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# Pendant arm pyrrolic amide cleft anion receptors

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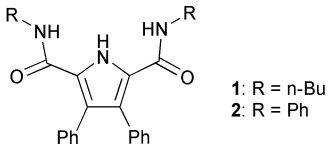
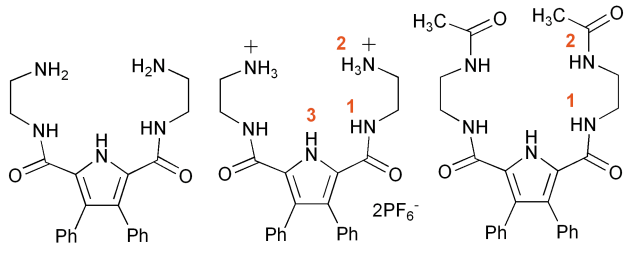
**The propensity of amine, ammonium and amide pendant arm 2,5-diamidopyrrole derivatives to act as anion receptors has been investigated; the anion-coordination ability of these species has been determined by $^1$H NMR titration techniques revealing a marked selectivity of the amine functionalised receptor for hydrogen sulfate anions.**

Recent developments in the area of anion recognition and sensing have produced a variety of new selective complexation agents for anionic guests.[1] However, the great variety of anionic species and their importance in the environment, in biological systems and potential medical applications presents a continuing challenge to design selective receptors.[2] We have recently reported that simple 2,5-diamidopyrroles such as **1** and **2** function as oxo-anion selective anion receptors in acetonitrile-$d_3$ and DMSO–0.5% $H_2O$ solutions.[3]




These receptors offer a number of possible avenues for modulating the anion affinity of the bis-amidopyrrole unit. For example the pyrrole group could carry alternate functional groups in the 3- and 4-positions[4] to withdraw or donate electron distribution to the receptor site and hence modulate the anion binding affinity or alternatively, functional groups may be appended to the amides to alter the selectivity.[5] Bowman-James *et al.* have found that amine containing macrocycles show a marked selectivity for protonated oxo-anions, binding these species strongly due to a proton transfer from the anion to the receptor causing the formation of a more highly charged anion and receptor pair.[6] We therefore decided to synthesise amine (**3**), ammonium (**4**) and amide (**5**) pendant arm receptor species in order to ascertain whether the amine pendant arm receptor would form stonger complexes with protonated oxo-anions such as $HSO_4^-$ than the analogous ammonium and amide pyrrole clefts.




3,4-Diphenylpyrrole-2,5-dicarboxylic acid chloride was prepared *via* literature methods.[3,7] This material was reacted directly with ethylenediamine in dichloromethane in the presence of a catalytic quantity of 4-dimethylaminopyridine. Removal of the solvent and subsequent purification by column chromatography on silica gel (eluting with dichloromethane–methanol 10 : 3 v/v) afforded the bis-amine **3**[8] in 70% yield. This receptor was protonated by dissolving the receptor in methanol followed by addition of 2 equivalents of hexafluorophosphoric acid to the solution. After stirring for 5 min the solvent was removed affording receptor **4**. Receptor **5**[9] was prepared by reaction of compound **3** with 2.5 equivalents of acetyl chloride in dichloromethane in the presence of triethylamine and a catalytic quantity of DMAP. After purification by column chromatography on silica gel (eluting with dichloromethane–methanol 10 : 1 v/v) the product was obtained in 41% yield.

Although we have yet to obtain a crystal structure of **3**, **4** or **5**, we have obtained crystals of the mono-hexafluorophosphate salt of **3** by dissolving compound **3** in methanol and adding 2 equivalents of $HPF_6$. Stirring the solution for 3 h resulted in the formation of a white precipitate that was collected by filtration. This material was crystallised from MeOH–water affording X-ray quality crystals from which the structure could be elucidated (Fig. 1).† Data for **3**·$HPF_6$·$2H_2O$ were collected on a Bruker Nonius Kappa CCD area detector equipped with a molybdenum rotating anode generator following standard procedures. The asymmetric unit contains $C_{22}H_{26}O_2^+ \cdot PF_6^- \cdot 2H_2O$. The hydrogens on the oxygen and nitrogen atoms were located from the difference map and fully refined. Although it was possible to refine three hydrogens on N5, the temperature factors where consistently higher than for those on N1 and therefore this group was modelled as a disordered $NH_2$ with each hydrogen having an occupancy of 2/3. This is consistent with having two water molecules and one $PF_6^-$. The structure consists of hydrogen bonded dimers interlinked in to a three-dimensional array by further extensive hydrogen bonding interactions involving $PF_6^-$, and $H_2O$.

