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Anion complexation properties of 2,2′-bisamidodipyrrolylmethanes†

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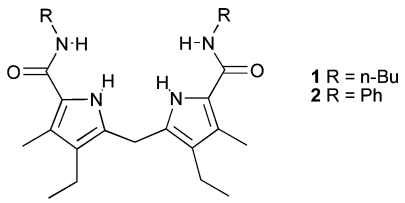
Two new bis-amido dipyrrolylmethanes (bis-*N*-butylamide-5,5′-methylenebis(4-ethyl-3-methyl-2-pyrrolecarboxylate) 1 and bis-*N*-phenylamide-5,5′-methylenebis(4-ethyl-3-methyl-2-pyrrolecarboxylate) 2 have been synthesised and shown to exhibit selectivity for oxo-anions from among a variety of putative anionic guest species in DMSO/water solution.

Biological examples of anion complexation by pyrrole are quite rare. In 1992, crystallographic studies on porphobilinogen deaminase[1] revealed the presence of a dipyrrolylmethane co-factor coordinating a carboxylate group from the protein backbone (Asp 84) *via* NH···OC hydrogen bond interactions. Other natural examples include the prodigiosins, tripyrrolic molecules that function as HCl symport agents.[2] Inspired by this former biological example of carboxylate complexation by a dipyrrolylmethane, we decided to extend our recent work on 2,5-bisamidopyrrole anion complexation[3] to dipyrrolylmethane systems by synthesising amide functionalised dipyrrolic molecules and studying their anion complexation ability. We have recently shown that in the solid state, a bis-*n*-butyl-2,5-diamidopyrrole forms a complex with benzoate wherein two hydrogen bonds (one pyrrole NH and one amide NH) are formed to one oxygen atom of the anion whilst the other oxygen accepts a third hydrogen bond from the other amide group.[4] The receptors reported here have the potential to form four hydrogen bonds to an oxo-anionic guest and hence we believed that these receptors may show enhanced oxo-anion selectivity.

Compounds **1** and **2** were synthesised by reaction of diethyl-5,5′-methylenebis(4-ethyl-3-methyl-2-pyrrole carboxylate) with *n*-butylamine or aniline in the presence of trimethylaluminium in dry dichloromethane at 35 °C.[5] The reactions were quenched with dilute HCl and were extracted with dichloromethane, dried over $MgSO_4$, reduced *in vacuo* and purified by column chromatography on silica gel gradient eluted with dichloromethane–dichloromethane/2% methanol affording the compounds **1**[6] and **2**[7] in 43 and 40% respective yields.



1 R = n-Bu
2 R = Ph

Crystals of compounds **1**‡ and **2**§ were obtained by slow evaporation of solutions of the receptors in dichloromethane/methanol mixtures. Thermal ellipsoid plots of the structures are shown in Fig. 1.

The compounds **1** and **2** form extended hydrogen bonded sheets in the solid state. For example the packing diagram of compound **2** is shown in Fig. 2. Pyrrole NH and amide NH groups form a convergent hydrogen bonding array coordinating a carbonyl group from an adjacent molecule. A similar array is formed by compound **1** in the solid state (see ESI†).

Proton NMR titrations in DMSO-d_6/5% water were used to determine the association constants of **1** and **2** with a variety of anionic guests.[8] The results, shown in Table 1, show that receptors **1** and **2** bind fluoride and benzoate with significant affinities in this solvent mixture with a 1 : 1 receptor : anion stoichiometry. The titration with dihydrogen phosphate and compound **1** could not be fitted to a 1 : 1 receptor : anion binding model. This behaviour has been observed before in related

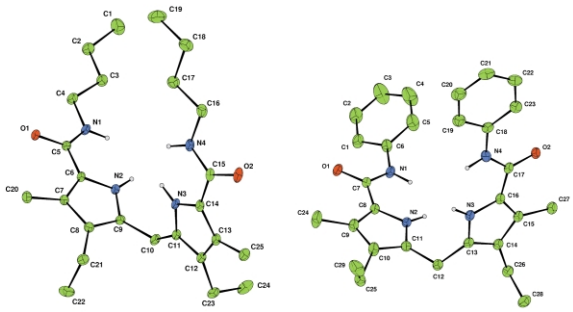


Fig. 1 The crystal structures of **1** (left) and **2** (right). Ellipsoids drawn at the 35% probability level and non NH hydrogens omitted for clarity.

