Acyclic pyrrole-based anion receptors: design, synthesis, and anion-binding properties†‡

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A series of novel, acyclic pyrrole-based anion receptors is described that bind nitrite and carboxylate anions with good selectivity in dichloroethane solution. These systems, which are based on pyridine 2,6-dicarboxamides, also bind cyanide anions weakly. Control systems, incorporating a benzene-1,3-dicarboxamide spacer or wherein the connectivity of the amide linkage is "reversed", either failed to act as effective anion receptors or displayed very different selectivities.

Introduction

In recent years, anions have come to be increasingly appreciated as important targets for study. Anions play key roles in a wide range of catalytic processes, both chemical and biochemical, with phosphate anions, in particular, being involved in a range of transformations associated with energy transduction and information storage.[1] In contrast, deficiencies in the binding and transport of chloride anions are implicated in a range of diseases, including cystic fibrosis and Dent's disease.[1–3] On the environmental level, soluble pollutants, such as nitrate and phosphate, are responsible for the eutrophication of rivers and lakes, while the presence of sulfate anions in waste streams interferes with the vitrification processes currently proposed for the stabilization of nuclear waste.[4,5] This ubiquity of function has made the area of synthetic anion receptor design one of the fastest growing subdisciplines within supramolecular chemistry.[1,6] However, in spite of considerable advances, the construction of new, easy-to-make anion receptors remains a challenge. This is particularly true for systems that display anion-binding selectivities that differ from those expected on the basis of anion charge density or relative basicity.[1,5,6]

Pyrrole-containing species, due to their versatility and diversity, have attracted considerable attention, both as anion-binding agents and as sensors.[1,7] Pyrroles are easily functionalized, are capable of reversible hydrogen-bonding with anions and can be easily incorporated into various neutral, charged, cyclic, or acyclic systems. Thus, they have been used in numerous applications, ranging from anion recognition and sensing to the construction of elaborate anion-binding supramolecular complexes.[7–9] Pyrroles have a potential advantage over most other nitrogen–hydrogen bond-containing entities (*e.g.*, amides, amines, ureas) in that they lack an internal hydrogen-bond acceptor, obviating what are common complications associated with intra- and inter-receptor hydrogen-bonding interactions. Finally, the relatively high pK_a of the pyrrole N–H group (about 16–17) helps prevent competition from anion-induced deprotonation except under forcing conditions.[10–13]

In recent years, there has been an increased focus on acyclic pyrrole-based anion receptors that incorporate an amide moiety.[1,8]§¶ This effort has its antecedents in seminal studies by Crabtree and Anslyn *et al.*, who demonstrated that isophthaloyldiamide- and pyridine-2,6-dicarboxamide systems are capable of anion complexation through hydrogen bonding, a theme to which we and others have recently contributed.[14–16] Subsequent to the report by Crabtree *et al.*, Schmuck demonstrated that pyrrole-amide-containing guanidinium receptors have an ability to complex amino acids, while Gale was able to show that simple pyrrole-amide ligands, derived from pyrrole-2,5-dicarboxylic acids, are single-handedly capable of selective anion-complexation.[17,18] Inspired by these efforts, our own group has been working to develop amide-based receptors where the amide nitrogen is derived from an amino-pyrrole subunit.[18] In this report, we describe a new series of acyclic anion receptors (**3** and **4**; Scheme 1) that incorporate a central pyridine unit flanked by two pyrroles through pyrrole-amine-derived amide linkages, as well as control systems wherein the central pyridine ring has been replaced by a phenyl group (*i.e.*, isophthaloyldiamide spacer) or the configuration of the amide linkages is reversed (*cf.* structures **5** and **6**; Schemes 1 and 2, respectively). These systems, which provide a set of analogous compounds wherein several important design predicates may be examined, including the presence or absence of an internal hydrogen-bond acceptor group and the orientation of the amide group, were found to act as effective receptors for nitrite and carboxylate anions in dichloroethane solution.

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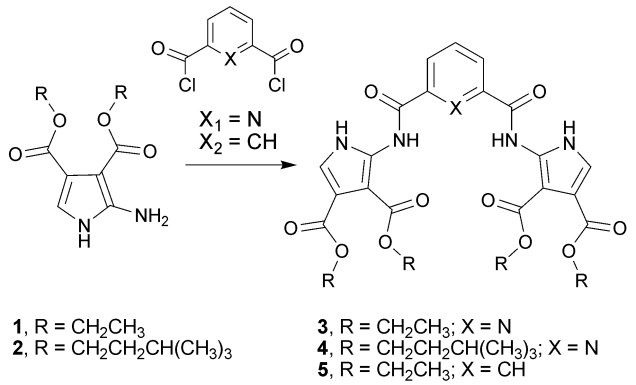
† Dedicated to Professor George Gokel on the occasion of his 60th birthday.

‡ Electronic supplementary information (ESI) available: Anion binding and job plot titration data; NOE spectroscopic data. See DOI: 10.1039/b615673h.

§ For publications from our own group, see: ref. 4.

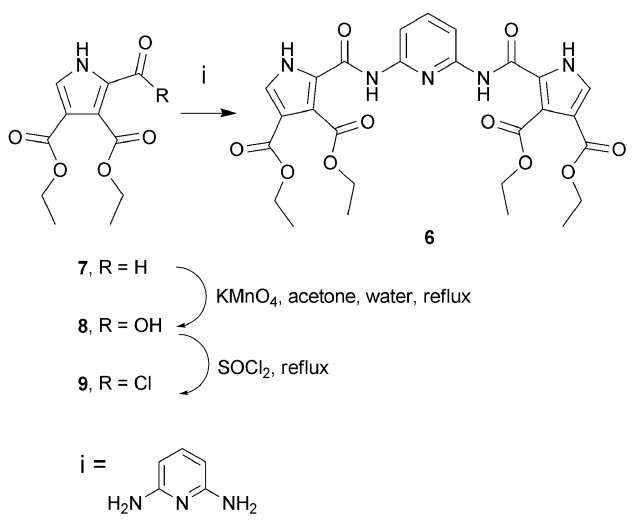
¶ Beer, and Reinhoudt and Antonisse were among the first to show the ability of an amide to participate in anion binding *via* hydrogen-bonding interactions involving the anion and the amide proton; see ref. 23.



