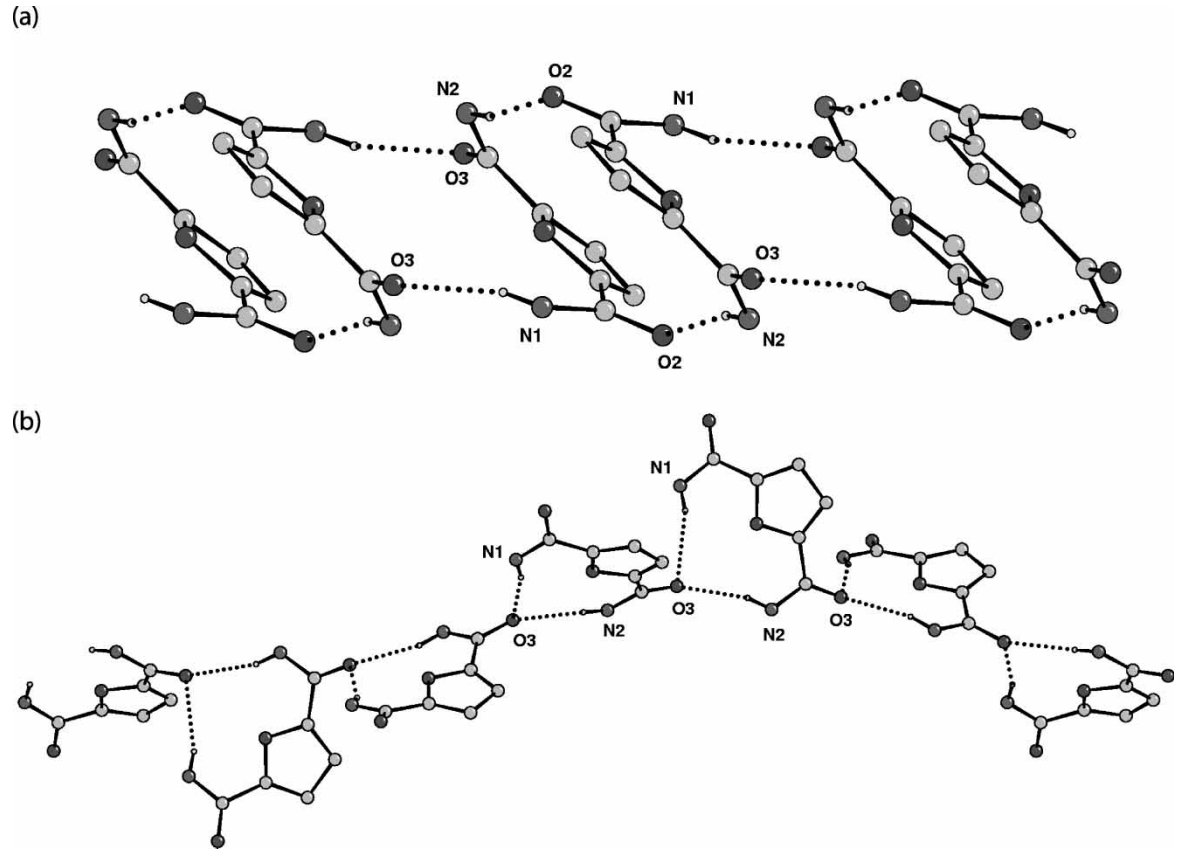


FIGURE 2 The X-ray crystal structures of compound **1** obtained from diethylether (a) and ether:acetonitrile:dimethyl sulfoxide (2:2:1) (b) solutions revealing different hydrogen bond arrays. Butyl and phenyl groups and non-acidic hydrogen atoms have been omitted for clarity.

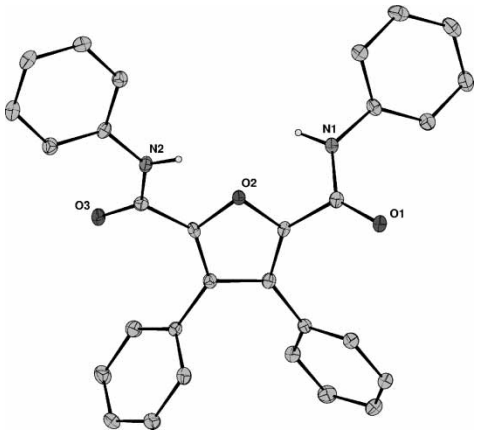


FIGURE 3 Thermal ellipsoid plot of the X-ray crystal structure of compound **2**. Non-acidic hydrogen atoms have been omitted for clarity.

as independent pairs; the shorter pair (N···O, 3.008(2) Å (N2—O1)) link the molecules into centrosymmetric dimers and the longer pair (N···O, 3.248(2) Å (N1—O3)) connect the dimers into chains.

Crystals of compounds **3** and **4** were both obtained by evaporation of acetonitrile solutions of the receptors. Compound **3** crystallised with the thioamide groups in an 'anti-anti' conformation while **4** adopted a cleft type conformation (Fig. 5).

No hydrogen bonding was observed in the extended structure of **3** presumably because the amide NH donors are unable to form hydrogen bonds due to the steric limitations introduced by the phenyl rings. However in the case of **4** the molecules form dimers (Fig. 6) through two NH···S hydrogen bonds (N···S distance of 3.469(7) Å) one from each receptor, the amide involved in this interaction shows a deviation from the furan plane of 18.0°. The other thioamide NH donor has a dihedral angle of 30.7° with the furan ring and is involved in hydrogen bonding to an acetonitrile molecule via NH···N hydrogen bonds (N···N distance of 3.063(5) Å (N1—N3)).

Crystals of compound **5** suitable for single crystal X-ray diffraction were obtained from an acetonitrile solution of the receptor. The receptor adopts an 'anti-anti' conformation with no hydrogen bond formation to either bound solvent or other molecules (Fig. 7).

Crystals of compound **6** were obtained from a methanol solution of the receptor by slow evaporation of the solvent. The crystal structure reveals four independent molecules in the asymmetric unit, with each one adopting an 'anti-anti' conformation (Fig. 8). The receptor forms layers of hydrogen-bonded sheets that alternate their direction and are perpendicular to the *c*-axis. Each sheet contains two of the four independent molecules. The hydrogen bonds are formed between the amide NH and a carbonyl group of an adjacent molecule, all the amide groups involved in hydrogen bonding have N···O distances within the range of 2.839(9) (N5—O2)–2.950(10) Å (N8—O3).

Crystals of compound **7** were obtained from a dimethyl sulfoxide solution of the receptor. In this case the receptor adopts a similar conformation to that of **6** but crystallised with two molecules of hydrogen-bonded solvent (Fig. 9).

