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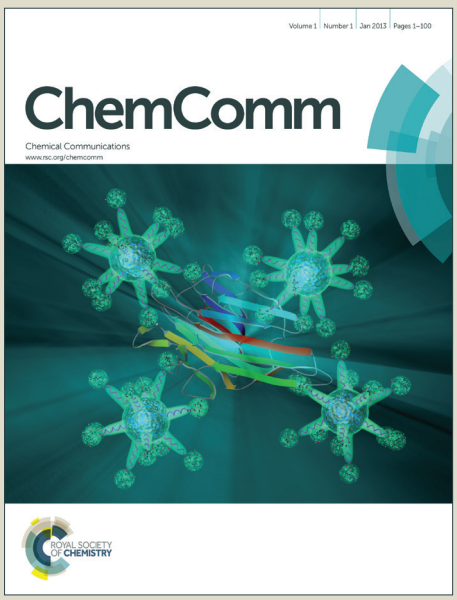

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Conformationally switchable non-cyclic tetrapyrrole receptors: Synthesis of tetrakis(1*H*-pyrrole-2-carbaldehyde) derivatives and their anion binding properties

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A series of tetrakis(1*H*-pyrrole-2-carbaldehyde) receptors (2, 4, and 6) were synthesized in two steps from commercially available starting materials. The anion binding properties of these receptors can be tuned through electronic switching to stabilize a conformation displaying high affinity for the dihydrogenphosphate and pyrophosphate anions (as the tetrabutylammonium salts) in chloroform.

Anions play essential roles in many biological processes. They are also of critical interest in the areas of synthetic and industrial chemistry.[1] The challenges associated with binding anions compared to their isoelectronic cations have been well documented, and include the larger size-to-charge ratios of anions, the diverse geometries they can take on, and the higher energies of hydration and solvation that must typically be overcome.[1] Binding anions in polar, protic solvents (*i.e.* water), is highly desirable for applications, such as the remediation of phosphates and nitrates resulting from fertilizer runoff and the selective removal of phosphates in the context of dialysis. However, such recognition is rendered difficult both as the result of hydration (e.g. ΔG_h = -300 kJ/mol for NO_3^- and ΔG_h = -465 kJ/mol for $H_2PO_4^-$)[2] and competitive hydrogen bond donation associated with the solvent shell.[3]

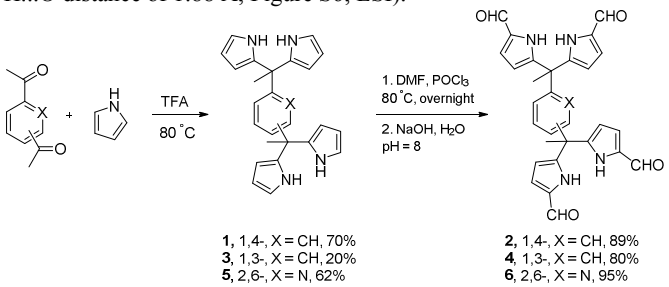
Another hurdle associated with anion binding is that certain anions, including oxoanions, such as phosphate and hydrogensulfate, are susceptible to proton transfer.[4] As a result care must be taken in working with anion receptors to ensure binding rather than deprotonation (acid-base chemistry).[1] One motif that is relatively less susceptible to deprotonation is pyrrole. In previous work, calix[4]pyrrole (C4P), a semi-flexible pyrrole-based macrocycle, was shown to bind halides with an accompanying conformational change upon binding (the macrocycle switches from a 1,3-alternate conformation to a cone conformation), as observed both in solution and in the solid state.[5] Building upon these initial results, and in an effort to improve the selectivity and binding affinity of the macrocycle, the C4P receptor has been modified by tuning the electronics and by preorganising or "locking" the conformations of the tetrapyrrolic.[6-10] Particularly successful in this latter regard have been efforts pioneered by Lee to append "strap" the calix[4]pyrrole framework across two of the *meso*-positions; this has allowed the introduction of further hydrogen bond donors and a fine-tuning of the inherent size selectivity of this now well-studied class of receptors.[7] Separately, Ghosh *et al.* developed C4P receptors wherein the *meso*- linker was changed to alter the configuration of the C4P receptor and create systems better preorganised for substrate recognition.[8]

The success of the calix[4]pyrrole framework for anion recognition has inspired efforts to prepare other simple pyrrole-based anion receptors.[11] In this communication, we report a series of new pyrrole-based anion receptors, specifically the *tetrakis*(1*H*-pyrrole-2-carbaldehyde) compounds **2**, **4**, and **6**. As detailed below, these new receptors, which are designed to function as open chain analogues of C4P, may be prepared in two steps from commercially available materials. Moreover, both the electronics and conformation of these new calixpyrrole analogues may be tuned to create systems that display high affinities for the dihydrogenphosphate and pyrophosphate anions in chloroform.

