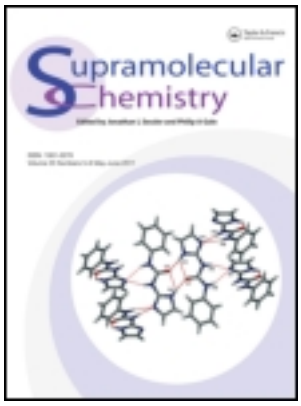

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Oxoanion recognition by benzene-based tripodal pyrrolic receptors

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Two new tripodal receptors based on pyrrole- and dipyrromethane-functionalised derivatives of a sterically geared precursor, 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene, are reported; these systems, compounds **1** and **2**, display high affinity and selectivity for tetrahedral anionic guests, in particular dihydrogen phosphate, pyrophosphate and hydrogen sulphate, in acetonitrile as inferred from isothermal titration calorimetry measurements. Support for the anion-binding ability of these systems comes from theoretical calculations and a single-crystal X-ray diffraction structure of the 2:2 (host:guest) dihydrogen phosphate complex is obtained in the case of the pyrrole-based receptor system, **1**.

Keywords: anion receptors; dihydrogen phosphate; hydrogen sulphate; X-ray structure; theoretical calculations

Introduction

The development of anion receptors for the purpose of molecular recognition and sensing is a very active discipline within the broader field of supramolecular chemistry (*1*). Due to their important roles in biology (*2*), chemistry (*3*) and the environment (*4*), oxoanions, such as phosphate and sulphate (and their protonated forms), have attracted particular interest in the context of anion recognition. In fact, considerable effort has been devoted to the creation of artificial receptors capable of binding these particular anions. Many of these efforts have been guided by naturally occurring anion-binding systems including the sulphate-binding protein and the phosphate-binding protein that recognise their respective substrates, with extreme selectivity via the use of multiple hydrogen bonds within the interior of a deep and relatively hydrophobic cleft (*5*).

The use of multiple hydrogen bonds for oxyanion recognition is a particularly important design principle in the case of neutral receptors. Here, amides, sulphonamides, ureas and thioureas have been widely used as the requisite hydrogen bond donors (*6*). Our group and several others have also exploited pyrroles for this purpose (*7*).

Another important design element that affects binding strength and selectivity in supramolecular interactions is the geometric shape of the host. The implementation of tripodal-shaped neutral receptors has attracted considerable attention in recent years (*8*). Among the core systems that can provide a tripodal arrangement, the 1,3,5-trisubstituted benzene skeleton is particularly attractive; it can provide a preorganised ligand structure that is particularly well suited for the recognition of tetrahedral oxoanions (*9*). Many hydrogen bond-donating groups have been incorporated onto a tripodal scaffold and the anion-binding properties are thoroughly investigated. While pyrrole-based tripodal receptors are known, surprisingly, their study has been largely limited to sugar recognition (*10*). We thus set out to test whether pyrrole-containing receptors based on a 1,3,5-trisubstituted benzene skeleton would act as effective anion receptors. Here, we report that appropriately designed systems, specifically 'tripods' **1** and **2**, display a highly inherent selectivity for the hydrogen sulphate and dihydrogen phosphate oxoanions, as inferred from isothermal titration calorimetry (ITC) measurements carried out in acetonitrile. Support for the anion-binding ability of these systems comes from theoretical calculations and a single-crystal X-ray diffraction structure of the 2:2 (host:guest) dihydrogen phosphate complex is obtained in the case of the pyrrole-based receptor system, **1**.

Results

The synthesis of receptors **1** and **2** proved to be relatively straightforward (cf. Scheme 1). Receptor **1** was prepared by stirring a 1:3 mixture of the sterically geared precursor 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene, **3** (*11*), with commercially available pyrrole-2-carboxaldehyde, **4** (*12*), in methanol. After 10 h, **1** was filtered off as a white solid. Compound **2** was synthesised in a similar fashion by combining **3** in methanol with mono-formyl