Crystallisation of compound **9** was achieved from a dimethyl sulfoxide solution of the receptor. The X-ray crystal structure of the DMSO solvate is shown in Fig. 10. As seen with the amide derivative **7**, the thioamide analogue of **9** adopts an 'anti-anti' conformation with two hydrogen-bonded dimethyl sulfoxide molecules. One of the molecules is bound by a single NH···O interaction (N···O distance 2.768(5) Å) while the other has both NH···O (N···O distance 2.868(6) Å) and NH···S (N···S distance 3.643(4) Å) hydrogen bonds. The shorter NH···O hydrogen bond lengths observed with **9** compared to those seen with **7** are consistent with the formation of stronger hydrogen bonds (in the solid state).

Crystals of compound **11** were obtained from a dimethyl sulfoxide solution of the receptor (Fig. 11a). The structure is disordered with a carbon C10 and sulfur S1 atom sharing the same site. The side arms are in the 'anti-anti' conformation forming hydrogen bonds to an adjacent molecule (Fig. 11b).

Compound **12** was crystallised from a dimethyl sulfoxide solution of the receptor. The X-ray crystal structure is shown in Fig. 12. The molecules form chains along the *a*-axis via formation of hydrogen bonds from an amide NH (and thiophene CH) to a carbonyl oxygen of an adjacent molecule (Fig. 13). The alternating molecules are nearly orthogonal to each other.

The stability constants for receptors **1**–**12** with a variety of anionic guests (added as their tetrabutylammonium salts) were determined by ^{1}H NMR titration techniques with the data fitted using the EQNMR computer program [26]. The results of these studies are summarised in Table III. Due to solubility reasons and to maintain a consistent data set all of

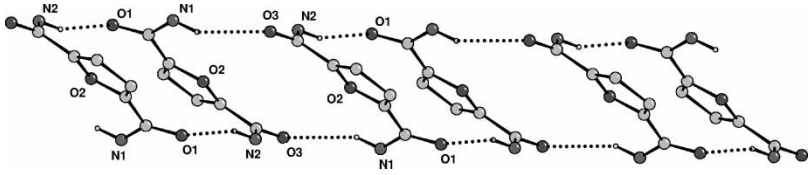


FIGURE 4 The hydrogen-bonding array present in the crystals of compound **2**. Phenyl rings and non-acidic hydrogen atoms have been omitted for clarity.

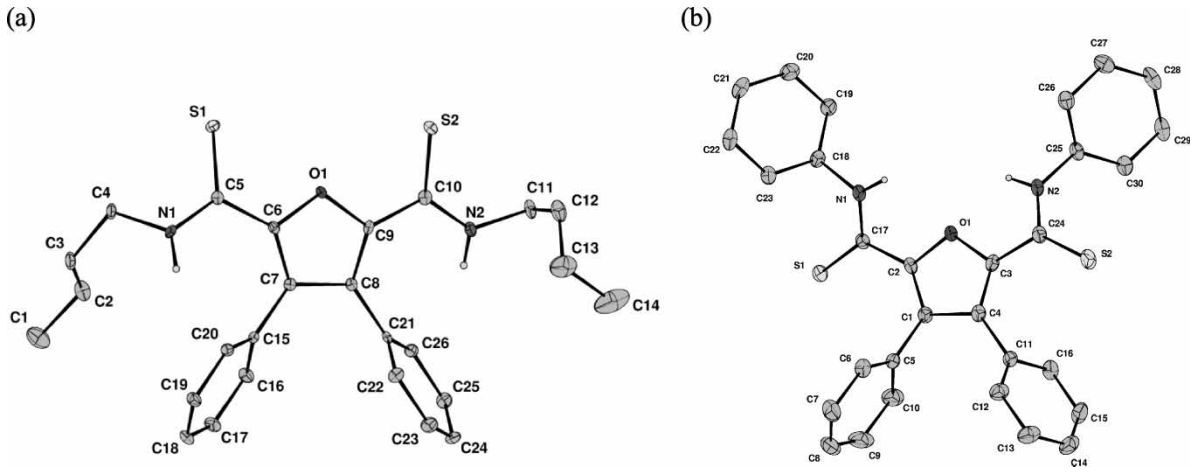


FIGURE 5 X-ray crystal structures of compounds **3** (a) and **4** (b). Non-acidic hydrogen atoms have been removed for clarity.

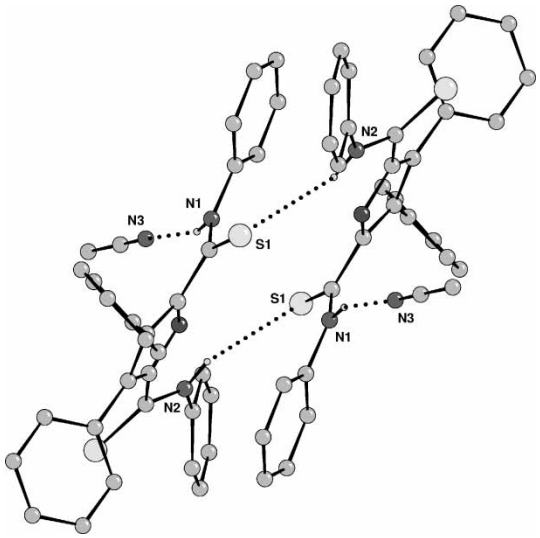


FIGURE 6 The X-ray structure of the 2:2 assembly formed between **4** and acetonitrile in the solid state. Non-acidic hydrogen atoms have been omitted for clarity.

the titrations were performed in dimethyl sulfoxide-d_6/0.5% water solution. The values reported in Table III were obtained by fitting the shifts of the amide NH resonance upon addition of various anionic guests using a 1:1 receptor:anion binding model. As seen in the majority of cases, addition of fluoride induced a broadening of the amide NH proton resonance such that a fit could not be obtained. Titrations with hydrogensulfate and bromide anions were conducted, although the data have been omitted as negligible or no binding was observed with any of the receptors under these conditions.