Receptors **2**, **4**, and **6** were synthesized in high yields as shown in Scheme 1. The requisite *bis*(dipyrromethane) (bisDPM) compounds **1**, **3**, and **5** were obtained via the electrophilic aromatic substitution of pyrrole by various aromatic diketones. In our hands, better yields (>60%) than typically seen for the synthesis of DPMs.[12] This finding is ascribed to the fact that products **1** and **5** precipitate from solution under the conditions of the reaction. The bisDPMs **1**, **3**, and **5** were then formylated by the Vilsmeier-Haack reaction to produce **2**, **4**, and **6** in relatively high yields (>80%). Purification of **2** and **4** was carried out by recrystallization from hot dimethylformamide (DMF) at 80 °C. The molecular structures were fully characterized by ^{1}H NMR, ^{13}C NMR, HRMS (see ESI), and, in the case of **2** and **4**, a single crystal X-ray diffraction analysis (Figure 1). Both these latter systems, after purification by recrystallization from DMF, were isolated as the corresponding bis-DMF complexes, **2**•2DMF and **4**•2DMF.

Initially we evaluated the anion binding affinity of the crystalline form of **2**, namely **2**•2DMF by means of ^{1}H NMR spectroscopic titrations carried out in $CDCl_3$. Unfortunately, analysis of the resulting data led to the conclusion that the presence of DMF from the crystal interferes with the anion binding by acting as a competitive inhibitor. The relatively strong interaction inferred between **2** and DMF is supported by the solid state structure wherein a short N-H...O distance of 1.98 Å is observed. A separate structural study was then carried out, wherein receptor **2** was crystallized in the

presence of DMSO. Here, evidence for even stronger hydrogen bonding to the DMSO solvate was observed in the solid state (N-H...O distance of 1.88 Å, Figure S6, ESI).



Scheme 1 Synthesis of compounds **1**-**6**.

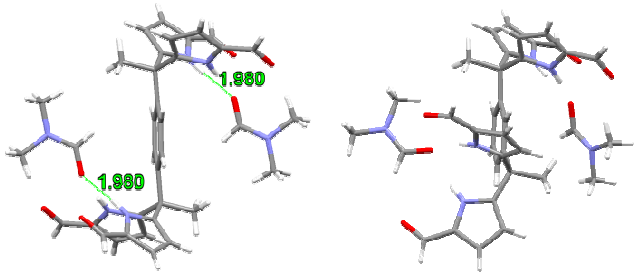


Figure 1 Single crystal X-ray crystallography structures of **2**•2DMF (left structure) and **4**•2DMF (right structure). Distances are shown in Å.

In an effort to study the anion binding of compound **2** under conditions of minimal competition, the DMF was removed from samples of **2**•2DMF by sonicating the solvated complex in a bath of $CHCl_3$.[13] The DMF-free form obtained in this way, **2**, displayed noticeably lower solubility in $CDCl_3$. Although solutions of **2** proved turbid at concentrations 1.0 mM and above, signals in the ^{1}H NMR spectrum could be observed in the case of dilute solutions. Upon addition of tetrabutylammonium dihydrogenphosphate ($TBAH_2PO_4$), the solubility increased noticeably. In fact, upon the addition of one equivalent of $TBAH_2PO_4$ to a turbid 1.0 mM[14] mixture of **2** in $CDCl_3$, the solution mixture became completely clear/soluble. Moreover, in the ^{1}H NMR spectra (in $CDCl_3$) an additional set of signals other than the proton signals attributed to **2** appeared (Figure S17, ESI). When receptor **2** (turbid 1.0 mM mixture in $CDCl_3$) was titrated with $TBAH_2PO_4$ in a stepwise manner, peaks corresponding to both the free host and the receptor-anion complex were observed in the ^{1}H NMR spectrum. This was taken as evidence of a strong interaction between the receptor and the anionic guest ($H_2PO_4^-$), as well as a recognition process that involved exchange kinetics that are slow on the NMR time scale. Unfortunately, the incomplete solubility displayed by **2** at the concentrations used for the titrations prior to the addition of a full molar equivalent of $TBAH_2PO_4$ precluded a quantitative estimate of the K_a corresponding to the receptor-anion interaction. Treatment of turbid mixtures of **2** with approximately 1.2 molar equivalents of the TBA salts of various test anions ($H_2PO_4^-$, $HP_2O_7^{3-}$, HSO_4^-, $C_6H_5CO_2^-$, Cl^-, and NO_3^-) allowed for visual differentiation between the various anion salts (Figure 2). While the vials containing $TBAH_2PO_4$ and $(TBA)_3HP_2O_7$ became transparent, the remaining vials containing other salts remained turbid.