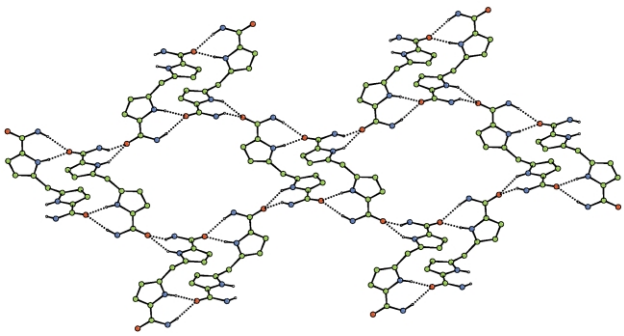


Fig. 2 Hydrogen bonded sheets formed in the solid state by compound **2** *via* NH···OC hydrogen bonds. Side chain ethyl, methyl and phenyl groups and non-acidic hydrogen atoms have been omitted for clarity.

Table 1 Stability constants K_a (M^{-1}) of compounds **1** and **2** with a variety of putative anionic guests (added as tetrabutylammonium salts) at 298 K in DMSO-d_6/5% water (except where noted)[a]

Anion	Compound **1**	Compound **2**
F^-	7560	8990
Cl^-	23	43
Br^-	13	10
$H_2PO_4^-$	[b]	[b]
HSO_4^-	44	128
Benzoate	354	424
F^-[c]	11	114
$H_2PO_4^-$[c]	20	234

[a] Errors estimated to be no more than ±15%. [b] An adequate fit could not be obtained (see Fig. 3). [c] Measured in DMSO-d_6/25% water.

† Electronic supplementary information (ESI) available: H-bonded sheets in **1** in the solid state; NMR and ES+ MS spectra. See http://www.rsc.org/suppdata/cc/b3/b303532h/

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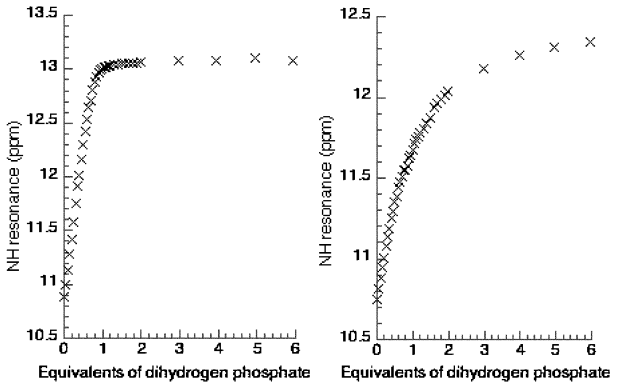
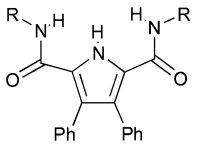


Fig. 3 Proton titration curve for titration of compound **2** *vs.* tetrabutylammonium dihydrogenphosphate in DMSO-d_6/5% water (left) and DMSO-d_6/25% water (right).

systems.[3] In the case of compound **2**, the addition of aliquots of $H_2PO_4^-$ gave a very sharp titration curve in DMSO-d_6/5% water (Fig. 3) and hence the titrations with dihydrogen phosphate were performed in DMSO-d_6/25% water with both compounds in order to obtain reliable stability constant values. These were found to be 19 M^{-1} and 234 M^{-1} for compounds **1** and **2** respectively.

In order to compare these compounds with the previous generation of pyrrole–amide cleft systems (*e.g.* **3** and **4**) titrations were repeated with benzoate with these receptors in DMSO-d_6/5% water. In these cases it was observed that the affinity of compound **4** was lower for benzoate (103 M^{-1}) whilst with compound **3** broadening of the amide NH resonance prevented a stability constant determination by this method under these conditions.



3 R = n-Bu
4 R = Ph

Compounds **1** and **2** both bind fluoride strongly in DMSO-d_6/5% water, but perhaps the most notable result from these studies is the fact that compound **2**, a neutral hydrogen bond donor, was found to complex dihydrogen phosphate very strongly in this solvent mixture and even forms a complex with this anion in DMSO-d_6/25% water (an extremely competitive solvent mixture) with a stability constant of 234 M^{-1}. However, this anion is bound only weakly by compound **1** (20 M^{-1}) under these conditions. In order to provide a benchmark to which we could compare these results we re-determined the stability constants of **1** and **2** with fluoride in this more polar solvent mixture. We found that fluoride is bound by receptors **1** and **2** with stability constants of 11 and 114 M^{-1} respectively in DMSO-d_6/25% water.