The results reveal that the both of the oxoamide derivatives **1** and **2** are selective for fluoride, this is in contradistinction to the previously reported 2,5-diamidopyrroles that showed selectivity for oxo-anions [13–19]. The selectivity for oxo-anions by the pyrrolic systems is believed to be due to the formation of three hydrogen bonds to the anion [13–19]. The 'substitution' of furan for the pyrrole heterocycle

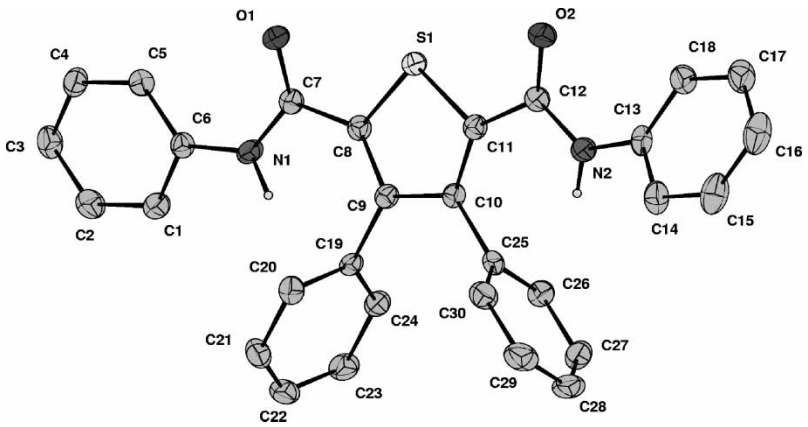


FIGURE 7 Thermal ellipsoid plot of the X-ray crystal structure of compound **5**.

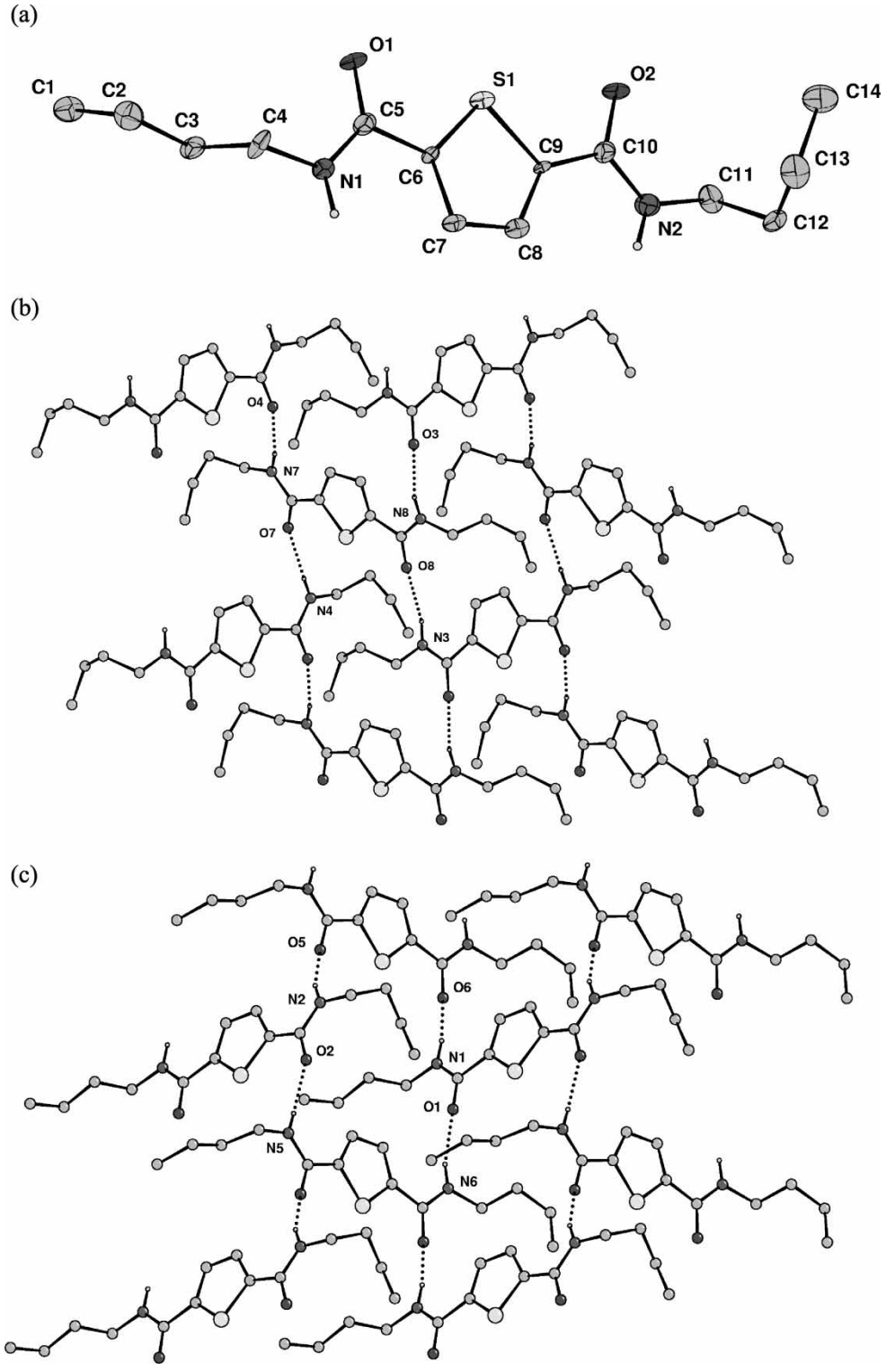


FIGURE 8 (a) Thermal ellipsoid plot of the X-ray crystal structure of compound **6** (the first of four independent molecules in the asymmetric unit—the others are labelled in a similar fashion). This compound packs in alternating hydrogen-bonded sheets. North–South in the ab plane (b), East–West in the ab plane (c) with an average N···O distance of 2.879(9) Å. Non-acidic hydrogen atoms have been omitted for clarity.

at the core of the receptor has replaced an NH bond donor for an oxygen atom and also introduced a repulsive electrostatic component upon anion binding. Previous work by Crabtree and co-workers showed that 2,6-diamidopyridines also showed enhanced selectivity for fluoride over larger halides as compared to analogous isophthalamides [8].

The thioamide **3** shows enhanced anion binding when compared to the analogous oxoamide **1**. This receptor binds chloride, benzoate and dihydrogen

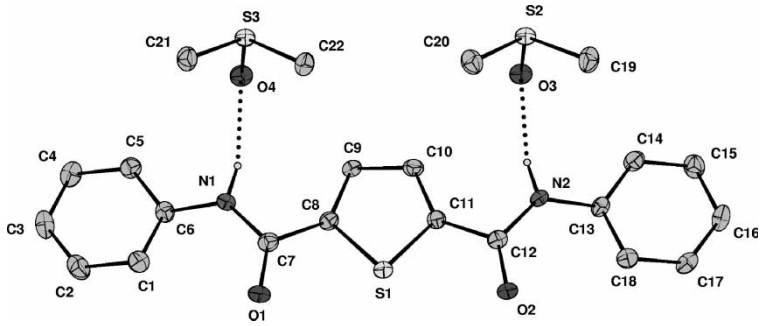


FIGURE 9 Thermal ellipsoid plot of the crystal structure of compound **7** with N···O distances of 2.945(2) (N1—O4) and 2.907(2) Å (N2—O3). Non-acidic hydrogens have been omitted for clarity.

phosphate anions with higher affinities, with the latter having the most notable improvement in binding affinity with an increase from 46 to 176 M^{-1}. The enhancement in anion binding is presumably a direct result of the increased acidity of the thioamide NH hydrogen bond donor, thus forming stronger complexes with anions. The increased acidity of the thioamide can also account for the broadening of the amide resonance seen in titrations with compound **4**.