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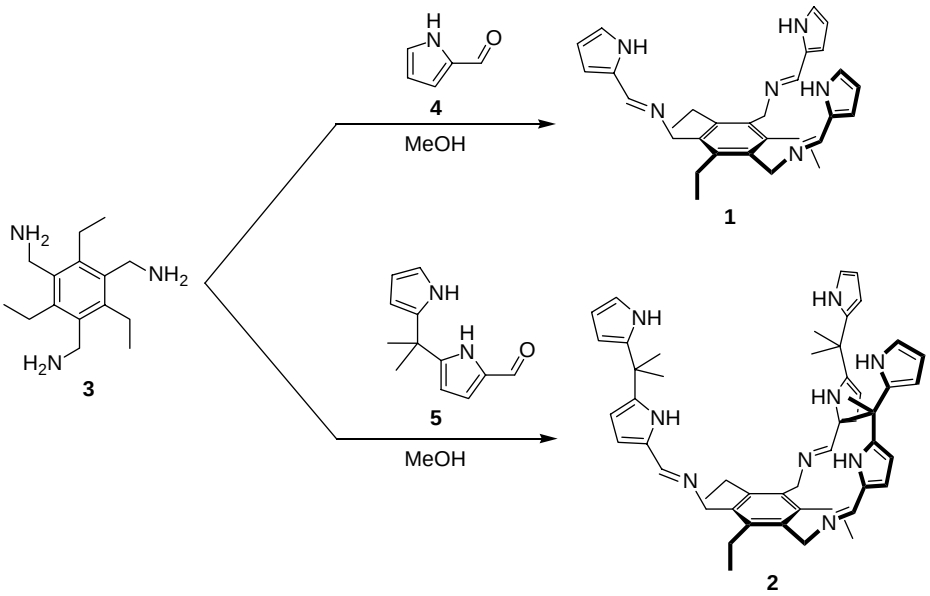

Scheme 1. Synthesis of receptors **1** and **2**.

dipyrromethane, **5**, an intermediate that was prepared through the reaction of dipyrromethane with one stoichiometric equivalent of the Vilsmeier reagent (see Electronic Supplementary Information[1] available online).

As noted above, both receptors **1** and **2** are constructed from precursor **3**. The use of this well-known tripodal core facilitates the synthesis and has the added benefit of imparting preorganisation to the final products (i.e. **1** and **2**) by restricting rotation through steric clashes. This causes the 'arms' of these two receptors to be closer together than might otherwise be expected. All final products were isolated, purified by filtration and washing with methanol and fully characterised by NMR spectroscopic methods, as well as via high-resolution mass spectrometric analyses.

The structure of **1** was also confirmed via a single-crystal X-ray diffraction analysis of its dihydrogen phosphate complex (Figure 1). Single crystals suitable for X-ray diffraction were grown by dissolving receptor **1** and tetrabutylammonium (TBA) dihydrogen phosphate in dichloromethane, and allowing *n*-hexane to diffuse slowly into the solution. The resulting structure revealed an overall 2:2 complex in the solid state. In this structure, each receptor interacts with one molar equivalent of the dihydrogen phosphate anion, which is contained within a cleft-like pocket. Hydrogen-bonding interactions between the anions give rise to the overall 2:2 stoichiometry.

The above structure led to the inference that tripod **1** would serve as a good receptor for oxoanions. To test this hypothesis, thermodynamic data for the binding process between the receptor and various anions in acetonitrile were obtained using ITC. In accordance with design expectations, receptor **1** was found to bind strongly the tetrahedral-shaped oxoanion, dihydrogen phosphate, as well as the pyrophosphate anion. The binding isotherm corresponding to a representative titration is reproduced in Figure 2. Anions characterised by other limiting geometries including spherical, trigonal planar and Y-shaped species, such as the halides, nitrate or test carboxylate anions, displayed either no appreciable binding or gave rise to interactions that were too weak to quantify by ITC. Interestingly, the hydrogen sulphate anion, which is similar in size and shape to the dihydrogen phosphate anion, was bound less effectively than this latter species, albeit better than the test anions with non-tetrahedral geometries (Figure 2). A summary of the thermodynamic data obtained from the various ITC titrations is presented in Table 1.

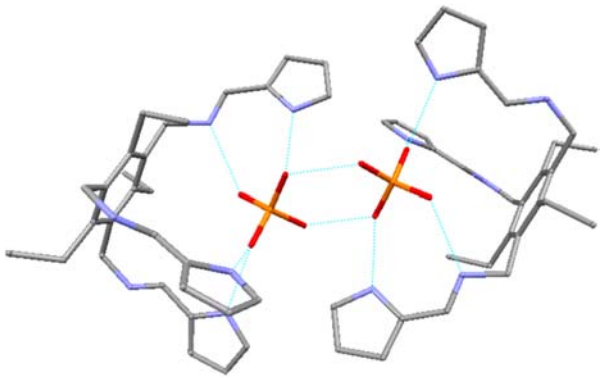

Figure 1. View of the solid-state structure of the 2:2 dihydrogen phosphate ion complex formed with receptor **1**, as determined from a single-crystal X-ray diffraction analysis. The TBA counter cations and H atoms have been omitted for clarity.