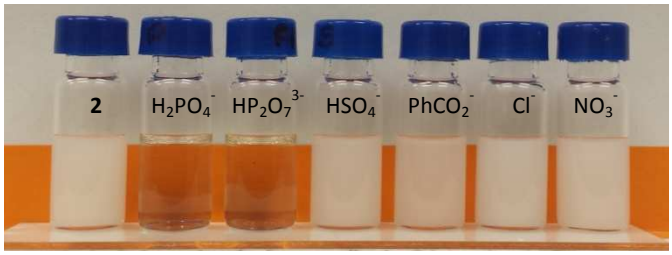


Figure 2 From left to right: Photos of solutions of **2** in $CHCl_3$ containing, respectively, no added salt, 1.2 equiv. of $TBAH_2PO_4$, $(TBA)_3HP_2O_7$, $TBAHSO_4$, TBAbenzoate, TBACl, and $TBANO_3$, respectively. Note that an orange background is used to aid in visualization.

In an effort to quantify the selectivity between anions, titration studies were performed with the anion-induced changes (if any) being monitored by UV-Vis spectroscopy under conditions where compound **2** is fully soluble. Compound **2** (ca. 10 μM) was first titrated with $TBAH_2PO_4$ in dry $CHCl_3$. A significant change in the absorption spectrum of **2** was observed with saturation occurring after the addition of about one equivalent of $TBAH_2PO_4$. Two isosbestic points at 293 and 315 nm were seen. This is taken as evidence that two absorbing species (only) are interconverting under the conditions of the experiment, namely the free host and the host-anion complex. To provide support for the proposed 1:1 stoichiometry, a Job plot was constructed using mixtures of **2** and $TBAH_2PO_4$ held at a total concentration of 1.2 x 10^{-5} M. Towards this end, the absorption maximum at 302 nm in the UV-Vis spectrum of **2** was monitored as the ratio of **2** and $TBAH_2PO_4$ was varied. Since the complex has a lower extinction coefficient than free **2**, a minimum in absorbance change was expected when complex formation was greatest; this minimum in absorbance was observed when the host mole fraction was equal to 0.5 (Figure S9, ESI). This finding is consistent with the formation of a 1:1 complex, **2**•$H_2PO_4^-$. On the basis of diffusion ordered NMR spectroscopic (DOSY) analyses, the formation of self-assembled polymeric structures is ruled out under the relatively high dilution conditions used for the spectroscopic studies (Figure S19, ESI).

Based on the optical titration studies involving different anions (studied as their TBA salts), the highest affinity was observed for $H_2PO_4^-$, followed by $HP_2O_7^{3-}$. All the binding curve fittings were performed in Origin, using the non-linear curve fitting feature described in the ESI. In all cases, the fits were consistent with a 1:1 binding stoichiometry.[15] Compounds **4** and **6** were likewise screened to determine their anion binding affinities in $CHCl_3$. A summary of the results is given in Table 1.

	2	**4**	**6**
$H_2PO_4^-$	(8±2) x 10^6	(8±2) x 10^6	(4.6±0.9) x 10^5
$HP_2O_7^{3-}$	(1.4±0.1) x 10^5	(1.9±0.3) x 10^5	(6.5±0.7) x 10^4
HSO_4^-	(4.1±0.2) x 10^3	(4.00±0.09) x 10^3	(1.6±0.1) x 10^3
$C_6H_5CO_2^-$	UD	(8 ±1) x 10^4	(6.7 ±0.1) x 10^3
Cl^-	NB	NB	NB
NO_3^-	NB	NB	NB

Table 1 Calculated binding affinities (M^{-1}) for **2**, **4**, and **6** with various tetrabutylammonium anion salts in $CHCl_3$ as determined by UV-Vis spectroscopy (see ESI). UD: could not be determined; NB: No discernible changes in the UV-Vis spectrum were observed.