The furan receptors have revealed interesting hydrogen bonding interactions in the solid state and for this reason we wished to discover whether any self association processes would occur in solution. We have recently seen the formation of pyrrole anion dimers in solution and the solid state with deprotonated 2,5-diamido-3,4-dichloropyrroles through the formation of four amide NH···N^- hydrogen bonds. Dilutions studies on compounds **1** and **2** were conducted in dimethyl sulfoxide-d_6/0.5% water solution; however, no perturbation of the amide resonances was observed. In dichloromethane-d_2 the amide NH resonance of the butyl derivative **1** shifts by 0.26 ppm (6.14–6.40 ppm) in a concentration range of 2–56 mM. Elaboration of the dilution curve using software provided by Professor C. A. Hunter [27] (NMRDILL_Dimer) showed that the compound appears to dimerise in solution, albeit weakly, with a dimerisation constant of 1.7 M^{-1}.

We decided to synthesise analogous thiophene based receptor **5** in order to investigate the effect of the central heteroatom. This receptor showed lower affinities for anions than **2** (presumably due to the presence of the larger heteroatom). Additionally we were unable to calculate a stability constant with fluoride due to the amide NH resonance broadening during the titration. We therefore decided to synthesise thiophene-based receptors **6** and **7** that would introduce additional thiophene backbone CH protons that could be followed during the titrations.

The results summarised in Table III indicate that the thiophene receptors bind dihydrogen phosphate more strongly than chloride, bromide, hydrogen sulfate and benzoate anions. The butylthioamide **8** binds both dihydrogen phosphate and benzoate anions more strongly than the similar oxoamide **6**. In both cases the stability constant has more than doubled. The NH resonance for compound **9** broadened upon addition of both dihydrogen phosphate and benzoate anions; however, it was possible to follow the thiophene CH resonance, although accurate values for the stability constant were not obtained due to odd profile curves.

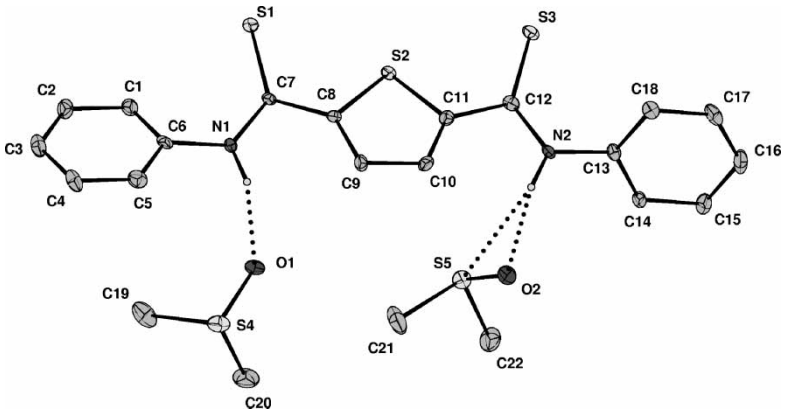


FIGURE 10 Thermal ellipsoid plot of the X-ray crystal structure of compound **9** co-ordinating two molecules of dimethyl sulfoxide. Non-acidic hydrogen atoms have been omitted for clarity.

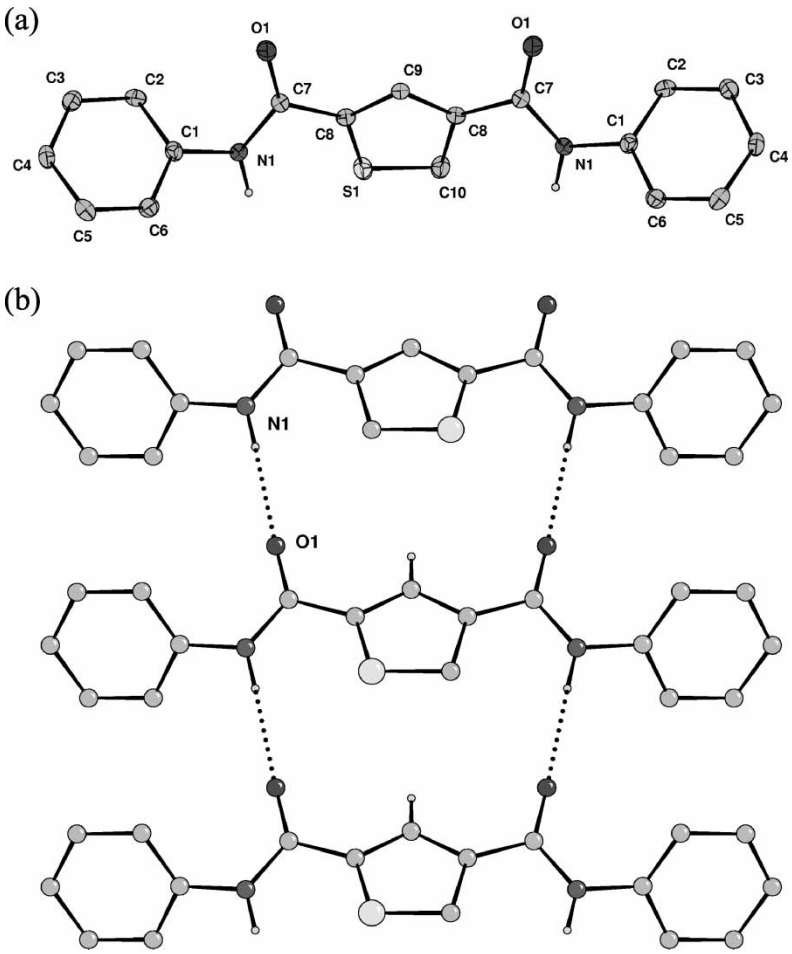


FIGURE 11 (a) Thermal ellipsoid plot of the X-ray crystal structure of compound **11** (disorder is not shown). (b) Hydrogen bonding in the solid state illustrating the disorder present in this structure. Non-acidic hydrogen atoms have been omitted for clarity.

