Organic & Biomolecular Chemistry

Accepted Manuscript

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Arylpyrrole oligomers as tunable anion receptors

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Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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A novel type of arylpyrrole oligomer possessing an appropriate electropositive cavity has been designed, prepared and analysed for use as readily accessible receptors for negatively charged guests. Affinities of the receptors for various anions were determined by UV/Vis titration experiments and in depth insights into the host-guest interactions were obtained by performing ^{1}H NMR titration experiments and X-ray crystallographic structure analyses. Experimentally determined association constants were correlated with the calculated maximum electrostatic potentials of the electropositive cavities of the receptors, permitting estimation of the strengths of host-guest associations in similar compounds. The joint contribution of aryl C–H and pyrrole N–H hydrogens was shown to be key to a strong guest association, resulting in the arylpyrrole oligomers being efficient anion receptors.

Introduction

Structurally simple anion receptors, tuned for their binding strength and lipophilicity, have been shown to mediate transmembrane transport of anions and may find uses in biological applications.[1] Much effort has been invested in developing hosts with various anion-responsive moieties including amides,[2] (thio)ureas,[3] squaramides,[4] *etc*.[5] The pyrrole unit is also useful for this purpose due to potentially strong hydrogen-bonding interactions with negatively charged species and, in particular, due to its high affinities for naturally abundant chloride and bicarbonate ions.[6] Therefore, the pyrrole ring has been used extensively as a building block for anion receptors and transmembrane transporting agents including synthetic prodigiosins and tambjamines (Fig. 1), which are related to secondary metabolites produced by a number of micro-organisms. They have a wide variety of important therapeutic properties leading to excellent potential for use as anti-malarials, immunosuppressants and chemotherapy agents.[7] Synthetic prodiginines have been intensively studied despite the preparation of these compounds being labour intensive and, unfortunately, these derivatives have failed to yield improvements in properties over those obtained from natural sources.[8] Therefore, further development of novel and potent anion receptors and transporters containing pyrrole as a fundamental component is required, although an alternative molecular configuration may be considered to optimize any potentially important properties.

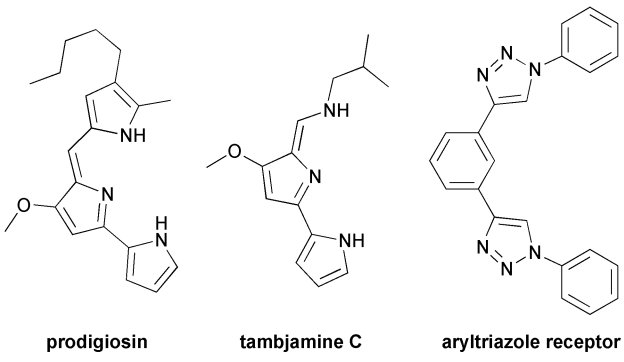


Figure 1 Naturally-occuring and oligomeric aryltriazole anion receptors.

The recent discovery that polarized C–H bonds can form hydrogen bonds strong enough to bind anions has played a crucial role in the development of a new class of neutral anion receptors.[9,10] The most widely explored of these are the macrocyclic and acyclic aryltriazole oligomers, which have been studied mostly due to their high affinity for chloride anions (Fig. 1).[10] Polarized C–H bonds, in conjunction with an alternating arrangement of hexagonal and pentagonal components, have been shown to form a binding pocket with dimensions ideal for encapsulation of chloride ions, resulting in a strong and selective interactions.

At the outset of this work we envisioned a novel type of oligomeric arylpyrrole receptors that unite the features of prodiginines, which offer the strong N–H hydrogen donating character of pyrrole units, with those of oligomeric aryltriazole receptors, which provide the appropriate dimensions and preorganization required to form a well-defined binding pocket. The preparation of molecules combining pyrrole and aryl moieties is expected to increase the binding strength of any host-guest interactions over the corresponding aryltriazole oligomers. Moreover, oligomeric or macrocyclic molecules

composed of pyrrole/aryl groups may offer advantages over the prodiginines, which consist exclusively of pyrrole or indole rings, since it is possible to readily tune association and lipophilicity characteristics through facile introduction of particular substituents.

Our novel methodology for synthesis of unsymmetrical 2,5-diarylpyrroles from readily available homopropargyl sulfonamides by a tetra-*n*-butylammonium fluoride (TBAF) mediated one-pot 5-endo-dig cyclisation-deprotection-tautomerisation reaction[11] has proven to be extremely valuable and applicable in the preparation of oligomeric arylpyrrole anion receptors, and was used here to prepare several arylpyrrole receptors.