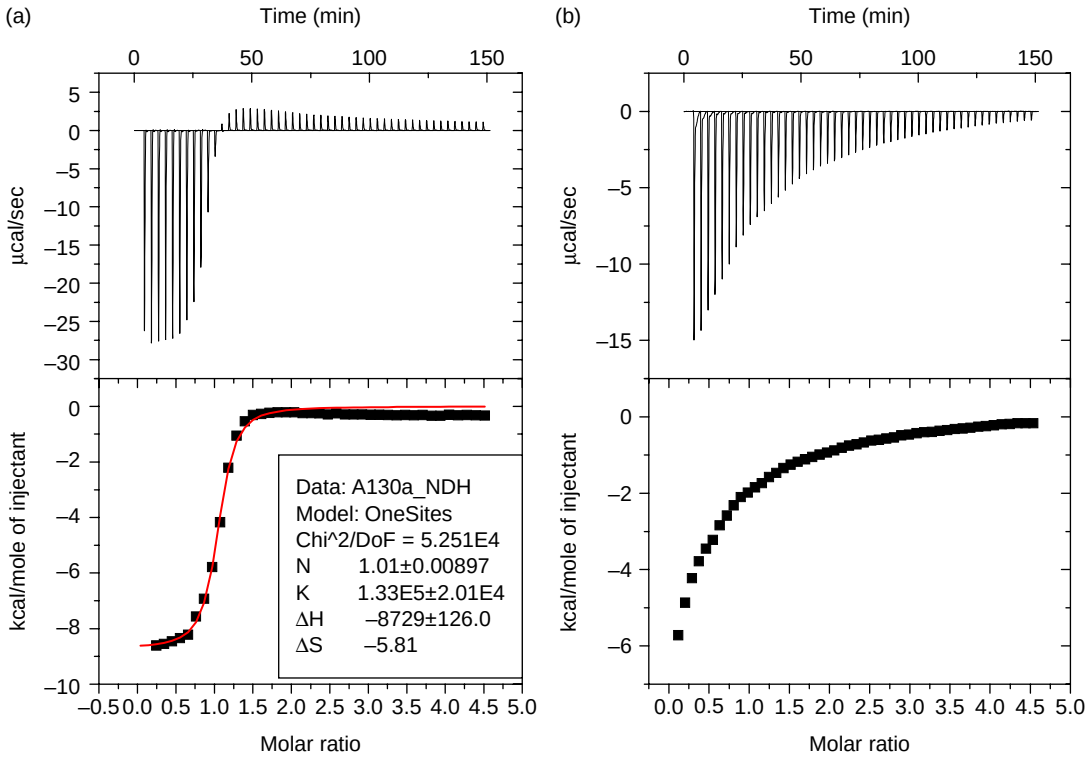

Figure 2. Results of ITC titrations carried out in acetonitrile with receptor **1** and (a) dihydrogen phosphate and (b) hydrogen sulphate.

The ΔH° and $-T\Delta S^\circ$ data in Table 1 provide support for the notion that complex formation, to the extent it occurs, is driven in all cases by a favourable enthalpy change and unfavourable entropy change. In the case of the strongly bound species, the isothermal titration curves for receptor **1** can be fit well to a one-site binding model. This model provides an association constant (K_a) of $6.8 \times 10^6\,M^{-1}$ between **1** and dihydrogen phosphate by reflecting a very strong interaction with a favourable $\Delta G^\circ(-6.55\,\text{kcal/mol})$. The inflection point of this system occurs near a molar ratio of 1.0 ($n = 1.08$). Such a finding is consistent with a 1:1 interaction and represents a stoichiometry consistent with the 2:2 binding mode seen for dihydrogen phosphate in the solid state as inferred from the X-ray structural data discussed above.

Table 1. Thermodynamic data for host–guest complexation determined by ITC[a].

Host	Guest[b]	$\Delta H^{\circ c}$	$-T\Delta S^{\circ c}$	$\Delta G^{\circ c}$	K_a[d]	n[e]
1	Halides	–	–	–	–	–
1	NO_3^-	–	–	–	–	–
1	OAc^-	–	–	–	$\leq 10^3$	–
1	OBz^-	–	–	–	$\leq 10^3$	–
1	$HP_2O_7^{-3}$	-36.6 ± 1.0	30.1 ± 0.8	-6.4 ± 0.2	$4.84 \times 10^4 \pm 4.0 \times 10^3$	0.97 ± 0.06
1	$H_2PO_4^-$	-8.5 ± 0.2	1.5 ± 0.1	-7.1 ± 0.3	$1.38 \times 10^5 \pm 1.4 \times 10^4$	1.01 ± 0.02
1	HSO_4^-	–	–	–	$\leq 10^3$	–
2	Halides	–	–	–	–	–
2	NO_3^-	–	–	–	–	–
2	OAc^-	–	–	–	$\leq 10^3$	–
2	OBz^-	–	–	–	$\leq 10^3$	–
2	$H_2PO_4^-$	-12.7 ± 1.0	3.1 ± 0.4	-9.6 ± 0.7	$6.54 \times 10^6 \pm 2.4 \times 10^6$	0.98 ± 0.06
2	$HP_2O_7^{-3}$	-27.5 ± 1.4	21.4 ± 1.5	-7.2 ± 0.4	$2.88 \times 10^5 \pm 7.3 \times 10^4$	0.93 ± 0.03
2	HSO_4^-	-21.6 ± 1.9	13.3 ± 2.2	-8.4 ± 0.1	$1.33 \times 10^6 \pm 2.9 \times 10^5$	0.96 ± 0.03

[a] Determined in CH_3CN at 298 K.
[b] Bu_4N^+ salts.
[c] Unit: kcal/mol.
[d] Unit: M^{-1}.
[e] Host–guest stoichiometry.