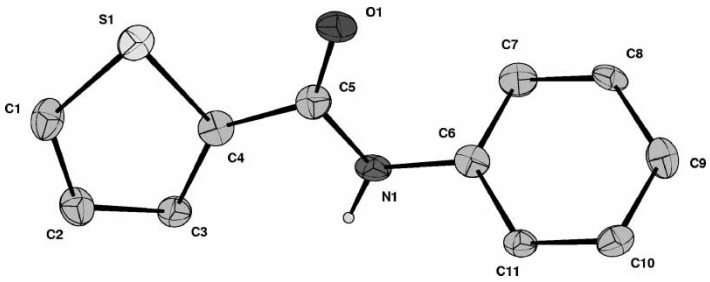


FIGURE 12 Thermal ellipsoid plot of the crystal structure of compound **12.** Non-acidic hydrogen atoms have been omitted for clarity.

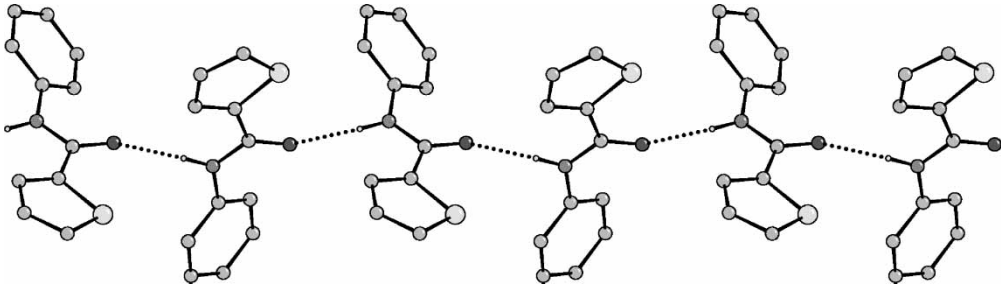


FIGURE 13 Compound **12** packs in infinite chains along the *a*-axis (N···O distance 2.891(4) Å). Non-acidic hydrogen atoms have been omitted for clarity.

TABLE III III Calculated association constants for compounds 1–12 (using NH resonance NMR shifts) in dimethyl sulfoxide-d_6/0.5% water solution at 298 K

	Association constants K_a (M^{-1})													
Anion:	1	2	3	4	5	6	7	8	9	10†	10‡	11†	11‡	12
Fluoride	557	1140	*	*	*	*	*	*	*	*	*	*	*	*
Chloride	14	47	23	20	n/a	< 10	< 10	< 10	11	< 10	< 10	< 10	< 10	n/a
Dihydrogen phosphate	46	78	176	*	97	13	48	45	*	156	159	1508	1625	21
Benzoate	28	48	68	*	10	< 10	23	24	*	36	37	173	169	10

Anions added as their tetrabutylammonium salts. *Resonance broadened during titration. †Calculated using most upfield amide resonance. ‡Calculated using most downfield amide resonance.

Interestingly with these anions the thiophene CH proton of **9** was observed to shift upfield, yet with all the other anions and receptors studied showed a downfield shift in the ^{1}H NMR spectrum. The downfield shift of the thiophene CH resonance allowed the calculation of stability constants that were in agreement with those obtained following the amide resonance.

The NH proton resonance broadened upon addition of tetrabutylammonium fluoride to solutions of the thiophene receptors **6**–**9**, while the thiophene CH protons remained sharp allowing them to be followed throughout the titrations. Using this method the binding data for compound **6** could be fitted using a simple 1:1 host:guest binding model giving an stability constant of 82 M^{-1}, while the data collected for **7**–**9** suggested that multiple equilibria processes were occurring in solution. The titration plots of chemical shift (of the thiophene CH resonance) against concentration of fluoride contained characteristic profiles that would not allow simple 1:1 or 2:1 fluoride: receptor binding models to be applied. In the case of compound **7** the thiophene resonance undergoes an initial downfield shift of around 0.3 ppm followed by a upfield shift after the addition around 1.3 equivalents of fluoride (Fig. 14).

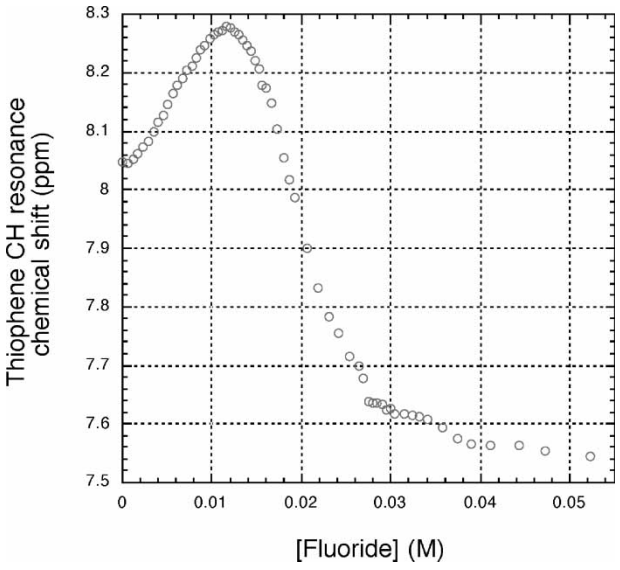


FIGURE 14 ^{1}H NMR titration curve of compound **7** with tetrabutylammonium fluoride in dimethyl sulfoxide-d_6/0.5% water solution following the thiophene CH resonance shift.

Addition of fluoride (and hydroxide, not shown) to compound **7** induces a dramatic colourless to yellow colour change (Fig. 15), a much weaker yellow colour is observed upon addition of benzoate and dihydrogen phosphate anions. There are previous reports in the literature that observe a colour change upon addition of anions to aromatic compounds that contain hydrogen bond donors [28]. Inspired by this unexpected colour change we attempted to gain solution phase complexation information by UV/Vis titration. Unfortunately numerous attempts to obtain stability constants by this method were unsuccessful as the data could not be fitted satisfactorily to a binding model. The absorbance spectrum of compound **7** in the absence and presence of ten equivalents of fluoride is shown in Fig. 16. The spectrum of the free

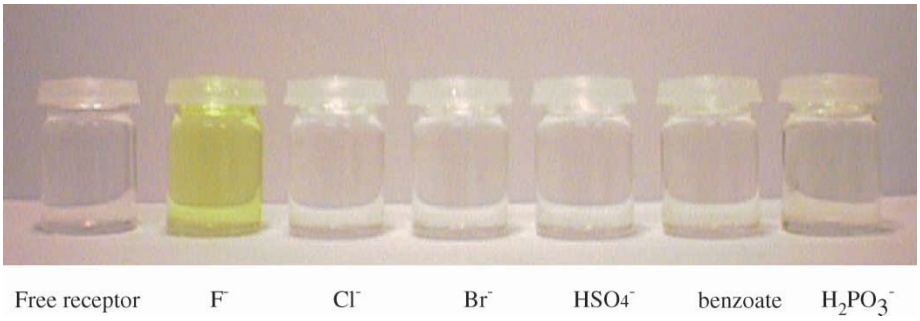


FIGURE 15 Solutions of compound **7** (2 mM) with 10 equivalents of tetrabutylammonium anion salt in dimethyl sulfoxide/0.5% water.