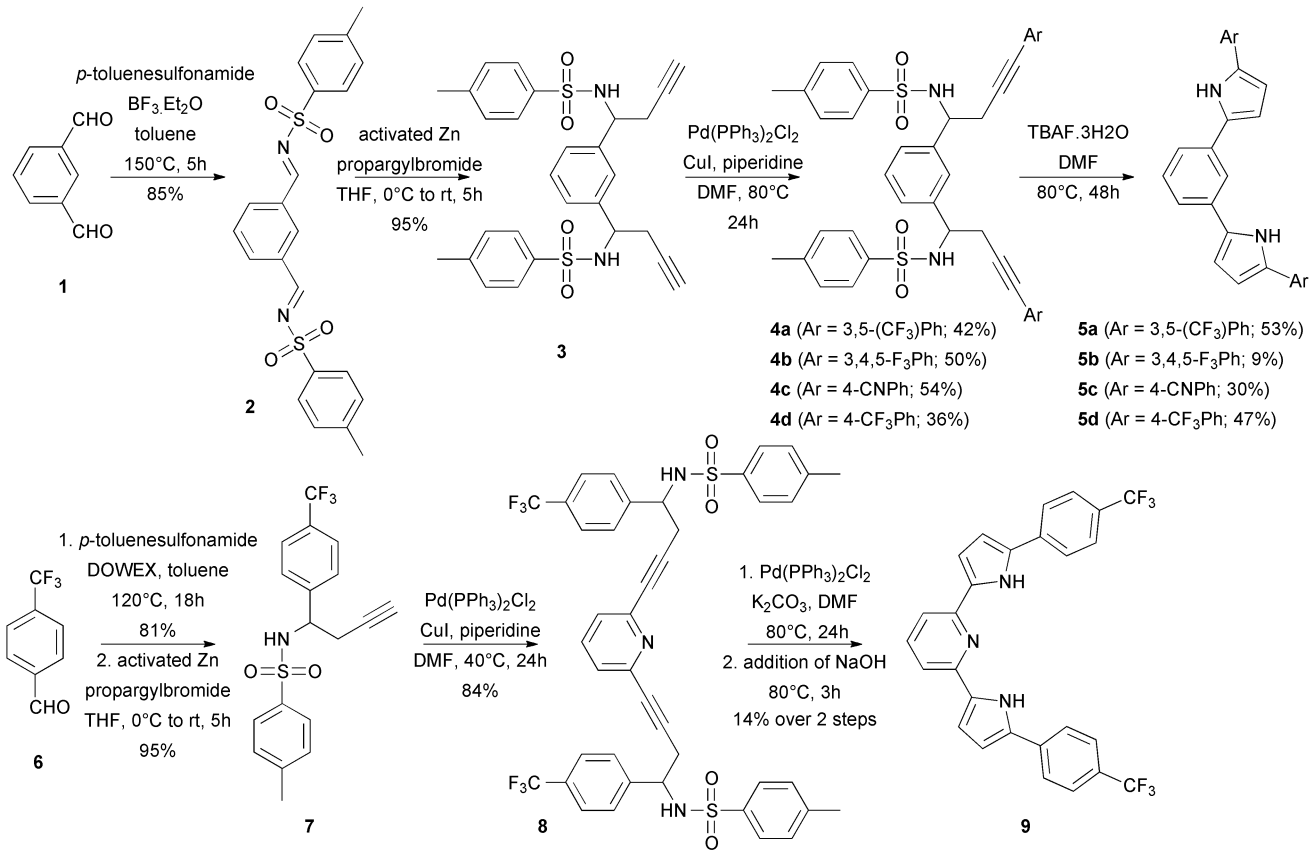
Results and discussion

Synthesis of oligomeric arylpyrrole receptors

A series of oligomeric arylpyrrole receptors was prepared from isophthalaldehyde **1** (Scheme 1). Condensation reaction with *p*-toluenesulfonamide ($BF_3.Et_2O$, toluene, reflux, 3h) gave, after simple filtration, sulfonimine **2** in good yield (81%). Barbier reaction of **2** with propargyl bromide (Zn, THF, 0 °C to rt, 5h) resulted quantitatively in homopropargyl sulfonamide **3**, which required no further purification. Sonogashira reactions ($Pd(PPh_3)_2Cl_2$, CuI, DMF, piperidine, 40 or 80 °C, 24h) of **3** with various substituted aryl halides gave compounds **4a-d**.[12]

These compounds were subjected to 5-endo-dig cyclisation with *in situ* deprotection and tautomerisation to the respective pyrrole using TBAF as base and deprotecting agent (DMF, 80 °C, 48h) affording receptors **5a-d**.