The association constants of **3**, **4** and **5** with a variety of anions (determined by $^1$H NMR titrations[10] in DMSO-$d_6$–0.5% water except where noted) are shown in Table 1. When binding was observed with chloride, bromide, benzoate or hydrogensulfate the data fitted a 1 : 1 receptor:anion binding model well. The NMR titration curves with fluoride showed the presence of multiple equilibria in solution with **3**, **4** and **5**. We are currently investigating these systems further. The bis-amine receptor **3** is a weak chloride receptor and does not appear to interact with bromide under these conditions. In addition, in this

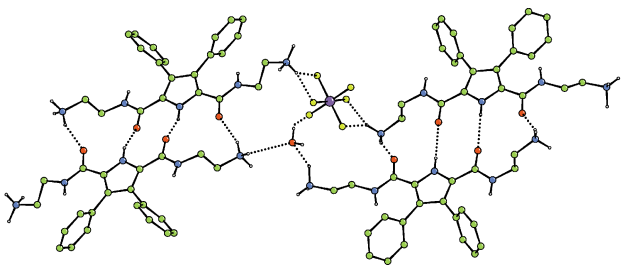


**Fig. 1** Part of the three dimensional hydrogen bonded network showing the formation of dimers and their linking *via* bridging $PF_6^-$ and $H_2O$ groups. Key: carbon – green, nitrogen – blue, oxygen – red, fluorine – light green, phosphorus – purple. Selected hydrogen atoms have been omitted for clarity.

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case the association with benzoate is weak (in contrast to other 2,5-diamidopyrrole clefts such as **1** and **2**). Dihydrogenphosphate was found to bind strongly to this receptor (with a plateau at one equivalent of anion), however large errors were present in the least squares non-linear fit of the titration curve. We therefore attempted to weaken the interaction by carrying out an NMR titration in the presence of 5% water. Even under these competitive conditions an association constant of 2050 $M^{-1}$ was found, although this value should be treated with caution as the systematic errors in this data set were non-random. In the presence of 0.5% water in DMSO-$d_6$, a very strong complex was formed with $HSO_4^-$ ($K_a > 10^4$ $M^{-1}$). It is likely that these strong interactions are due to protonation of the receptor by the anion, as observed by Bowman-James and co-workers[6] in amine containing macrocyclic systems, so adding an electrostatic component to the binding interaction (and the bound anion now carrying a higher negative charge). Therefore where proton exchange is occurring, the association constant can only be regarded as 'apparent' data as the binding process is accompanied by proton transfer. Further evidence for this mechanism comes from the data found for receptor **5**. In this case, protonation of the receptor is not possible, a fact that is reflected in the lower affinity constants for dihydrogenphosphate and the failure of the receptor to interact with hydrogensulfate. The bis-ammonium based receptor **4** shows enhanced binding of halide anions as compared to receptor **3** reflecting the extra electrostatic component to the binding interaction. It is unlikely that hydrogensulfate is being deprotonated by this receptor and instead the lack of an interaction may once again reflect the absence of proton exchange (and hence no formation of $SO_4^{2-}$). Wherever possible, we have calculated the asscociation constant by following a variety of protons on the receptor (in the case of **4** with chloride and **5** with dihydrogenphosphate and benzoate). These protons are marked 1, 2 and 3 on the structures of the receptors and the association constants determined by their shifts are so designated in Table 1.

In the case of **4** with chloride, the association constants determined by the shift of the pyrrole and amide NH protons are in close agreement, whereas the association constant determined by following the shift of the ammonium protons is considerably lower. In the case of receptor **5** and dihydrogenphosphate and benzoate, the association constants determined by following the shift of the amide group closer to the pyrrole ring gives a higher $K_a$ value. Presumably, the pyrrole NH and directly attached amides interact more strongly with the bound anion than the pendant hydrogen bond donors, however it is interesting that the same result is not obtained for all these protons.