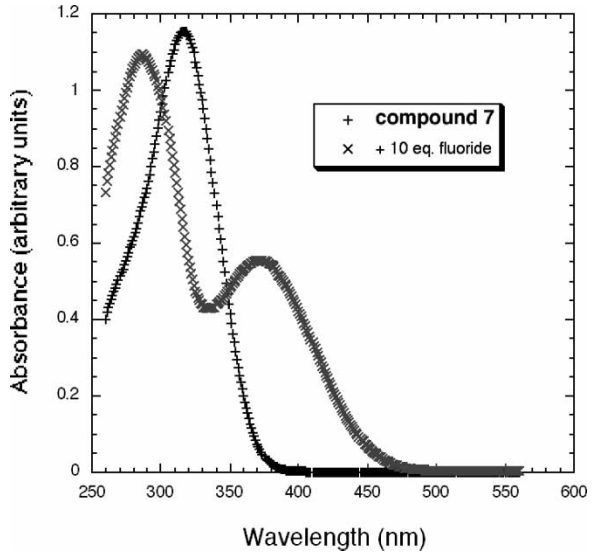


FIGURE 16 UV/Vis spectra of compound **7** (0.05 mM) in dimethyl sulfoxide/0.5% water in the absence and presence of 10 equivalents of fluoride.

receptor shows a single peak at 317 nm, when the receptor is in the presence of ten equivalents of fluoride this peak disappears and two new peaks form at 286 and 371 nm.

Crystals of the fluoride complex of **7** suitable for single crystal X-ray analysis were obtained by slow evaporation of a dichloromethane solution of the receptor in the presence of an excess of tetrabutylammonium fluoride. The 2:2 cyclic receptor:fluoride complex contains both NH···F^- (with N···F distances of 2.5903(16) (N1—F1) and 2.6187(16) Å (N2—F1) and N—H···F^- angles of 157.3 and 168.4°, respectively) and CH···F^- (with C···F distances of 3.13(4) (C9—F1) and 3.05(4) Å (C10—F1) and C—H···F^- angles of 140.6 and 148.5°, respectively) hydrogen bonds in the solid state (Fig. 17).

The crystal structure revealed that in the solid-state fluoride is bound by **7** in a 2:2 complex, via CH hydrogen bonds from the thiophene backbone to the fluoride anion. As previously discussed, the thiophene proton resonance could be followed in the titrations of compounds **6**–**9** and apart from a couple of instances (compound **9** with benzoate and dihydrogen phosphate) a downfield shift of this resonance was observed, consistent with hydrogen bond formation in solution. We therefore decided to synthesise thiophene receptors that could utilise this hydrogen bond donor in conjunction with the both amide groups by producing 2,4-diamidothiophenes.

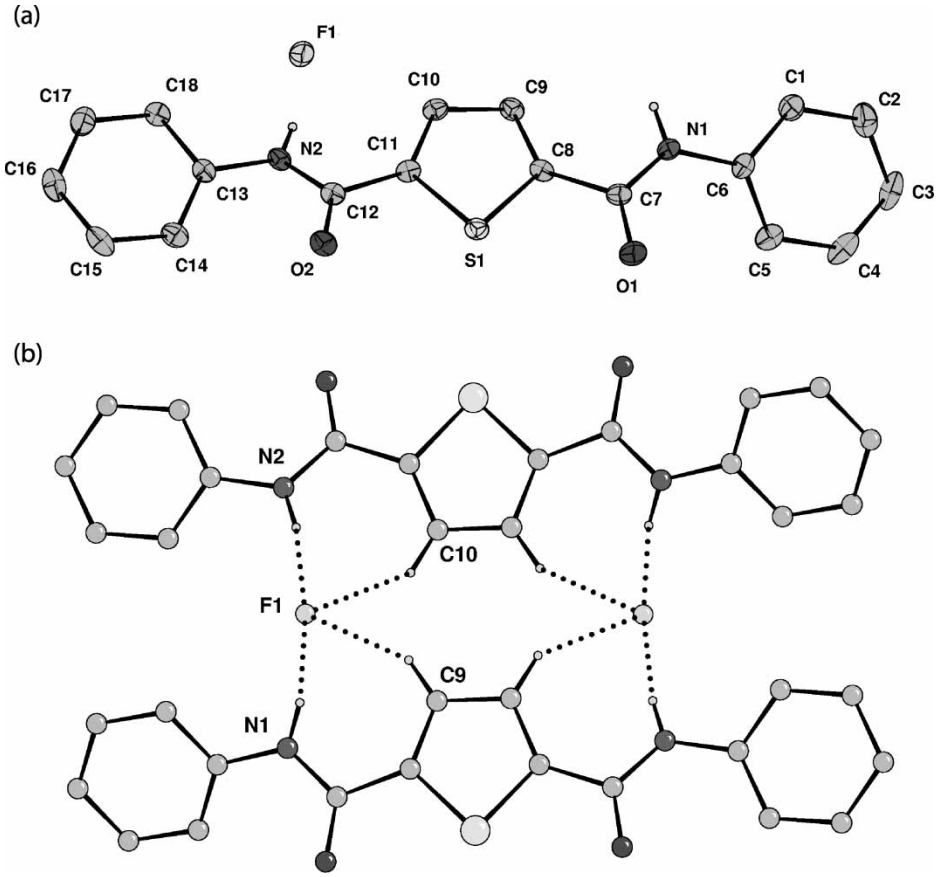


FIGURE 17 (a) Thermal ellipsoid plot of the X-ray crystal structure of the complex formed between **7** and fluoride. Tetrabutylammonium counter cations and non-acidic hydrogen atoms have been omitted for clarity. (b) Coordination environment of the two fluoride anions in the 2:2 complex.

Receptors **10** and **11** do not contain a C_2 symmetry axis through the sulfur atom and therefore the amide and thiophene protons present in the molecule are inequivalent in the proton NMR spectrum. In most cases it was possible to follow all four of the proton shifts, with each titration profile producing stability constants that were in good agreement with each other. These results show similar trends to those previously seen for the 2,5-substituted compounds. The phenylamide receptor **11** forms stronger complexes with anions than the butyl receptor **10** with both binding dihydrogen phosphate more strongly than benzoate, chloride, bromide and hydrogen sulfate. However there is a much higher affinity and selectivity shown for dihydrogen phosphate by the 2,4-diamido derivatives, with **11** showing an stability constant K_a of $1508\,M^{-1}$, which is over 100 times greater than that obtained with **6**. Again broadening of the NH proton resonances upon addition of tetrabutylammonium fluoride was observed; however, the thiophene protons could be followed throughout the titrations. The *n*-butyl functionalised derivative **10** gave data that could be fitted using a 1:1 binding model, a stability constant of $203\,M^{-1}$ was calculated using the most upfield thiophene resonance. As with compound **7** the titration profiles obtained with **11** and fluoride were complicated (Fig. 18) and we have been unable to fit the data using simple binding models. Addition of basic anions to solutions of **11** resulted in a colourless to yellow colour change analogous to that seen for **7**.

