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Hydrophilic and hydrophobic carboxamide pincers as anion hosts†

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Hydrophobic and hydrophilic, monotopic and ditopic carboxamide pincer hosts containing ethyl, hexyl, 2-hydroxyethyl and 2-hydroxyethyl ethyl ether pendant arms were synthesized. Solubility trends indicated that solubilities in water or hydrocarbon solvents varied depending on the nature of the pendant arms. Binding constants for hydrophilic pincers were larger in general than their hydrophobic analogs. Significant synergistic binding effects for the ditopic hosts were not observed.

Designing supramolecular hosts that bind anions has been a challenge facing supramolecular chemists for a number of years. In addition to the important role of intermolecular interactions, solvent also has a major influence on the binding affinity as a result of solvation and desolvation influences.[1] The magnitude of these thermodynamic effects can vary greatly considering the nature of the solvent. An especially active area of host–guest chemistry research is the design of hosts that display selective binding in water. Nature's solvent is water, and thus understanding supramolecular interactions in water is of great importance. However, this quest of hosts capable of high binding in aqueous solutions is also due to the challenge of overcoming steep hydration energies in order to form strong host–guest interactions.[2] Since many guests of Nature involve anions, significant focus has been on supramolecular host–guest chemistry of anions in water.

Anion coordination chemistry depends on various non-covalent interactions such as hydrogen bonding and anion-π stacking, and now boasts a variety of applications, ranging from sensors, to anion separations, transport, and catalysis.[3] Isophthalamides and the related pyridine-based picolinamides have been widely studied as anion hosts[4] since the first seminal paper of Crabtree and Kavallieratos describing bromide binding in the pincer pocket of a simple phenyl appended isophthalamide.[5]

Recently, our interest in macrocyclic hosts containing pyridine-2,6-dicarboxamides led to our synthesis of a ditopic analog of the NNN pincer, *e.g.*, a "duplex" pyridine-2,3,5,6-tetracarboxamide pincer.[6,7] An appealing aspect of this new class of ligand/host systems is the ease with which the pendant groups can be modified, which led us to speculate whether hydrophilic or hydrophobic chains could influence the effectiveness of anion binding in different solvents. Furthermore, anion binding in ditopic *versus* monotopic dicarboxamides could potentially reveal synergistic influences on binding a second anion. Here we compare anion binding between the monotopic 2,6-pyridine dicarboxamides traditionally utilized for anion recognition and the potentially ditopic 2,3,5,6-pyrazine tetracarboxamides. We also report the solubility preferences of the two classes of hosts (Fig. 1).

The methyl ester of 2,6-pyridine dicarboxylate was used from a commercially available source. Tetramethyl pyrazine-2,3,5,6-tetracarboxylate was prepared by the reaction of pyrazine-2,3,5,6-tetracarboxylic acid with thionyl chloride followed by reaction with methanol. The di- and tetra-carboxamide-based (**1a–d** and **2a–d**, respectively) derivatives were synthesized by the condensation reaction of various amines with pyridine-2,6- and pyrazine-2,3,5,6-methyl esters, respectively (Scheme 1). Yields ranged from 96 to 58% for the monotopic, and 87 to 64% for the ditopic pincers, varying from higher to lower for shorter to longer pendant arms, respectively. The

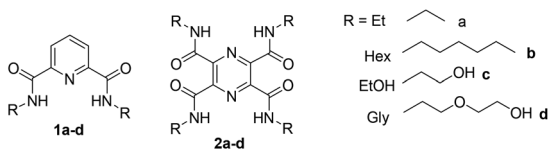

Fig. 1 Monotopic pyridine (**1**) and ditopic pyrazine (**2**) pincers with both hydrophobic (**a** and **b**) and hydrophilic (**c** and **d**) pendant chains.