Scheme 1 Synthesis of receptors **3**, **4** and **5**.

Results and discussion

One of the caveats to emerge from the study of previous acyclic amide-based receptor systems is that, in addition to the external hydrogen-bonding between the anion and receptor, intramolecular hydrogen-bonds can play a key role in stabilizing certain favorable structures and, in so doing, modulating the anion-binding affinity. Such effects have been invoked to explain the higher affinity for pyridine-2,6-dicarboxamide-derived systems, as opposed to the corresponding isophthaloyldiamide congeners.[14,16,20] Specifically, it has been suggested that intramolecular amide proton-to-pyridine nitrogen hydrogen-bonding helps lock the molecule into a pocket-like structure, wherein all the necessary hydrogen-bonding donors and acceptors are orientated "inward" such that anion binding is optimized. A similar rationale, supported by solid state structural data, was invoked by the Gale group to explain the high affinities of their cleft-like pyrrole-amide receptors.[7–9,18] Given this, the specific objectives of the present study were to generate pyridine- and phenyl-containing bis(pyrrole) receptors wherein the amino functionality was derived from the pyrrolic subunit. Such systems, which would be formally "reversed" (as far as the amide moieties are concerned) relative to the previous receptors of Gale, could contribute to a further understanding of internal hydrogen-bonding effects in particular, as well as those factors that influence anion recognition in a more global sense. This study was also expected to increase our understanding of 2-amino-pyrroles and their chemistry, since this is a class of potentially useful precursors that has not hitherto been extensively explored.



Scheme 2 Synthesis of receptor **6**.

Amino-pyrroles **1** and **2** were synthesized utilizing a procedure first described by Duffy and Wibberely, as modified recently by us.[19,21] The amino-pyrrole was then coupled to either pyridine-2,6- or benzene-1,3-diacid chloride in dichloromethane to yield diamides **3**, **4**, and **5** (Scheme 1). As detailed below, it was found that the pyridine-containing systems **3** and **4** possessed the ability to interact with selected anions in dichloroethane solution, whereas analogue **5** proved ineffective as an anion receptor.

Systems **3–5** were fully characterized by normal spectroscopic and mass spectrometric means. Further support for the proposed connectivity came from a single crystal X-ray diffraction analysis of receptor **3** (Fig. 1).‖ Suitable crystals were obtained by slow diffusion of hexane into a chloroform solution of **3**. As evidenced from this structure, the solid state conformation of receptor **3** is stabilized through a series of intramolecular hydrogen-bonds between O2 and N5H (2.71 Å, 119°), O1 and N1H (2.70 Å, 118°), N3 and N4H (2.71 Å, 106°), N3 and N2H (2.70 Å, 102°), O7 and N4H (2.81 Å, 121°), and O5 and N2H (2.73 Å, 122°).

Support for this structure being dominant in solution was obtained through NOE studies of the more soluble analogue, **4**, in chloroform-*d* at both high (40 °C) and low (0 °C) temperature. In particular, the NOE studies show that, when irradiated, the pyrrole N–H proton is strongly coupled with the α-proton of the pyrrole and weakly coupled with the amide proton (see ESI‡). These data support a conformation in which the pyrrole N–H is in close proximity to the α-proton of the pyrrole (as expected) and within the general vicinity of the amide proton. If the pyrrole N–H were directed inward, strong coupling between the amide proton and the N–H proton of the pyrrole would be expected. The absence of such coupling, while not a proof, provides support for the conclusion that the conformation seen in the solid state is retained in chloroform solution. Furthermore, when the amide proton is instead irradiated, no appreciable couplings to any other protons are observed, again supporting the hypothesis that receptors **3** and **4** adopt a conformation in chloroform solution that is similar to that seen in the solid state.

‖ Crystallographic summary for **3** ($C_{27}H_{29}N_5O_{10}\cdot CH_2Cl_2$). Very long, colorless lathes were grown by slow evaporation from dichloromethane, triclinic, $P\bar{1}$ (No. 2), $Z = 2$ in a cell of dimensions: $a = 11.6399(4)$, $b = 12.1551(4)$, $c = 12.5581(4)$ Å, $\alpha = 75.915(2)$, $\beta = 72.576(2)$, $\gamma = 76.920(2)°$, $V = 1621.52(9)$ Å^3, $\rho_{calc} = 1.37$ g cm^{-3}, FW = 668.48, $\mu = 0.262$ cm^{-1}, $F(000) = 696$. A total of 10314 reflections were measured, 5681 unique ($R_{int} = 0.036$), on a Nonus Kappa CCD using graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å) at −120 °C. The structure was refined on F^2 to an w$R = 0.215$, with a conventional $R = 0.0735$ (3283 reflections with $F_o > 4[\sigma(F_o)]$), and a goodness of fit = 1.16 for 388 refined parameters. The dichloromethane molecule was disordered and its contribution to the structure factors was removed by use of the utility Squeeze in Platon98.[24] CCDC reference number 625744. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b615673h

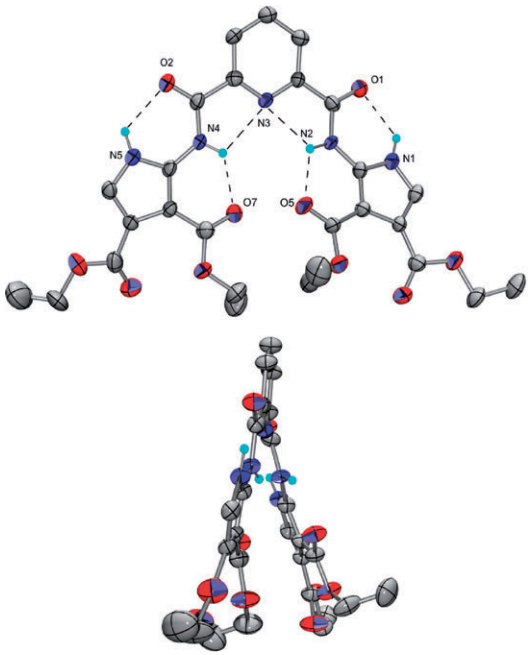


Fig. 1 (Top) Single crystal X-ray diffraction structure of receptor **3**, demonstrating the intramolecular hydrogen-bonding network; (bottom) side-view. The thermal ellipsoids are scaled to the 50% probability level.