In order to understand the electronic effects of the pyrrole on the anion binding properties of receptor **2**, a series of control compounds were prepared and studied. In a first study, the $H_2PO_4^-$ binding properties of the bisDPM **1** were studied with $TBAH_2PO_4$ in chloroform. Bisdipyrromethane **1** is the precursor to **2** and has protons, rather than formyl, substituents at the α-positions. Unfortunately, efforts to monitor the anion binding features of **1** via UV-Vis spectroscopy were precluded due to the fact that the $CHCl_3$ absorption in the UV portion of the spectrum overlaps with that of the pyrrole rings. Thus, we turned to ^{1}H NMR spectroscopy.

Although **1**, like **2**, is poorly soluble in $CDCl_3$ and forms turbid mixtures at the mM concentrations required for NMR spectroscopic analyses, the pyrrole NH chemical shifts could nevertheless be followed as $TBAH_2PO_4$ was added. Upon the addition of 7.0 molar equivalents of $TBAH_2PO_4$, a shift in the NH signal from 7.8 ppm to 10.9 ppm was observed (Figure S13 ESI). No appreciable changes were seen as further equivalents were added. Greater changes were observed in the case of **2**; here, the NH signal is seen to undergo a change from 9 ppm to 13.6 ppm upon the addition of only one equivalent of $TBAH_2PO_4$ (Figure S17 ESI). From this disparate behaviour we conclude that the affinity of **2** for $H_2PO_4^-$ is greater than that seen for the control system **1**.

	1	**2**	C4P
NH δ shift	7.8-10.9[a] 9.0-10.9[b]	9.0-13.6[a] 11.3-13.3[b]	7.0-NR[c]
Saturation	~7 equiv.	~1 equiv.	NR
K_a (M^{-1})	~1000[a,e] 184 ± 5[b]	>10^5[a,d] 3200 ± 900[b]	97 ± 4[c]

Table 2 Summary of ^{1}H NMR spectral changes seen for **1**, **2**, and calix[4]pyrrole (C4P) upon addition of $TBAH_2PO_4$. [a]Study performed in $CDCl_3$, [b]Study performed in $CDCl_3$/DMSO-d_6 (8/1). [c]Study performed in CD_2Cl_2 (Ref. 5). NR: not reported; [d]value beyond the range that may be determined accurately by ^{1}H NMR spectroscopy. [e]Approximate value based on an analysis of what was initially a turbid mixture.

In order to assess the importance of preorganization and receptor shape on anion binding, receptors **2**, **4**, and **6** were compared. The positions of the two diformyldipyrromethane (diformyl-DPM) units on the aromatic ring did not appear to affect significantly the binding affinities and specificities for the various test anions considered in the present study. Support for this conclusion came from the finding that the isomeric *para* (**2**) and *meta* (**4**) systems displayed similar selectivity and anion affinity trends (cf. Table 2). On the other hand, the pyridine-based receptor **6** was a characterized by affinities that were an order of magnitude lower.

	by UV-Vis			by ^{1}H NMR	
	2[a]	**7**[a]	**8**[a]	**2**	C4P[c]
$TBAH_2PO_4$	(8 ±2) x 10^6	NC	NC	3200 ± 900[b]	97 ± 4
TBACl	ND	ND	ND	121 ± 7[a]	350 ± 6

Table 3 Binding affinities as calculated from UV-Vis and ^{1}H NMR spectral titrations for **2**, **7**, **8**, and C4P with TBACl and $TBAH_2PO_4$ in [a]$CDCl_3$ and [b]$CDCl_3$/DMSO-d_6 (8/1). [c]Study performed in CD_2Cl_2 (Ref. 5). NC: No spectral change. ND: Not determined.

Another control compound, dipyrromethane **7**, was prepared according to the literature.[16,17] Structure **7** lacks the second diformyl-DPM unit present in **2** and we therefore hypothesized that this should lead to a weaker binding affinity. Although **7** is very similar to **2** in terms of electronics and may be viewed as being "half" of the full receptor system present in the latter bisDPM, no spectral change were observed in the UV-Vis spectrum when it (compound **7**) was titrated with $H_2PO_4^-$ in $CHCl_3$. On this basis, we conclude that the increased number of NH hydrogen bond donors present in **2** (four vs. two) as compared to **7** and the creation of what may be a better organized receptor system leads to a substantial increase in binding affinity. Compound **8** was also studied as a control. This flexible system has the same number of α-formylpyrroles as **2**; however, it lacks a similar degree of preorganization. It displays very little affinity for pyrophosphate or the other test anions, as inferred from the lack of observed spectral changes (Figure 3).