Pyridine analogue **9** was also prepared since it contains a central nitrogen atom which directs both pyrrole N–H hydrogens to the central cavity due to intramolecular hydrogen bonding. This should prevent conformations of the oligomeric arylpyrrole backbone inappropriate for optimum binding of an anionic guest and removes any requirement for reorganization of the host molecule. Receptor **9** was synthesized according to a similar synthetic route as that for **5a-d** but working in from the molecular periphery (Scheme 1). DOWEX-assisted condensation reaction of *p*-trifluoromethylbenzaldehyde with *p*-toluenesulfonamide (81% yield) and subsequent Barbier reaction (95% yield) gave homopropargyl sulfonamide **7**. Compound **8** was obtained by Sonogashira reaction ($Pd(PPh_3)_2Cl_2$, CuI, DMF, piperidine, 40 °C, 24h) of **7** with 2,6-dibromopyridine in good yield (84%).[12] As described in our previous work,[8] an alternative method for the cyclisation of pyridine substituted alkynes was required and consisting of a palladium catalysted 5-endo-dig cyclisation with a consecutive deprotection step. The pyridine analogue **9** was obtained using $Pd(PPh_3)_2Cl_2$ as catalyst and K_2CO_3 as base in dry DMF at 80 °C during 5h, followed by the addition of NaOH (40 equiv) and a few drops of water (14% over 2 steps).



Scheme 1 Synthesis of oligomeric arylpyrrole receptors **5a–d**, **9**.

Anion binding studies

UV/Vis titration experiments. The host-guest chemistry between the receptor molecules and a variety of anions (Cl^-, HCO_3^-, AcO^-, $H_2PO_4^-$, NO_3^- or Br^- as their tetrabutylammonium or tetraethylammonium salts) was analysed by means of UV/Vis titration experiments. Titration curves were fitted to a 1:1 stoichiometry, as determined by Job plot analysis and supported by single-crystal X-ray analysis (see ESI), using HypSpec software (Table 1).[13]

Table 1. Association constants K_{ass} (M^{-1}) for 1:1 complexation between hosts **5a–d**, **9** (1×10^{-5} M, 298K) and anionic guests in dry MeCN.[a]

Receptor	Cl^-	HCO_3^-	AcO^-	$H_2PO_4^-$	NO_3^-
5a	9.3×10^3	1.9×10^4	2.4×10^5	7.9×10^3	<10[c]
5b	2.5×10^4	4.4×10^4	3.0×10^5	4.0×10^4	<10[c]
5c	1.3×10^4	1.8×10^4	9.1×10^4	2.3×10^4	11
5d	8.5×10^3	1.4×10^4	4.8×10^4	1.9×10^4	<10[c]
9	<10[c]	1.2×10^2	–[b]	<10[c]	<10[c]

[a] Calculated on the basis of UV/Vis titration data using HypSpec.[13] Values are the average of at least three separate wavelengths and are considered reproducible to 15%. [b] Proper fitting could not be obtained. [c] No notable spectral changes.

Receptor **5a**, substituted with two electron-withdrawing trifluoromethyl groups in *meta*-positions at each end of the molecule, exhibits a broad absorption band centred at 345 nm. Slow addition of Cl^- resulted in a hypochromic shift of the initial band at 345 nm and a concurrent hyperchromic shift around 400 nm (Fig. 2). There is a clear isosbestic point at λ = 366 nm. Titration curves for the changes in absorbance were fitted and an association constant $K_{ass} = 9.3 \times 10^3$ M^{-1} was obtained.