In order to test the interactions of anions with receptors **3**, **4**, and **5**, UV-Vis spectrophotometric titrations in dichloroethane were carried out. Dichloroethane was chosen because it is a relatively nonpolar, aprotic solvent and does not interfere with receptor–anion hydrogen bonding. It also has the advantage of being less volatile than, *e.g.*, dichloromethane. When titrations were attempted using acetonitrile and dimethyl sulfoxide (DMSO) as the solvents, it was found that the solvent interacted strongly with the receptor, precluding an analysis of the presumed anion-based changes to the spectrum.

As can be seen from an inspection of Table 1, which contains a summary of the binding data for receptors **3–6** derived from studies carried out in dichloroethane, receptor **3** binds carboxylate (acetate, benzoate), nitrite, and cyanide anions well (studied as the corresponding tetrabutylammonium (TBA) salts), with the strongest interaction being seen in the case of benzoate anion. Little evidence of anion binding was seen for a range of other anions tested, including simple halides, hydrogen sulfate and nitrate, making this receptor noteworthy for its ability to bind selectively nitrite over nitrate.** This selectivity is rationalized in terms of nitrite being a stronger base than, *e.g.*, nitrate and, thus, a better hydrogen-bond acceptor.††

Table 1 Binding constants K_a (M^{-1}) of receptors **3–6** with a variety of anionic guests (added as the corresponding tetrabutylammonium salts) at 29 K in dichloroethane[a]

Anion	Receptor **3**	Receptor **4**	Receptor **5**	Receptor **6**
Benzoate	43 000	NB	WB	NB
Acetate	19 000	13 900	WB	NB
NO_2^-	13 000	WB[c]	WB	NB
CN^-	5 600	WB	WB	WB
NO_3^-	NB[b]	NB	NB	WB
Cl^-	NB	NB	NB	805
Br^-	NB	NB	NB	WB
HSO_4^-	NB	NB	NB	NB

[a] Errors estimated to be no more than 15%. [b] NB = No binding interaction observed. [c] WB = Evidence consistent with weak binding was observed; however, it was not possible to fit the data adequately to a 1 : 1, a 1 : 2, or 2 : 1 binding profile.

A slight color change (from clear to yellow) is observed upon addition of acetate, benzoate, nitrite, and cyanide anions to receptor **3** in dichloroethane. A similar color change is observed when the receptor is dissolved in acetonitrile and DMSO. However, to allow comparison to the NMR spectroscopy-based studies (carried out in chloroform-*d* for reasons of cost) only the first of these solvent systems was studied in detail. Job plot analysis of the UV-Vis titrations carried out in dichloroethane revealed a maximum at a 50% mole fraction, in accord with the proposed 1 : 1 binding stoichiometry; this proved true for all four anions for which an appreciable binding interaction was noted (Fig. 2).

The binding isotherms (Fig. 3) used to calculate binding constants of receptor **3** were "truncated" with respect to the full data set obtained from the anion titrations. While typical curved binding isotherms were seen upon the addition of 1–2 equivalents of anion, the adding of additional molar equivalents of the anion resulted in the appearance of a linear region in the binding isotherm. This finding is explained in terms of a second binding event that is too weak to cause the Job plot derived from the UV-Vis spectroscopic analysis to deviate from the functional behavior expected in the case of 1 : 1 binding stoichiometry. An alternative rationale, involving deprotonation of the pyrrole N–H protons, is considered unlikely in light of the relatively low basicity of the anions tested, and the fact that differing anions gave rise to similar behavior.

Further support for the notion that N–H deprotonation effects were not contributing to the anion-induced effects came from ^{1}H NMR spectroscopic analyses. These were carried out in chloroform-*d* under normal conditions of so-called NMR titration, with the spectra of the receptors being recorded in the presence of increasing concentrations of anions (*cf.*, *e.g.*, Fig. 4 and 5). A notable feature of these titrations is that the resonances corresponding to the pyrrole N–H proton, as well as the amide N–H signal, shift downfield over the course of the titration. However, the fact that these signals are observable throughout the titration is inconsistent with a deprotonation process involving the receptor. This is true for both receptors **3** and **4**. In the specific case of receptor **4**, the greater solubility of the receptor and, as a presumed consequence, the receptor–

** No clean binding profile was obtained in the case of TBA–H_2PO_4; while further analysis of the anion-induced effects are in progress, it is clear that this anion does not interact with receptor **3** in a simple 1 : 1, 1 : 2, or 2 : 1 manner under conditions identical to those employed in the case of the other anions. It was thus excluded from the present study.

†† Interestingly, a similar discrimination between nitrite and nitrate was recently observed by García-España, albeit in a very different inorganic zinc-based anion receptor; see ref. 25.

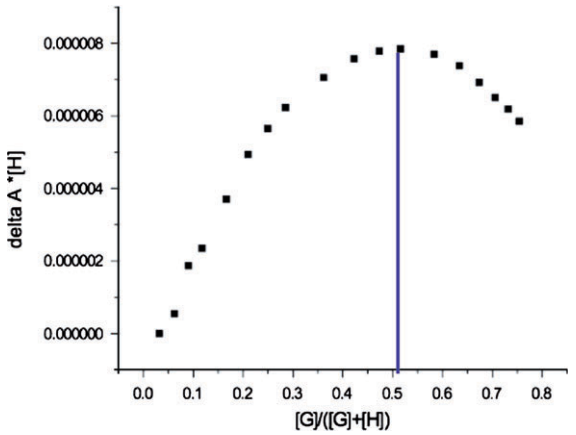


Fig. 2 Sample Job plot titration demonstrating 1 : 1 binding. Shown: TBA–CN titrated into receptor **3** in DCE.