The anion-binding behaviour of receptor **2** was also probed via ITC analyses. As with **1**, these studies were carried out in acetonitrile. In analogy to what was seen for this latter system, the more elaborate dipyrromethane-based receptor **2** displayed only weak affinities for spherical and planar anions and was found to bind the dihydrogen phosphate and pyrophosphate anions well. However, in contrast to what proved true for receptor **1**, receptor **2** displayed a very high affinity for the hydrogen sulphate anion. In fact, in the case of receptor **2**, the hydrogen sulphate anion was bound with the same order of magnitude as dihydrogen phosphate. A summary of the thermodynamic data for the interaction of various test anions with receptor **2** is also included in Table 1.

When comparing the ITC data recorded for **1** and **2** in the presence of various anions, it is interesting to note that the addition of three hydrogen bond-donating pyrroles in **2**, with respect to **1**, had nearly no effect on the interaction in the case of most anions. For example, the magnitude of the association constants for the binding of dihydrogen phosphate by these two receptors proved to be rather insensitive to the change in the number of hydrogen bond-donating moeities by the elaborated tripods. However, in the case of hydrogen sulphate, the association constant drastically increases by several orders of magnitude on passing from **1** to **2**. This finding underscores how modifications in the size, shape and donor ability of a given class of receptors can be exploited to enhance the affinity for one particular analyte.

In an attempt to better understand this phenomenon, the molecular modelling calculations were carried out using the data from the crystal structure of **1** with dihydrogen phosphate as a reference. Binding energies (E_{bind}) were calculated as the difference in energy between the receptor–ligand structure energy and the sum of the energies of the free ligand and the appropriate anion (see Supplementary Information available online). These results are shown in Table 2. Receptor **1** showed identical binding energies with both hydrogen sulphate and dihydrogen phosphate (-16.9 kcal/mol), which is not consistent with the experimental ITC data (in which $H_2PO_4^-$, whereas receptor **2** was calculated to prefer minimally dihydrogen phosphate over hydrogen sulphate (3 kcal/mol)).

The discrepencies between the calculated and experimental data are more than likely a result of solvent effects (calculations assume gas phase interactions). More experimentation is required, and possible changes to the molecular calculation models are needed in order to determine the true nature of the system. Nevertheless, the present comparison between experiment and theory is important. It highlights the need to develop methods, both theoretical and experimental, which will allow us to understand more completely the underlying mechanisms that influence the selectivity of complex receptor systems, such as **1** and **2**. Certainly, the availability of new calculation methods that would allow us to define with greater precision the design criteria needed to obtain systems capable of selectively binding one oxoanion over another, is viewed as a worthy goal and work along these lines is in progress.

Table 2. Calculated binding energies of **1** and **2** with hydrogen sulphate and dihydrogen phosphate.

Structure	Ligand	E_{bind} (kcal/mol)
1	HSO_4^-	-16.9
1	$H_2PO_4^-$	-16.9
2	HSO_4^-	-32.2
2	$H_2PO_4^-$	-35.4

Conclusion

In conclusion, we have demonstrated that the easy-to-make tripodal systems **1** and **2** can be used to recognise selectively tetrahedral oxoanions, such as hydrogen sulphate and dihydrogen phosphate. The formation of strong complexes with net 1:1 host/guest stoichiometry was inferred from ITC measurements carried out in acetonitrile and from a single-crystal X-ray diffraction analysis of the dihydrogen complex of **1**. Although most of the anions tested interacted with receptors **1** and **2** with similar strength, hydrogen sulphate displayed greatly enhanced affinity for **2** relative to **1**. Additional efforts to develop new pyrrole-based anion receptors based on the use of organised threefold symmetric scaffolds are currently under way. Studies of these putative new systems are expected to allow the relationship between theory and experiment as it relates to the recognition of oxoanions to be better defined. Appropriate results will be reported in due course.

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Note

1. Electronic Supplementary Information (ESI) available online: Crystallographic data presented as CIF file, and synthetic experimental section (PDF). CCDC number: 833333. See DOI: 10.1039/b000000x/.

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