Titration of **5a** with the more basic HCO_3^- resulted in only a slight increase in the host-guest interaction ($K_{ass} = 1.9 \times 10^4$ M^{-1}), whereas for AcO^- a notably stronger association ($K_{ass} = 2.4 \times 10^5$ M^{-1}) was observed (see ESI). Interestingly, receptor **5a** binds Cl^- more effectively than the much more basic $H_2PO_4^-$ ($K_{ass} = 7.9 \times 10^3$ M^{-1}). In general, the $H_2PO_4^-$ anion is bound stronger than Cl^- and only in rare cases has this affinity order been reversed, usually in sterically congested binding sites.[14] This suggests that the large CF_3 groups and the well-defined dimensions of the cavity prevent strong interaction of $H_2PO_4^-$ with the electropositive cavity of the receptor. Slow addition of trigonal NO_3^- did not induce any discernable spectral changes in the UV/Vis profile.

For receptor **5b**, fluorinated in both *meta* and *para*-position, an overall improved interaction was found for all the studied anions with an affinity pattern similar to **5a** with the highest affinity for AcO^-, except for $H_2PO_4^-$, which in this case is bound more strongly than Cl^- (most probably due to the lower steric hindrance of the smaller F substituent relative to the large CF_3 group). Receptor **5c** and **5d**, having respectively CN or CF_3 groups at their *para*-positions, exhibit further elevation of the association constant of $H_2PO_4^-$ over that of Cl^- and HCO_3^- most likely due to their lack of *meta*-substituents and the resulting loss of steric hindrance. Furthermore, a reduction in number of electron-withdrawing groups from four CF_3 groups to two CF_3 (similarly for CN groups) did not significantly affect their association with anionic guests.

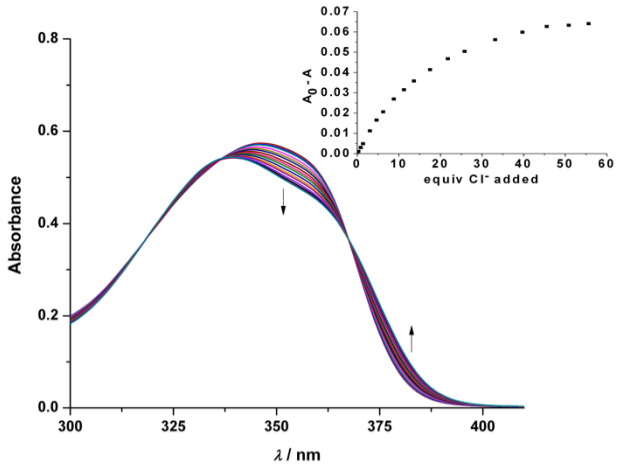


Figure 2 UV/Vis titration of **5a** with tetra-*n*-butylammonium chloride in MeCN. Inset: variation of absorbance at λ = 350 nm vs. equiv Cl^- added.

For pyridine analogue **9**, which is expected to possess a greater degree of preorganization compared to the benzene derivatives, titration with HCO_3^- resulted in only a small hypochromic shift of the spectrum from which a modest association constant of $K_{ass} = 1.2 \times 10^2$ M^{-1} could be determined. Additionally, slow addition of Cl^-, $H_2PO_4^-$ or NO_3^- did not induce any spectral changes while for AcO^- no proper fitting could be obtained. Overall, the pyridine derivative **9** appeared to be a much poorer anion receptor compared to the benzene derivatives **5a–d**. Most probably the lower affinity is caused by a greater loss in binding energy, due to repulsion between the electron pair of the pyridyl nitrogen atom and the negatively charged guest, over the binding energy gained by preorganizing the oligomeric arylpyrrole backbone. In addition, the intramolecular hydrogen bonds cause a contraction of the central cavity (see ESI) shielding the electropositive pocket and allowing only the strongest hydrogen-accepting guests, able to disrupt these hydrogen bonds, to associate with receptor **9**.

Variation of the solvent used for binding studies offers a clear insight into its effect (Table 2). Performing the titration experiments for **5a** in a competitive solvent such as DMSO/0.5% H_2O resulted in a strong decrease in association to the extent that only a small interaction with AcO^- was observed ($K_{ass} = 1.2\times10^2$ M^{-1}). When a less competitive solvent such as acetone was used generally much stronger association constants were obtained, as expected due to weaker solvation of the anions. For Cl^- anions, an association constant of 1.8×10^5 M^{-1} was obtained while for AcO^- a large value of 1.4×10^7 M^{-1} was derived. In comparison to Cl^-, a much weaker association was observed with Br^- as guest ($K_{ass} = 3.9\times10^2$ M^{-1} in acetone and $K_{ass} = 51$ M^{-1} in MeCN), emphasizing the preference of receptor **5a** for smaller and more basic anions.