anion complex, allowed the NMR spectroscopic titrations to be carried through the addition of 11.5 molar equivalents of acetate anion (*cf*. Fig. 5). At this latter juncture, where the anion-induced changes to the spectral features appeared complete, two distinct peaks corresponding to the amide protons, as well as two peaks representing the pyrrole N–H protons are seen. This finding is consistent with the conclusion that the receptor is not undergoing deprotonation in the presence of excess anion. However, at this point, what earlier in the titration is an initial splitting of the protons on the 2- and 4-positions of the pyridine ring is resolved into a doublet of doublets. A complete disappearance of the original pyrrole α-proton signal is also observed, a transformation that is correlated with the appearance of two additional peaks; one shifted slightly upfield (7.2 ppm; mostly likely representing the α-position of a pyrrole subunit that is not involved in anion

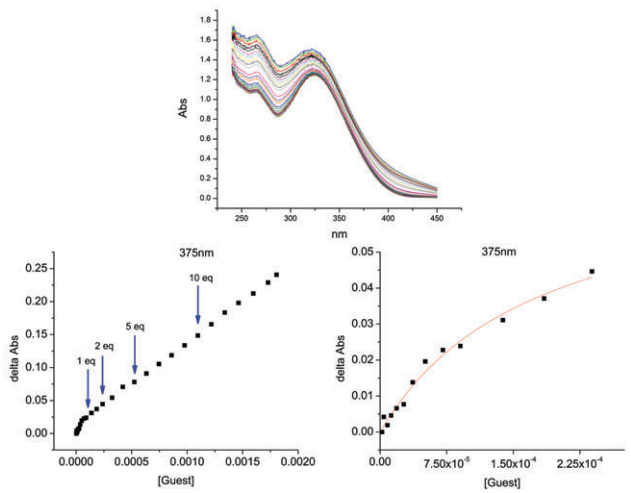


Fig. 3 (Top) Increase in UV-Vis spectral intensity seen when receptor **3** is titrated with increasing quantities of TBA–CN in dichloroethane; (bottom left) binding isotherm of the above titration showing changes seen upon the addition of 0 through 20 molar equivalents of anion; (bottom right) truncated binding isotherm obtained when the region corresponding to the addition of 0–1.0 equiv. is magnified.

binding), and one peak appearing slightly downfield (7.8 ppm; presumably belonging to the α-proton of a pyrrolic moiety that is involved in anion binding).

The above findings are consistent with an interaction between the anion and the receptor that is asymmetric in nature. In particular, it is suggested that only one of the pyrrole subunits is involved in anion binding as inferred from the split nature of the pyrrole α-proton signals noted above. Further support for this conclusion comes from the observation that, over the course of the titration, the peaks corresponding to the protons on the 3- and 4-positions of the pyridine ring split into two distinct sets of doublets, while the peak corresponding to the proton on the 5-position splits into two sets of triplets.

Based on the crystal structure of the free host and the NMR spectroscopic data, we propose two possible binding conformers for receptors **3** and **4** (Fig. 6). The first of these, mode **A** (shown in structures **i** and **iii**, representing acetate and benzoate, respectively) involves rotation of one pyrrolic subunit inward to form a "central cleft" in which anion binding is mediated through the use of three hydrogen-bond donors (the two amide protons, as well as one pyrrole N–H proton). The second binding mode, **B**, (shown in structures **ii** and **iv**, representing acetate and benzoate, respectively), involves the rotation of the amide bond outward to form an "outer binding surface" in which anion binding is mediated *via* two receptor-derived hydrogen-bond donors (an amide proton, as well as the adjacent pyrrole N–H proton).

In order to determine which of these limiting structures provided a better representation of the presumed binding events monitored by the ^{1}H NMR spectroscopic titrations shown in Fig. 4 and 5, we carried out additional studies with receptor **4**. This system differs from **3** in that it contains larger ester side chains on the β-pyrrolic positions.

Initially, we postulated that the bulkier substitution would lead to rotation of the pyrrole inward to relieve steric constraints. This, in turn, would change the conformational distribution in favor of binding mode **A**, thereby supporting interaction with a bound anion within the cleft. However, in spite of this prediction, receptor **4** was found to bind only the acetate anion well. The lack of interaction between receptor **4** and the benzoate anion was initially puzzling, given the high affinity displayed for this anion by receptor **3**. However, the near complete reduction in affinity for benzoate anion observed upon passing from the less hindered system **3** to the bulkier receptor **4** can be explained by considering the nature of the binding interaction and the associated conformational modes. Proposed binding mode **A** (structure **i** for acetate anion and analogous structure **iii** for benzoate; *vide supra*) involves the rotation of one pyrrolic subunit inward to form a central binding cleft which utilizes three hydrogen-bond donors, namely the two amide protons as well as a single pyrrole N–H proton, to interact with acetate and benzoate anions, respectively. Conversely, the proposed binding mode **B** (structure **ii**, for acetate and structure **iv** for benzoate) involves the rotation of one amide bond outward to form an outer binding surface in which the anions (acetate and benzoate, respectively) are bound as the result of interactions with two receptor-derived hydrogen-bond donor groups,