The fluoride titration curve of the most up-field thiophene CH resonance is shown in Fig. 18(a), an initial downfield shift is followed by an upfield shift, with a further downfield shift seen at higher concentrations of the anion before reaching a plateau region. We presume this indicates that there are multiple equilibria occurring in solution although it may be that the fluoride is deprotonating the receptor. The titration curve of the most downfield CH resonance (Fig. 18(b)) is significantly different but again could not be fitted to a simple binding model.

Dilution studies were performed on compound **11** in dimethyl sulfoxide-d_6/0.5% water and showed no evidence of self-association in solution. Over the concentration range 0.5×10^{-4}–$7.1 \times 10^{-2}\,M$, no significant shifts in the proton NMR of either the amide or thiophene resonances were observed.

Compounds **10** and **11** show a higher affinity for anions than receptors **6** and **7**, presumably due to the absence of the sulfur atom between the amide groups. The largest improvement in binding was observed for the dihydrogen phosphate anion. Receptor **7** binds dihydrogen phosphate with $K_a = 48\,M^{-1}$ while the 2,4-diamido derivative **11** has a stability constant $K_a = 1508\,M^{-1}$. Previous studies on the anion binding properties of 2,5-diamidopyrrole clefts [13–19] have shown that these receptors are selective for oxo-anions, a finding attributed to the ability of the receptors to form three hydrogen bonds to the guest species [13–19]. Indeed, a diphenylamide pyrrole derivative bound dihydrogen phosphate with an stability constant $K_a = 1450\,M^{-1}$ in the same solvent system used to measure the anion binding abilities of the thiophene receptors. The value obtained with **11** is comparable to the pyrrole system, suggesting that in addition to removing the sulfur-anion repulsion interaction, the thiophene CH hydrogen was involved in anion binding. In order to investigate this hypothesis we decided to synthesise thiophene-2-phenylamide **12**.

Addition of fluoride to receptor **12** broadened the NH resonance, and therefore a stability constant could not be obtained. We therefore attempted to follow other proton resonances present in the receptor, again we have been unable to fit any of the data using standard NMR procedures due to strange titration profiles. This may suggest that a deprotonation process is occurring in solution, or

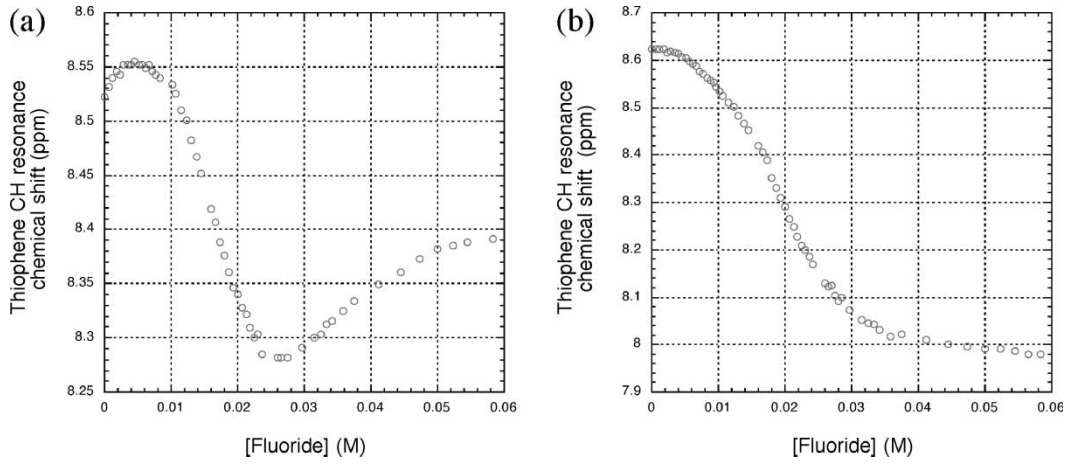


FIGURE 18 Plots of the observed shifts seen for the thiophene resonances of compound **11**, most upfield resonance (a) and downfield resonance (b).

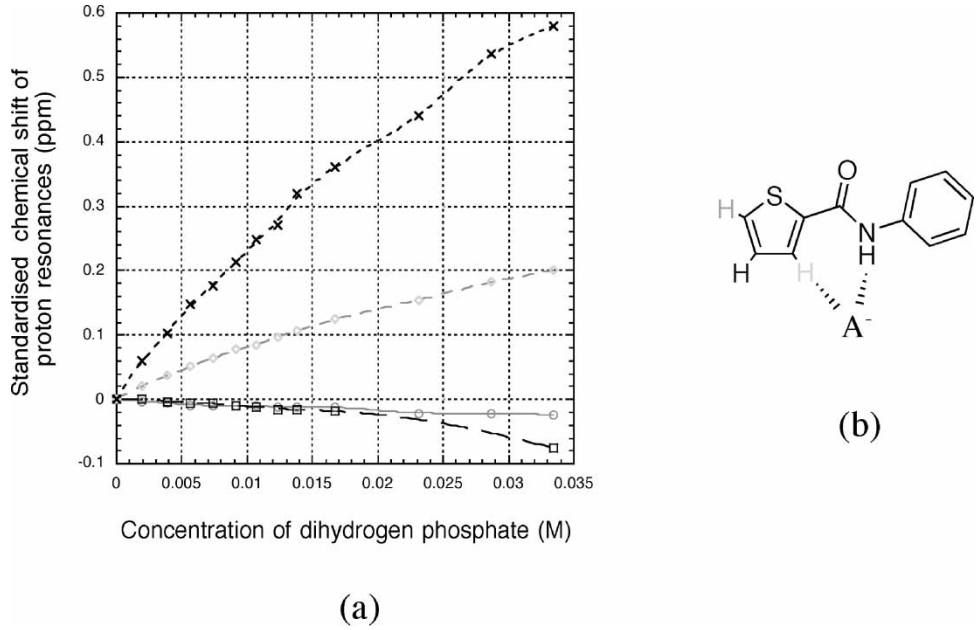


FIGURE 19 A standardised plot of the observed shifts seen for the thiophene and amide resonances of compound **12** upon addition of tetrabutylammonium dihydrogen phosphate (a). A schematic representation of the hydrogen bonds employed by **12** when binding anions (b).

that an ensemble of fluoride complexes of differing constitutions are forming in solution which cannot be fitted to simple binding models. The addition of less basic anions allowed stability constants to be obtained with **12** and anionic guests.