Compounds **5a-d** all demonstrate a higher affinity for AcO^- over Cl^-, however, placing this in respect to the anions basicity according to the pK_a of the conjugated acid (pK_a(AcO^-) = 4.76; pK_a(Cl^-) = –8.00) it should be noted that a remarkably strong interaction for Cl^- was found.[15] This high affinity for Cl^- can be attributed to the well preorganized cavity formed upon association with the ion. Overall these arylpyrrole oligomers show greatly improved anion association activity over their triazole analogues and a wide scope of linear pyrrolic systems.[10,16] Moreover, the aryl groups allow for facile introduction of different substituents that can alter the anion selectivity of the receptors, a characteristic that prodiginines lack. These arylpyrrole oligomers are thus a promising new class of anion receptors

Table 2 Association constants K_{ass} (M^{-1}) for 1:1 complexation between host **5a** (1×10^{-5} M, 298K) and anionic guests in different solvents.[a]

Solvent	Cl^-	HCO_3^-	AcO^-	$H_2PO_4^-$	NO_3^-	Br^-
DMSO	$<10^{[b]}$	$<10^{[b]}$	28	–[c]	–[c]	–[c]
MeCN	9.3×10^3	1.9×10^4	2.4×10^5	7.9×10^3	$<10^{[b]}$	51
Acetone	1.8×10^5	–[c]	1.4×10^7	1.5×10^6	26	3.9×10^2

[a] Calculated on the basis of UV/Vis titration data using HypSpec.[13] Values are the average of at least three separate wavelengths and are considered reproducible to 15%. [b] No notable spectral changes. [c] Not determined.

^{1}H NMR titration experiments. For a better understanding of the binding interactions between the oligomeric arylpyrrole receptor and the anionic guests a series of ^{1}H NMR titrations in CD_3CN (5×10^{-5} M, 298 K) was performed. During titration of **5a** with Cl^- resonances due to the pyrrole N–H protons and central aryl proton H^a shift downfield considerably (from 8.1 and 10.1 ppm to 9.7 and 12.7 ppm, respectively), with the more acidic N–H contributing slightly more to the interaction than H^a ($\Delta\delta$ = 2.6 versus 1.6 ppm, respectively). In addition, the outer aryl protons H^b apparently associate less strongly with a less significant downfield shift (from 8.3 ppm to 8.8 ppm) being observed. Peaks due to the remaining aromatic protons shift slightly upfield consistent with a general conformational reorganization (Fig. 3).

A very similar pattern was found upon slow addition of AcO^- with downfield shifts of peaks from 10.0 and 8.0 ppm to 14.0 and 9.0 ppm for the N–H and H^a protons, respectively, and from 8.2 to 8.7 ppm for the H^b proton resonance. Here, the largest perturbation is clearly experienced by the N–H protons ($\Delta\delta$ = 4.0 ppm) while H^a and H^b interact only modestly ($\Delta\delta$ = 1.0 and 0.5 ppm, respectively).

Upon addition of 0.5 equivalents of HCO_3^-, the peak due to N–H protons disappeared while the peaks due to H^a and H^b protons shift downfield (from 8.2 and 8.4 ppm to 8.8 and 8.6 ppm, respectively). In general, the disappearance of peaks corresponds to deprotonation of the host by the anion although at least 2 equiv. would be required for full deprotonation of both N–H hydrogens (slow proton exchange cannot really be excluded).[17] Nevertheless, a clear interaction between host and guest was observed as both H^a and H^b undergo downfield shifts (see ESI).