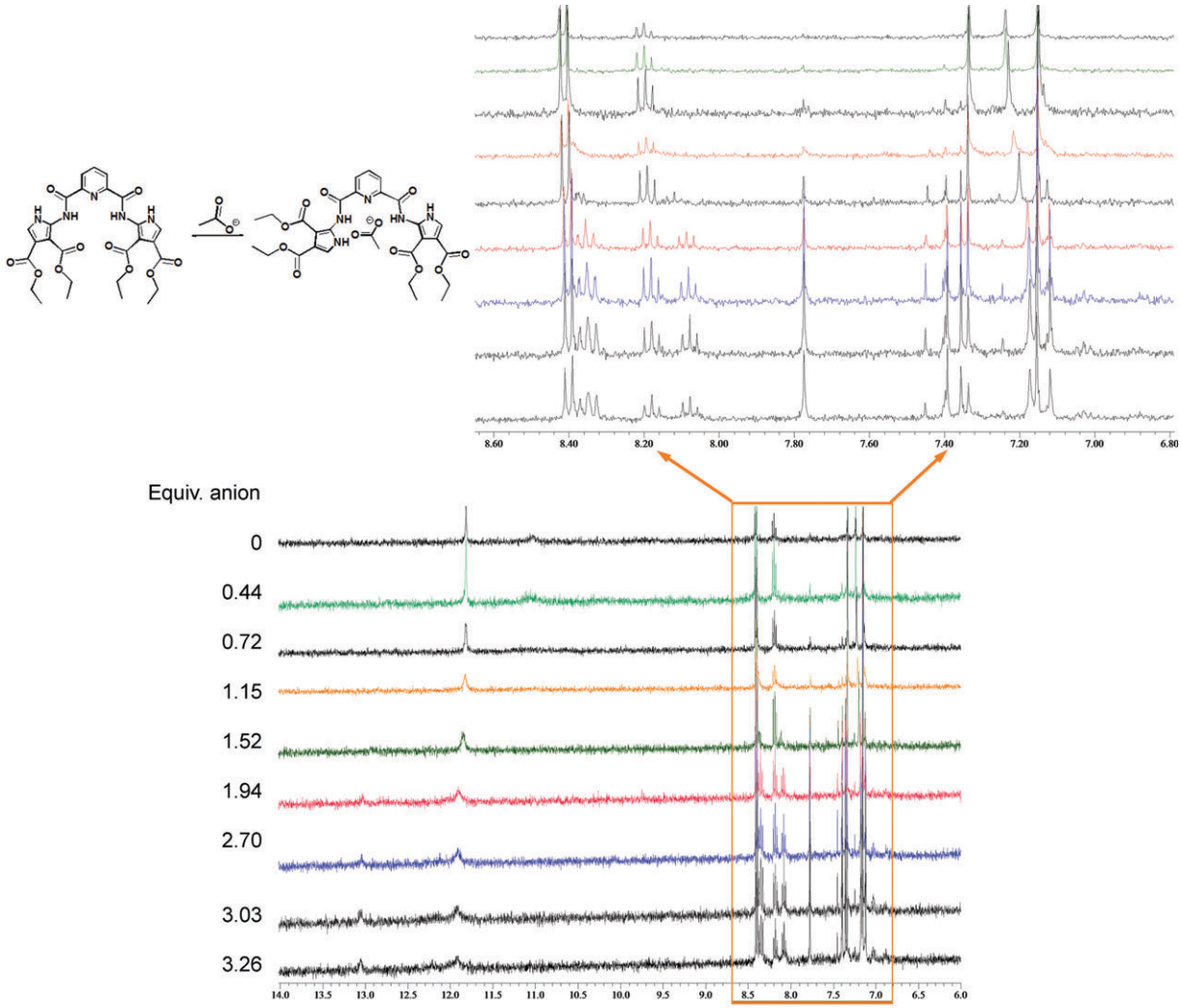


Fig. 4 ^{1}H NMR spectroscopic titration of **3** with TBA–acetate in chloroform-*d*. The splitting of the peaks corresponding to the hydrogen atoms on the 3- and 4-positions of the pyridine ring are considered indicative of an asymmetrical binding event.

namely the rotated amide proton as well as the adjacent pyrrole N–H proton.

In the case of receptor **3**, we propose that mode **A** is favored due to the increased number of receptor-based hydrogen-bond donors relative to the alternative limiting binding mode (*i.e.*, **B**). However, this same mode would not be favored in the case of the bulkier system **4**. Unfortunately, the NMR spectroscopic data acquired in the case of titrations of tetrabutylammonium acetate into solutions of **3** and **4** were not of sufficient precision to allow us to draw this conclusion with certainty. However, the inability of receptor **4** to bind benzoate anions provides strong support for both acetate and benzoate anion binding *via* mode **A**. This is because the large ester groups, present as β-pyrrolic substituents in the case of receptor **4**, are expected to interfere directly with anion binding. Specifically, these large substituents would make it difficult for benzoate to penetrate into the central binding cleft as required in binding mode **A** (structure **iii**). Therefore, as expected, this anion is bound poorly by receptor **4**, even though the smaller substrate, acetate anion, is still bound relatively well *via* the identical binding mode (structure **i**). On the other hand, were binding mode **B** dominant, it is likely that the binding affinity for benzoate anion would be relatively unaffected by a change in the size of the β-pyrrolic substituents (*i.e.*, on passing from receptor **3** to its more bulky congener **4**). This is because in this mode (structures **ii** and **iv**) the receptors adopt conformations such that the β-pyrrolic substituents are oriented away from the binding cleft. As a result, they would not be expected to exert much of an influence on the anion-binding selectivity. This, in turn, would lead to the prediction that the acetate-to-benzoate anion selectivity of **3** and **4** would be similar, a clear contrast with what is observed by experiment.

Receptor **5**, which is based on a phenyl, rather than pyridine, spacer was synthesized to determine the significance, if any, of the pyridine nitrogen atom. Although evidence for an interaction between **5** and several anions (notably acetate, benzoate and cyanide) could be inferred from UV-Vis titrations, the interactions proved too weak to allow for a reliable determination of binding constants. This result leads us to propose, as have others, that intramolecular hydrogen-bonds