These results have shown that bis-amido dipyrrolylmethanes are effective anion receptors even in partially aqueous solutions. Compounds **1** and **2** therefore expand the lexicon of acyclic pyrrolic anion receptors (the crystal structure of a fluoride complex of a simple dipyrrolylmethane has recently been reported by Sessler and co-workers)[9] and provide a new approach to anion complexation in competitive media. We are currently working to produce analogous receptors with two alkyl groups attached to each of the '*meso*-carbons' for improved stability[10] (these compounds discolour in solution over a few days due to oxidation) and to increase the anion affinity of these systems. The results of these studies will be reported in due course.

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Notes and references

‡ Crystal data for **1** $C_{25}H_{40}N_4O_2$, M_r = 428.61, T = 120(2) K, triclinic, space group $P\bar{1}$, a = 12.7164(2), b = 14.1868(2), c = 15.2266(2) Å, α = 77.200(1), β = 75.516(1), γ = 76.190(1)°, V = 2544.22(6) Å^3, ρ_{calc} = 1.119 g cm $^{-3}$, μ = 0.072 mm^{-1}, Z = 4, reflections collected: 48899, independent reflections: 8967 (R_{int} = 0.0559), final R indices [$I > 2\sigma I$]: $R1$ = 0.0501, $wR2$ = 0.1422, R indices (all data): $R1$ = 0.0599. $wR2$ = 0.1579.

§ Crystal data for **2** $C_{29}H_{32}N_4O_2$, M_r = 468.59, T = 120(2) K, monoclinic, space group $P2_1/c$, a = 11.011(3), b = 17.487(3), c = 13.771(2) Å, β = 95.628(16)°, V = 2638.9(9) Å^3, ρ_{calc} = 1.179 g cm $^{-3}$, μ = 0.075 mm^{-1}, Z = 4, reflections collected: 12855, independent reflections: 3783 (R_{int} = 0.0339), final R indices [$I > 2\sigma I$]: $R1$ = 0.0646, $wR2$ = 0.1685, R indices (all data): $R1$ = 0.0809. $wR2$ = 0.1831. CCDC 207873–207874. See http://www.rsc.org/suppdata/cc/b3/b303532h/ for crystallographic data in CIF or other electronic format.

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6 Spectroscopic data for compound **1**: ^{1}H NMR 300 MHz in DMSO-d_6 δ (ppm): 0.86 (m, 12H, CH_3), 1.30 (qt, 4H, CH_2), 1.46 (tt, 4H, CH_2), 2.13 (s, 6H, CH_3), 2.27 (q, 4H, CH_2), 3.19 (dt, 4H, CH_2), 3.27 (s, 2H, CH_2), 7.11 (t, 2H, NH), 10.56 (s, 2H, NH). ^{13}C NMR 75.4 MHz in DMSO-d_6 δ (ppm): 10.4, 13.8. 15.7, 16.8, 19.7, 22.2, 31.7, 38.2, 120.1, 120.9, 121.5, 127.5, 161.6. ES$^+$ mass spectrum, m/z, 451.3 (M·Na$^+$). Microanalysis: Calc. For $C_{25}H_{40}N_4O_2$·0.5MeOH: C 68.88, H 9.52, N 12.60, Found: C 68.75, H 9.53, N 12.72%.
7 Spectroscopic data for compound **2**: ^{1}H NMR 300 MHz in DMSO-d_6 δ (ppm): 0.89 (t, 6H, CH_3), 2.23 (s, 6H, CH_3), 2.33 (q, 4H, CH_2), 3.86 (s, 2H, CH_2), 7.02 (t, 2H, ArH), 7.30 (t, 4H, ArH), 7.64 (d, 4H, ArH), 9.26 (s, 2H, NH), 10.90 (s, 2H, NH). ^{13}C NMR 75.4 MHz in DMSO-d_6 δ (ppm): 10.4, 15.5, 16.7, 22.6, 119.7, 120.6, 122.4, 122.8, 123.0, 128.4, 128.6, 139.5. ES$^+$ mass spectrum, m/z, 469.4 (M·H$^+$), 491.4 (M·Na$^+$), 937.4 (2M·H$^+$), 959.5 (2M·Na$^+$). Microanalysis: Calc. For $C_{29}H_{32}N_4O_2$·MeOH: C 71.97, H 7.25, N 11.19, Found: C 72.14, H 6.93, N 10.92%.
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