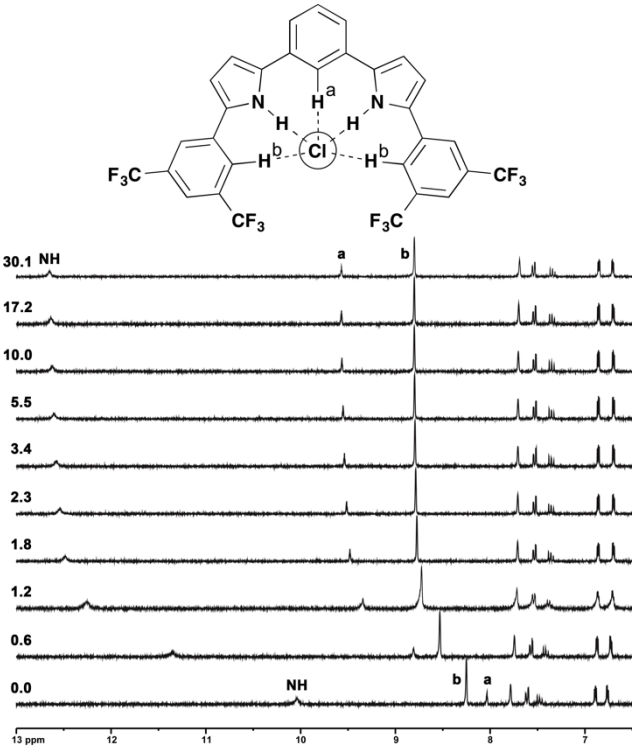


Figure 3 ^{1}H NMR titration of **5a** with increasing equivalents of tetra-*n*-butylammonium chloride in CD_3CN.

Calculations of electrostatic potential

To obtain further information regarding the interaction between the studied receptors and anions electronic structures of the arylpyrrole oligomers were evaluated. Computational *ab initio* calculations of electrostatic potential and geometry optimizations were carried out using density functional theory (DFT) in the Gaussian 09 software[18] at B3LYP/cc-pVDZ (C, H, N, and O) and aug-cc-pVDZ (F, Cl) levels. A conductor-like polarized continuum model (CPCM) was used to take into account the effect of MeCN solvent.

A substantially lower value was found for the maximum electrostatic potential mapped on the molecular electron density surface ($V_{S,max}$,; Fig. 4) of pyridine derivative **9** compared to the benzene-based hosts. This is in agreement with the higher repulsion of the anion by the free electron pair of the pyridyl nitrogen, which results in lower association constants.

Plotting the association constants (Log K_{ass}) found for receptors (**5a–d**) with Cl^-, HCO_3^- or AcO^- against the calculated $V_{S,max}$ values indicates a good correlation (Fig. 4). Therefore, the $V_{S,max}$ value serves as a good indicator from which the association constants for oligomeric arylpyrrole receptors may be estimated and against which new receptor designs in future work may be evaluated in advance of synthesis. Setting out the association constants for the hosts with $H_2PO_4^-$ against $V_{S,max}$ presented **5a** as an outlier in correspondence to the diminished association constant due to sterical hindrance by the *meta*-CF_3

substituents (see ESI, Fig. S38). Moreover, the outlier denotes a change in selectivity from the general pattern highlighting a lead compound in any search for anion selective receptors.

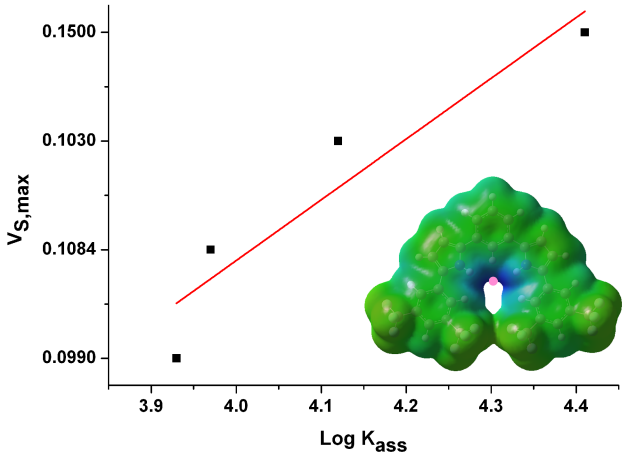


Figure 4 Graphical representation of the correlation between the association constant (Log K_{ass}) of the receptors with chloride and the maximum electrostatic potential mapped on the molecular electron density surface (pink dot corresponds to the location of the $V_{S,max}$).

X-ray crystallographic analysis

Single-crystals of **5a** suitable for X-ray analysis were grown by slow evaporation of a DMSO solution at 50 °C (Fig. 5a).‡ The molecule possesses a nearly planar form with pyrrole NH groups on opposite sides rather than forming a potential binding pocket with NH groups on the same side. Each NH group interacts with an individual DMSO molecule (see ESI).