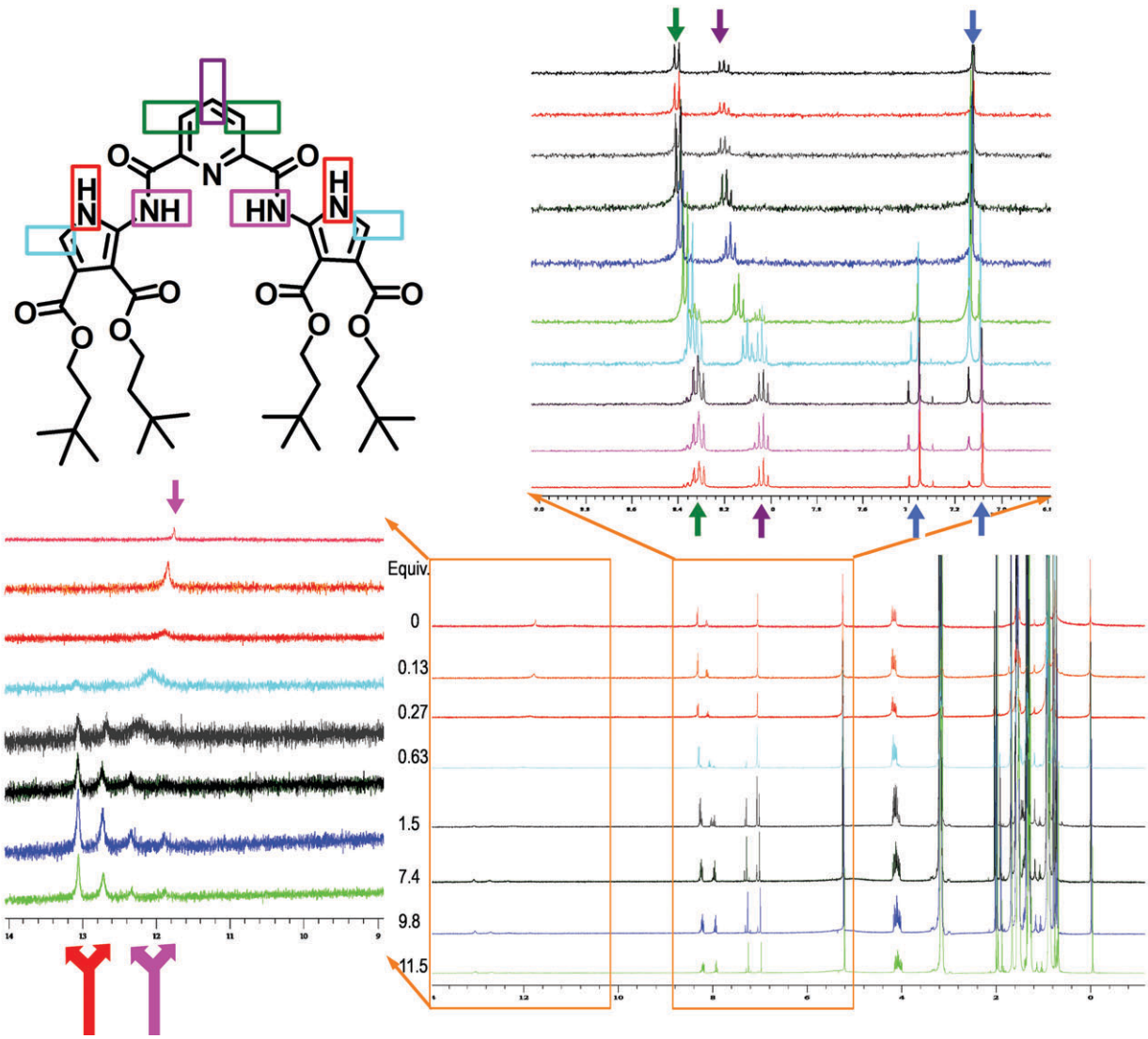


Fig. 5 ^{1}H NMR spectroscopic titration of receptor **4** with TBA–acetate in chloroform-*d*. The splitting of the peaks after the addition of 11.5 equiv. supports the conclusion that the receptor is saturated with the anion and that the latter is bound to the receptor in an asymmetrical conformation.

involving the pyridine nitrogen play an important role in stabilizing the receptor in a conformation that favors anion complexation.[14,16,20]‡‡ Interestingly, the inability of receptor **5** to interact significantly with anions further supports the notion that binding mode **A** is dominant, since it embodies the suggestion that intramolecular hydrogen-bonds between the amide proton and the pyridine nitrogen stabilize the molecule in a conformation that abets anion binding.

As noted in the introduction, previous pyrrole-amide receptors synthesized by Gale relied on the use of a pyrrole-carboxylic acid, rather than an amino-pyrrole, to produce the key receptor-generating amide linkages. Thus, receptors **3–5** represent systems that are a formally ''reversed'' configuration compared to these earlier anion-binding agents. However, the substitution pattern on the pyrrole in systems **3–5** differs from that appearing in the earlier Gale compounds; therefore, in order to determine the significance of such a reversal in our system, we synthesized receptor **6**, which represents the ''normal-amide'' version of receptor **3** (*i.e.*, the isomer with a linkage orientation analogous to that present in Gale's pyrrole-amide systems).

The synthesis of receptor **6** is shown in Scheme 2. Here, the key mono-formylated pyrrole was synthesized according to a literature procedure reported by Boiadjiev and Lightner.[22] The aldehyde was then oxidized to the carboxylic acid **7** by treating with potassium permanganate under reflux for 2 days in a 1.3 : 1 mixture of water and acetone. The resulting crude acid mixture was heated at reflux in neat thionyl chloride overnight to yield the acid chloride **8**. This latter intermediate was not purified but rather reacted directly with 2,6-diaminopyridine to yield receptor **6**.

‡‡ While this effect has been noted by a number of researchers, the structural studies of Mascharak *et al.* are particularly germane; they have shown that the loss of intramolecular hydrogen-bonds in shifting from pyridine-2,6-dicarboxamide to benzene-1,3-dicarboxamide results in a complete change of molecular conformation (see ref. 20).