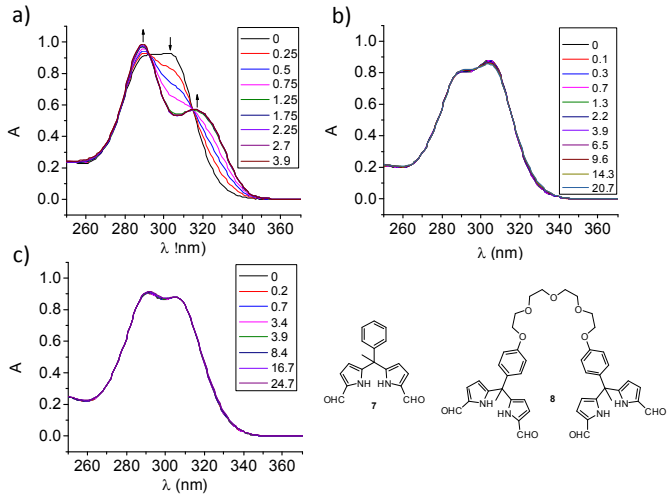


Figure 3 UV-Vis spectral changes seen when a) **2**, b) **7**, and c) **8** were treated with $TBAH_2PO_4$ in $CHCl_3$.

Lastly, the anion recognition features of compounds **1** and **2** were compared with those of unsubstituted C4P. This latter receptor system also contains four pyrrolic subunits and is a well-studied system that is known to undergo a conformational change upon exposure to Lewis basic anions in less polar media, such as dichloromethane.[5] It was thus considered a good reference system for evaluating the effect that structural and electronic changes can have on anion receptors built up formally from two sets of DPM subunits.

Although the $H_2PO_4^-$ binding affinity of **1** could only be determined approximately due to solubility limitations, it was found that **1** displayed roughly an order of magnitude higher affinity in $CDCl_3$ than seen for C4P in CD_2Cl_2 (cf. Table 1). The even lower solubility of **2** required the use of a $CDCl_3$/DMSO-d_6 (8/1) mixture to determine a reliable K_a value for $H_2PO_4^-$ (cf. Table 2). While not a direct comparison, it is noteworthy that the resulting binding affinity proved substantially higher than that recorded for C4P in CD_2Cl_2. Based on these comparisons, it is concluded that modification of the electronics from **1** to **2** increased the $H_2PO_4^-$ affinity by at least one order of magnitude. Overall, the K_a value increases on passing from C4P to **1** and then on to **2**. This benefit in binding is ascribed to a combination of structural and electronic effects. These structure-related changes appear to modulate not just the affinity, but also the inherent selectivity. Specifically, receptor **2** exhibits an inversion in selectivity compared to C4P. It displays a higher affinity for $TBAH_2PO_4$ (subject to the solvent-related caveat noted above). However, it possesses a ~3 fold lower affinity for TBACl in similar halogenated solvents (i.e., $CDCl_3$ vs. CD_2Cl_2; cf. Table 3).[5]

On the basis of the above findings, we conclude that the macrocyclic structure present in C4P is not required for effective anion recognition. In fact, the new tetrakis(1*H*-pyrrole-2-carbaldehyde)

receptors reported here bind the $H_2PO_4^-$ anion more strongly than C4P. The higher affinity is attributed to a combination of factors, including 1) the presence of better hydrogen-bond donor groups (i.e., the α-formyl pyrrole units present in receptor **2** and 2) a rigid aromatic linker between the individual DPM subunits that permits conformational flexibility and, presumably, accommodation of the bound anion. The present work thus serves to highlight how new design strategies can be exploited to achieve yet-improved anion recognition features in the case of synthetic, pyrrole-based receptors.

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Notes and references

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† Electronic supplementary information (ESI) available: Synthetic procedures, details of spectroscopic analyses, fitting of binding curves and X-ray crystallographic details. CCDC 1012698-1012700. For the ESI and crystallographic data in CIF form see DOI: xxxxx

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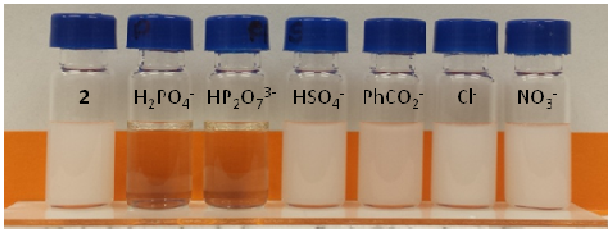
TOC Graphic



Acyclic tetrapyrrolic receptors display high affinity for dihydrogenphosphate and pyrophosphate anions in $CHCl_3$ with anion recognition enhancing the solubility of the receptor.