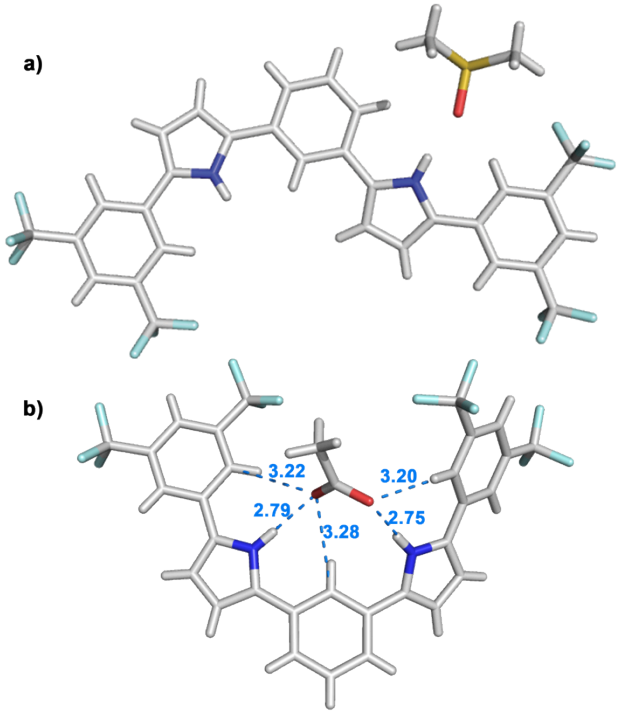


Figure 5 Crystal structure of a) receptor **5a** and b) complex [5a:AcO^-] (TBA^+ counter ion omitted for clarity).

Single-crystals of the complex [**5a**:AcO^-] could also be obtained by slow evaporation of an MeCN solution (Fig. 5b).‡ The structure shows that binding of a guest causes rotation of a pyrrole group (relative to the conformation for the structure of anion free **5a)** to form a central binding pocket in which a single AcO^- is bound. This is in good correlation with the 1:1 stoichiometry observed in solution. Host **5a** was found to form hydrogen bonds with one oxygen atom of the AcO^- through one N–H and two C–H hydrogens while interacting with the second oxygen atom through one N–H and one C–H hydrogen.
Important distances between the oxygen atom of the acetate guest and host found for the [**5a**:AcO^-] complex are 2.2–2.3 Å from pyrrole N-H nitrogen and 3.3–3.4 Å from the phenyl C-H. Hydrogen bonds have been categorized according to their donor-acceptor distances of 2.2–2.5 Å as "strong, mostly covalent", 2.5–3.2 Å as "moderate, mostly electrostatic", 3.2–4.0 Å as "weak, electrostatic".[19] Therefore, the AcO^- is bound to host **5a** by a combination of strong, mostly covalent interactions through the N–H hydrogens and moderate, mostly electrostatic interactions by the C–H hydrogens. The joint interaction of N–H and C–H hydrogens results in a strong binding of the anionic guest, demonstrating that arylpyrrole oligomers are a promising novel class of anion receptors.

Fluorescence analysis

An interesting additional feature of these oligomeric arylpyrroles is their fluorescent character. The spectra and intensity of emitted light proved to be highly dependent on the substitution pattern. Trifluoromethyl and fluoride substituents yield arylpyrrole oligomers emitting weak fluorescence. Upon excitation of **5a** at 350 nm (ε_{abs346} = 57000 M^{-1} cm^{-1}, Φ_{350} = 5 % in MeCN) only 5 % of absorbed photons are emitted with a maximum intensity around 455 nm and an additional shoulder around 520 nm giving a typical blue fluorescence (Fig. 6a).
Excitation of **5c**, decorated with nitrile groups, at 350 nm resulted in an intense emission around 425 nm with a high fluorescence quantum yield of 69%. The absorbance of this receptor is, in general, greater with its maximum shifted to 370 nm (ε_{abs370} = 72000 M^{-1} cm^{-1}, MeCN). Adding excess of Cl^- as guest to a solution of **5c** caused only a slight decrease in the fluorescence intensity (Fig. 6b). However, on addition of an equal amount of HCO_3^-, AcO^- or $H_2PO_4^-$ the fluorescence emission was completely quenched. Thus, further variation of the substituents may offer great potential for these new compounds as neutral fluorophores and sensors.