Further evidence for CH···anion hydrogen bond formation in solution is shown in Fig. 19. The plot shows standardised chemical shifts for the amide NH (upper plot) and the three thiophene CH protons upon addition of dihydrogen phosphate to a solution of **12**. In the case of the amide NH a downfield shift is observed and a stability constant $K_a = 21\,M^{-1}$ can be calculated. In addition one of the thiophene CH resonances also shifts downfield while the other two are perturbed slightly upfield. Calculation of the stability constant using the downfield shifted thiophene resonance gives a value in excellent agreement with that obtained using the amide with $K_a = 24\,M^{-1}$. The same effect is seen upon addition of benzoate anions to a solution of receptor **12**.

CONCLUSION

A variety of heterocycle-based amide and thioamide receptors have been synthesised (**1**–**12**). None of the 2,5-diamidofurans or thiophenes that were crystallised formed an orthogonal interlocked hydrogen bonding array (as we have been observed previously with analogous 2,5-diamidopyrrole anions) suggesting that this type of interlocked hydrogen bonding requires an electrostatic component from the negatively charged heterocycle in order to form [13–19]. In contradistinction to the 2,5-diamidopyrrole anion systems, the 2,5-diamidofuran and thiophenes cases so far studied, no involvement of the heteroatom of the heterocycle in hydrogen bond acceptance has been observed but rather for formation of amide-amide NH···OC or thioamide-thioamide NH···SC hydrogen bonds leading to a variety of non-interlocked hydrogen bonded solid state arrays.

The affinity for anions of the amidofurans and thiophenes was measured in polar solvent mixtures by ^{1}H NMR titration techniques. The central heteroatom has been shown to alter the selectivity and binding affinities displayed by the receptors.

The furan-based host species (e.g. **1**–**2**) show up to a 40-fold selectivity for fluoride (compound **1**) over other putative anionic guests. It is believed that the oxygen atom within the central ring promotes this selectivity because larger anionic guests are repelled more by the presence of the oxygen lone pairs. The strategy of converting the amide groups to thioamides was successful with more stable complexes being formed.

The thiophene-based receptors **6** and **7** were found to bind anions less strongly the furan analogues. The thioamide derivatives **8** and **9** showed a marginal enhancement in anion binding relative to the corresponding amide species. Unusual titration curves were obtained upon addition of fluoride anions to all of the phenylamide receptors suggesting that multiple equilibria are occurring in

solution or deprotonation of the receptors is occurring. Thiophene 2,4-diamides have been shown to be selective receptors for dihydrogen phosphate in solution showing comparable anion binding properties to 2,5-diamidopyrroles. NMR evidence suggests that compound **12** uses both CH and NH hydrogen bonds in anion co-ordination.

Acknowledgements

We would like thank the EPSRC for a quota studentship (C.N.W.) and for use of the crystallographic facilities at the University of Southampton. P.A.G. would like to thank the Royal Society for a University Research Fellowship. We would also like to thank Salvatore Camiolo for assistance with the synthesis of the furan derivatives.

References

[1] Kavallieratos, K.; de Gala, S. R.; Austin, D. J.; Crabtree, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 2325.
[2] Hossain, M. A.; Llinares, J. M.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2001**, *40*, 2936.
[3] Deetz, M. J.; Shang, M.; Smith, B. D. *J. Am. Chem. Soc.* **2000**, *122*, 6201.
[4] Mahoney, J. M.; Beatty, A. M.; Smith, B. D. *J. Am. Chem. Soc.* **2001**, *123*, 5847.
[5] Wisner, J. A.; Beer, P. D.; Drew, M. G. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 3606.
[6] Wisner, J. A.; Beer, P. D.; Drew, M. G. B.; Sambrook, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 12469.
[7] Coles, S. J.; Frey, J. G.; Gale, P. A.; Hursthouse, M. B.; Light, M. E.; Navakhun, K.; Thomas, G. L. *Chem. Commun.* **2003**, 568.
[8] Kavallieratos, K.; Bertao, C. M.; Crabtree, R. H. *J. Org. Chem.* **1999**, *64*, 1675.
[9] Szumna, A.; Jurczak, J. *Eur. Org. Chem.* **2001**, 4031.
[10] Lee, H-J.; Choi, Y-S.; Lee, K-B.; Park, J.; Yoon, C-J. *J. Phys. Chem. A* **2002**, *106*, 7010.
[11] Inoue, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* **2003**, *44*, 5167.
[12] Hossain, M. A.; Kang, S. O.; Llinares, J. M.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2003**, *42*, 5043.
[13] Gale, P. A.; Camiolo, S.; Chapman, C. P.; Light, M. E.; Hursthouse, M. B. *Tetrahedron Lett.* **2001**, *42*, 5095.
[14] Gale, P. A.; Camiolo, S.; Tizzard, G. J.; Chapman, C. P.; Light, M. E.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2001**, *66*, 7849.
[15] Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E. *Tetrahedron Lett.* **2002**, *43*, 6995.
[16] Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E.; Shi, A. J *Chem. Commun.* **2002**, 758.
[17] Gale, P. A.; Navakhun, K.; Camiolo, S.; Light, M. E.; Hursthouse, M. B. *J. Am. Chem. Soc.* **2002**, *124*, 11228.
[18] Camiolo, S.; Coles, S. J.; Gale, P. A.; Hursthouse, M. B.; Tizzard, G. J. *Supramol. Chem.* **2003**, *15*, 231.
[19] Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E. *Org. Biomol. Chem. Commun.* **2003**, *1*, 741.
[20] Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E.; Warriner, C. N. *Tetrahedron Lett.* **2003**, *44*, 1367.
[21] Gale, P. A.; Hursthouse, M. B.; Light, M. E.; Warriner, C. N. *Collect. Czech. Chem. Comm.* **2004**, in press.
[22] Backer, H. J.; Stevens, W. *Recl. Trav. Chim. Pays-Bas* **1940**, *59*, 423.
[23] Yde, B.; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S-O. *Tetrahedron* **1984**, *40*, 2047.
[24] MacDowell, D. W. H.; Ballas, F. L. *J. Org. Chem.* **1977**, *42*, 3717.
[25] Galvez, C.; Garcia, F.; Garcia, J.; Soldevila, J. *J. Heterocycl. Chem.* **1986**, *23*, 1103.
[26] Hynes, M. J. *J. Chem. Soc. Dalton Trans.* **1993**, 311.
[27] Bisson, A. P.; Hunter, C. A.; Morales, J. C.; Young, K. *Chem. Eur. J.* **1998**, *4*, 845.
[28] Miyaji, H.; Sessler, J. L. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 154.