**Table 1** Association constants of anions with receptors **3**, **4** and **5**

| Compound | Anion[a] | $K_a/M^{-1}$ |
|---|---|---|
| **3** | Chloride | < 20 |
| **3** | Bromide | [b] |
| **3** | Dihydrogenphosphate | 2050[c] |
| **3** | Benzoate | 47.6 |
| **3** | Hydrogensulfate | > $10^4$ |
| **4** | Chloride | (1) 110, (2) 39, (3) 140[d] |
| **4** | Bromide | 35 |
| **4** | Dihydrogenphosphate | 44 |
| **4** | Benzoate | 125 |
| **4** | Hydrogensulfate | (1,2) < 20[d] |
| **5** | Chloride | < 20 |
| **5** | Bromide | [b] |
| **5** | Dihydrogenphosphate | (1) 525 (2) 190[d] |
| **5** | Benzoate | (1) 152 (2) 19.5[d] |
| **5** | Hydrogensulfate | [b] |

[a] Anions added as tetrabutylammonium salts. Errors < 15% except where noted. Binding data with fluoride showed complex behaviour that could not be fitted to a simple 1:1 anion:receptor binding model. [b] No binding observed. [c] High errors were obtained when fitting this data to a 1:1 binding model for titrations carried out in DMSO-$d_6$–0.5% water therefore this titration was repeated in DMSO-$d_6$–5% water solution (error 29%). [d] Several NH proton resonances were followed during the NMR titration with association constants being calculated for each. The protons can be identified by the numbers shown which correspond to the labels present in the diagrams of the structures of **2** and **3**.

We have shown that the nature of the pendant arm groups present in 2,5-diamido-cleft anion receptors has a profound modulating influence on the anion selectivity of the receptor. In particular, the presence of a protonatable amine alters the affinity of the receptor in favour of acidic oxo-anions.

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## Notes and references

† *Crystal data* for **3**·$HPF_6$·$2H_2O$: $C_{22}H_{30}F_6N_5O_4P$, $M_r$ = 573.48, $T$ = 120(2) K, orthorhmobic, space group *Pbca*, $a$ = 16.1973(5), $b$ = 9.3378(2), $c$ = 34.0104(12) Å, $V$ = 5144.0(3) Å$^3$, $D_c$ = 1.481 g cm $^{-3}$, $\mu$ = 0.19 mm$^{-1}$, $Z$ = 8, reflections collected: 18704, independent reflections: 4519 ($R_{int}$ = 0.156), final $R$ indices [$I > 2\sigma I$]: $R1$ = 0.065, $wR2$ = 0.138, $R$ indices (all data): $R1$ = 0.174. $wR2$ = 0.177. CCDC reference number 186190. See http://www.rsc.org/suppdata/cc/b2/b204295a/ for crystallograpic data in CIF or other electronic format.


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8 *Spectroscopic data* for compound **3**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.62 (m, 4H, $CH_2NH_2$), 3.24 (m, 4H, $NHCH_2$), 5.87 (s, 2H, CONH), 7.07–7.28 (m, 10H, ArH), + obscured amine $NH_2$, 4H). $^{13}$C NMR (75.4 MHz, DMSO-$d_6$) $\delta$ 41.0, 42.3, 124.4, 126.2, 126.5, 127.6, 130.6, 134.2, 160.4. ES$^+$ mass spectrum: $m/z$, 392 (M + H$^+$), 785 (2M + H$^+$). Microanalysis: Calc. for $C_{22}H_{25}N_5O_2$·$0.2CH_2Cl_2$·$0.2CH_3OH$: C 64.85, H 6.37, N 16.88. Found: C 65.24, H 6.06, N 16.52%.

9 *Spectroscopic data* for compound **5**: $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.88 (s, 6H, $CH_3$), 3.12 (q, 4H, $J$ 5.47 Hz, $CH_2NHCOCH_3$), 3.20 (q, 4H, $J$ 5.47 Hz, PyrroleCONHCH$_2$), 7.14–7.32 (m, 10H, ArH), 7.36 (t, 2H, $J$ 5.69 Hz, N*H*COCH$_3$), 7.94 (t, 2H, $J$ 5.69 Hz, N*H*COPyrrole), 11.99 (s, br, 1H, N*H*-Pyrrole). $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 23.2, 38.9, 40.1, 123.9, 126.7, 128.3, 128.9, 130.7, 133.1, 161.5, 170.7. ES$^+$ mass spectrum: $m/z$, 476 (M + H$^+$), 951 (2M + H$^+$). Microanalysis: Calc. for $C_{26}H_{29}N_5O_4$·$0.25CH_2Cl_2$·$0.25CH_3OH$: C 63.05, H 6.09, N 13.87. Found: C 63.14, H 5.86, N 13.44%.

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