Conclusions

A new class of anion receptors was developed consisting of an oligomeric arylpyrrole framework, which benefits from the presence of both acidic pyrrole N–H protons and the ideal dimensions of the alternating aryl-pyrrole backbone. Both UV/Vis and ^1H NMR titration experiments confirm that strong guest association occurs due to contributions from aryl C–H and pyrrole N–H hydrogens. This is further supported by X-ray

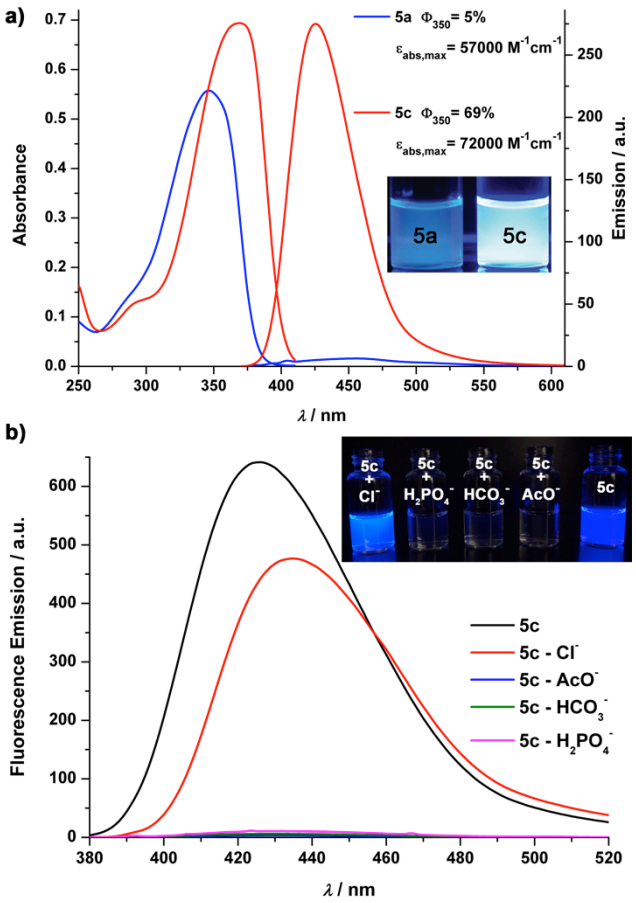


Figure 6 a) Absorbance and fluorescence emission spectra for **5a** and **5c** (in MeCN). Inset: Visual representation of the fluorescence. b) Fluorescence quenching for **5c** upon addition of anionic guests (in MeCN). Inset: Visual representation of the fluorescence after addition of an excess of anion.

crystal structure analyses. The correlations found between the calculated electrostatic potentials and the experimentally determined association constants provide a tool for preliminary evaluation of the binding affinity in the search for anion selective receptors. The strongly fluorescent character of the non-halogenated compounds also suggests that these compounds might be suitable as fluorophoric sensors. Further improvements and preorganization of the oligomeric arylpyrrole receptors will allow for continued exploration of the potential of these receptors in various applications.

Acknowledgements

The authors gratefully acknowledge the Japan Society for the Promotion of Science (JSPS) for financial support and a postdoctoral fellowship for W.VR. The World Premier International (WPI) Research Center for Materials Nanoarchitectonics (MANA) is also thanked for financial support.

Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed synthetic procedures, ^{1}H and ^{13}C NMR spectra, additional information regarding UV/Vis and ^{1}H NMR titrations, crystallographic data and CIF files for **5a** and [**5a**:AcO^{-}], and electrostatic potential data. See DOI: 10.1039/b000000x/

‡ X-ray Crystallographic data **5a**: Rigaku Varimax Saturn; T = 110(2) K. monoclinic, space group P $2_1/a$, a = 9.4849(8) Å, b = 18.4276(16) Å, c = 19.2588(17) Å, α = 90°, β = 92.1781(15)°, γ = 90°, V = 3363.7(5) Å^3, Z = 4, ρ_{calc} = 1.557 g cm^{-3}, μ = 0.261 mm^{-1}. 7632 reflections, 6010 independent. Final wR_2 = 0.1182, R_1 = 0.0435. GOOF = 1.088.
X-ray Crystallographic data [**5a**:AcO^{-}]: Rigaku Varimax Saturn; T = 110(2) K. monoclinic, space group P $2_1/n$, a = 17.1963(19) Å, b = 22.354(3) Å, c = 24.519(3) Å, α = 90°, β = 97.389(2)°, γ = 90°, V = 9347(2) Å^3, Z = 8, ρ_{calc} = 1.327 g cm^{-3}, μ = 0.114 mm^{-1}. 20016 reflections, 8961 independent. Final wR_2 = 0.2581, R_1 = 0.1229. GOOF = 1.071.

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