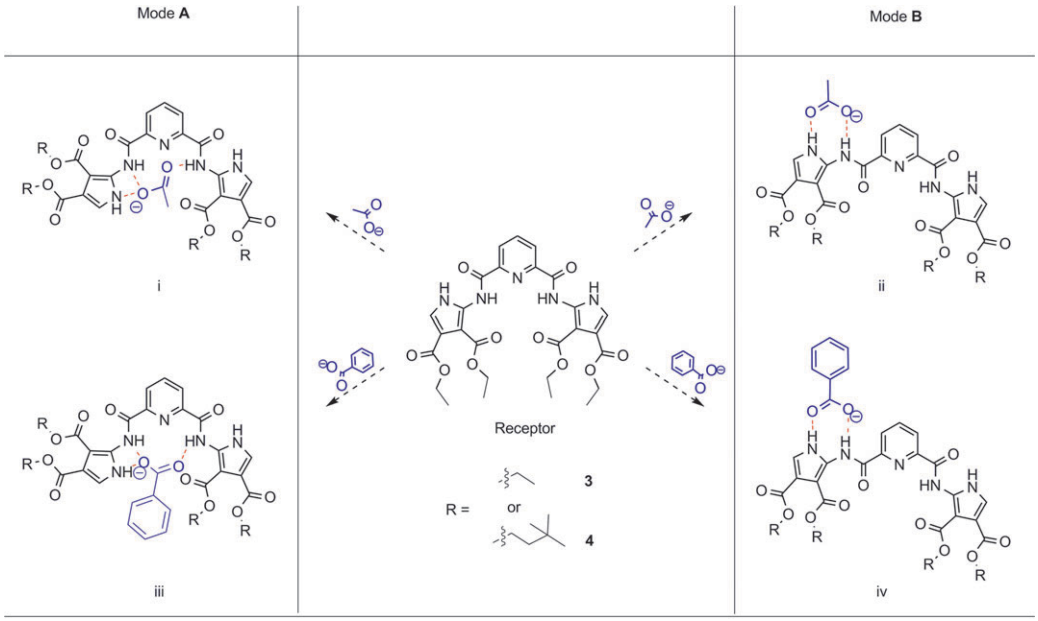


Fig. 6 Limiting binding modes **A** and **B**, showing the possible interactions between receptors **3** and **4** and the acetate and benzoate anions. Anions are shown in blue, anion–receptor hydrogen bonds are shown in red.

Variable-temperature NMR experiments (40 °C to 110 °C in DMSO-d_6) lead us to suggest that receptor **6** exists in two conformations in solutions (Fig. 7). These two conformations are the result of amide bond rotations, and appear to be present in equal amounts. As evidenced by the NMR spectroscopic data, each proton of receptor **6** appears as two peaks, present in a 3 : 1 ratio. This particular ratio arises from the presence of one symmetrical and one asymmetrical species in solution. Between the resulting two conformers, there are a total of four pyrroles present in the sample, three of which exist in an identical magnetic environment, and one of which exists in a different environment. To the extent this assignment is correct, it leads to the conclusion that the two conformers are present in roughly equal concentrations in solution. Additionally, the failure of the spectral features ascribed to these two independent conformers to converge even at high temperature (110 °C in DMSO-d_6) provides support for the notion that they are separated by a fairly high rotational barrier.

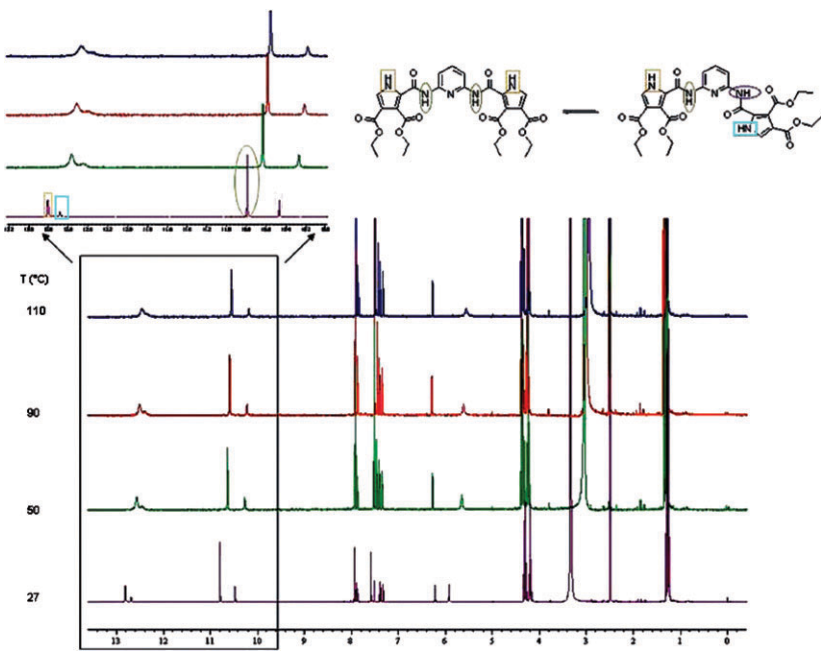


Fig. 7 Temperature-dependent ^{1}H NMR spectroscopic study of receptor **6** in DMSO-d_6. The 3 : 1 ratio of the peaks supports the presence of the amide rotamers depicted. The inability of the spectrum to converge even at high temperature is consistent with rotation being hindered by a relatively high energy barrier.

As above, anion-binding titrations involving receptor **6** were carried out using UV-Vis spectroscopy in dichloroethane. As summarized in Table 1, the synthetic "reversal" of the connectivity of the amide resulted in a complete change in the inherent substrate selectivity, such that only the chloride anion is bound well. Job plot analyses again provided confirmation for a 1 : 1 binding stoichiometry.

Attempts to gain insight into the dominant binding mode reflecting the interaction of **6** with chloride anion using standard ^{1}H NMR spectroscopic titrations were unsuccessful. This is because the interaction proved too weak to produce a measurable change in the peak shifts for **6**. Nonetheless, if the limiting binding conformations proposed for receptors **3** and **4** are relevant in the case of receptor **6** as well, it seems reasonable to conclude that the greater distance between the pyrrole proton and amide proton results in a larger binding cavity. To the extent that this assumption is correct, it would result in an ability to bind selectively a different series of anions, as indeed is seen by experiment.

Experimental section

General preparation of receptors 3, 4 and 5

The corresponding amino-pyrrole (**1**, **2**) was dissolved in dry dichloromethane under argon. To this solution was then added 0.5 equiv. of the corresponding acid chloride (pyridine-2,6-dicarbonyl dichloride, isophthaloyl dichloride) and a catalytic amount of triethylamine. The solution was stirred under argon at room temperature overnight. The reaction mixture was washed with $NaHCO_3$ (2 × 50 ml) and dried over Na_2SO_4 before the solvent was removed *in vacuo*. Purification by column chromatography (silica gel, 5% MeOH–DCM eluent) afforded **3–5** as white powders.

Receptor 3 (63% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.2–1.4 (m, 12H, CCH_3, J = 7 Hz), 4.21–4.39 (m, 8H, OCH_2, J = 7 Hz), 8.20–8.21 (t, 1H, pyridine-H, J = 5 Hz), 8.38–8.42 (d, 2H, pyridine-H, J = 5 Hz), 10.89–11.02 (br-s, 2H, pyrrole-NH), 11.91–11.95 (br-s, 2H, amide-NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.4, 14.6, 60.6, 60.7, 98.5, 115.0, 119.9, 126.2, 136.7, 139.9, 148.6, 162.6, 164.1, 164.9; HRMS (CI^+): calcd for $C_{27}H_{29}N_5O_{10}$ [M + H] 584.1914; found m/z: 584.1998. This product was further characterized by single crystal X-ray diffraction analysis.

Receptor 4 (76% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.0 (s, 18H, $C(CH_3)_3$, J = 5 Hz), 1.6–1.70 (m, 8H, $CH_2CH_2(CH_3)_3$, J = 5 Hz), 4.22–4.37 (m, 8H, OCH_2, J = 5 Hz), 8.32–8.41 (t, 1H, pyridine-H, J = 6 Hz), 8.40–8.43 (d, 2H, pyridine-H, J = 6 Hz), 10.89–10.95 (br-s, 2H, pyrrole-NH), 11.82–11.91 (br-s, 2H, amide-NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 29.7, 29.8, 29.9, 30.0, 41.9, 42.1, 62.4, 62.6, 98.7, 115.4, 119.7, 126.1, 136.6, 140.0, 148.7, 162.9, 163.9, 164.8; HRMS (CI^+): calcd for $C_{43}H_{61}N_5O_{10}$ [M + H] 808.4418; found m/z: 808.4496.

Receptor 5 (30% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.3–1.6 (m, 12H, CCH_3, J = 4 Hz), 4.25–4.41 (m, 8H, OCH_2, J = 4 Hz), 8.61–8.67 (s, 1H, benzene-H), 8.25–8.27 (t, 1H, benzene-H, J = 7 Hz), 8.36–8.41 (d, 2H, benzene-H, J = 7 Hz), 10.87–10.95 (br-s, 2H, pyrrole-NH), 11.89–11.93 (br-s, 2H, amide-NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.5, 14.6, 24.2, 59.9, 61.1, 90.7, 115.4, 118.8, 126.4, 138.5, 14.3, 150.2, 164.2, 165.3, 171.7; HRMS (CI^+): calcd for $C_{28}H_{30}N_5O_{10}$ [M + H] 582.1962; found m/z: 582.1999.

Synthesis of reverse amide receptor 6 (38% yield)

The formylated pyrrole **7** (0.182 mmol) was dissolved in acetone (10 ml). To this mixture was added dropwise a solution of $KMnO_4$ (0.728 mmol) dissolved in 13 ml water–acetone mixture (5 : 8 v/v). The mixture was then heated at reflux for 48 hours. After allowing the reaction mixture to cool, acetone was removed under reduced pressure. Dichloromethane (12 ml), water (8 ml), and sodium metabisulfite (0.6 mol) were added with vigorous stirring. Concentrated HCl (roughly 1 ml) was then added until the solution became colorless. The water and organic layers were separated and the water layer extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The resulting solid was then dried overnight using a high vacuum pump and subsequently dissolved in neat thionyl chloride and heated to reflux overnight. The thionyl chloride was distilled off, and to the resulting solid was added 2,6-diaminopyridine (0.06 mmol) in dry dichloromethane under argon in the presence of a catalytic amount of triethylamine. The reaction mixture was then washed with $NaHCO_3$ (2 × 50 ml) and dried over Na_2SO_4 before the solvent was removed *in vacuo*. Purification by column chromatography (silica gel, 5% MeOH–DCM eluent) afforded **6** as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.31–1.49 (m, 24H, CCH_3, J_1 = 7 Hz, J_2 = 3 Hz), 4.25–4.35 (m, 12H, OCH_2, J = 7 Hz), 4.41–4.48 (q, 2H, OCH_2, J = 3 Hz), 4.49–4.57 (q, 2H, OCH_2, J = 3 Hz), 7.35–7.40 (d, 1H, α-H), 7.40–7.43 (d, 3H α-H), 7.49–7.51 (t, 1H, benzene-H, J = 8 Hz), 7.75–7.81 (t, 1H, benzene-H, J = 5 Hz), 7.52–7.54 (d, 1H, pyridine-H, J = 8 Hz), 8.01–8.05 (d, 3H, pyridine-H, J = 5 Hz), 10.33–10.41 (br-s, 3H, amide-NH), 10.51–10.62 (br-s, 1H, amide-NH), 11.51–11.53 (br-s, 3H, pyrrole-NH), 11.54–11.61 (br-s, 1H, pyrrole-NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.4,14.8, 35.0, 41.1, 60.7, 62.0, 110.0, 111.2, 117.2, 127.2, 150.7, 157.9, 163.5, 166.5; HRMS (CI^+): calcd for $C_{27}H_{29}N_5O_{10}$ [M + H] 584.1914; found m/z: 584.1998.

Conclusions

In conclusion, we have shown that receptors incorporating an amino-pyrrole into pyridine-dicarboxamide systems are capable of anion complexation. In contrast, the corresponding phenyl-bridged systems were ineffective as anion receptors, further demonstrating the importance of preorganization in the development and control of synthetic anion receptors. We have also found that "reversal" of the amide in these systems, from pyridine-dicarboxamide to pyrrole-dicarboxamide,

results in a complete reversal in the substrate selectivity. This latter finding is particularly noteworthy, because it highlights how small changes in ostensibly similar systems can have a large effect on the resulting function, specifically anion binding in the present instance.

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