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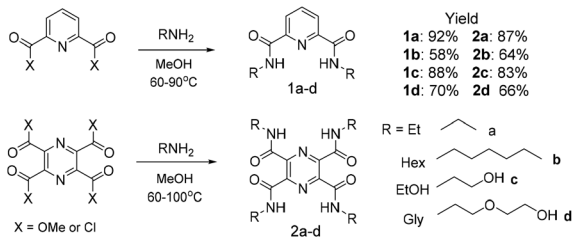
†Electronic supplementary information (ESI) available: Materials, instrumentation, experimental details, NMR spectral data, binding studies and X-ray data. CCDC 2092504 (**2b**), 1974541 (**2c**) and 1453984 (**2d**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ob01605a



Scheme 1 Synthesis of pincers with pendant chains. R: **a** = $-CH_2CH_3$ (Et); **b** = $-CH_2(CH_2)_4CH_3$ (Hex); **c** = $-CH_2CH_2OH$ (EtOH); **d** = $-CH_2CH_2OCH_2CH_2OH$ (Gly).

characterization data correspond to the structures of compounds **1a–d** and **2a–d** (Fig. S1–S3†).

The impetus for our design strategy was to determine if host solubility could be manipulated in simple dicarboxamide- and tetracarboxamide-based hosts/ligands for future applications in separations. The hydrophobic ligands, **a**, ethyl (Et) and **b**, hexyl (Hex), were soluble in organic solvents such as acetone, DMSO, and DMF. The hexyl derivatives were also soluble in $CHCl_3$ and hexane, aided by sonication. The hydrophilic hosts, **c**, hydroxyethyl (EtOH) and **d**, hydroxyethyl ethyl ether (Gly), were soluble in water, alcohols, DMSO and DMF. A more comprehensive solubility table is provided in the ESI (Table S1†).

While our solubility predictions were satisfied for the most part, the key question was whether the hosts were capable of overcoming solvation and desolvation influences in the respective media. We fully realized of course that these are not the ideal hosts, in terms of containing only two amide binding sites. However, the goal was to obtain some idea of the influence of hydrophobic (**a** and **b**) *vs.* hydrophilic (**c** and **d**) chains as part of the immediate "coordination area" of the anion. Due to the anticipated weak binding of most of these hosts, we used a mixture of 9 : 1 CD_3CN : DMSO-d_6.

Both monotopic and potentially ditopic hosts were screened for qualitative binding with anions F^-, Cl^-, NO_3^-, HSO_4^-, OAc^-, and $H_2PO_4^-$ as determined by downfield shifts of the amide N*H* signal. However, only F^-, OAc^-, and $H_2PO_4^-$ experienced significant shifts, typically >1 ppm. Table 1 contains the association constants for each of the pincers with the three selected anions, F^-, OAc^-, and $H_2PO_4^-$. FHF^- formation may have affected some of the F^- titrations.

Binding constants (K) were obtained by EQNMR least-squares analysis from ^{1}H NMR titrations,[8] and double checked using BindFit plots.[9] Monotopic hosts, **1**, binding constants were calculated using a 1 : 1 stoichiometry model, while duplex, tetracarboxamide hosts, **2**, were calculated from 1 : 1 and 1 : 2 models (Fig. S4–S12 and Table S2†).

While affinities were not very high, certain trends were noticeable. Both the monotopic and ditopic hydroxyl group-containing hosts underwent some deprotonation during F^- titrations. For hosts with longer chains, **1d** and **2d**, deprotonation occurred after 1 equivalent F^-, while for the shorter chain hosts, **1c** and **2c**, deprotonation was delayed until 2 equivalents. For all hydrophilic hosts, deprotonation led to the appearance of HF_2^- ions at 16.1 ppm in ^{1}H NMR and at −143 ppm in ^{19}F NMR (Fig. S13 and S14†).

Binding for the monotopic hosts was relatively straightforward, but not very strong (Table 1). Very low affinities (K < 300 M^{-1}) were observed for the hydrophobic di(Et), **1a**, and di(Hex), **1b** receptors. The hydrophilic di(EtOH), **1c**, and di(Gly), **1d**, hosts showed slightly higher interactions (most >1000 M^{-1}), probably due to the additional hydrogen bonding hydroxide groups and hydrophilic cavities. In all four binding curves, F^- consistently showed the largest downfield chemical shifts (Fig. 2).

K_{11} binding constants for the ditopic hosts, **2**, were for the most part higher than their monotopic analogs, **1**. Whether this is related or not to their ditopic nature is not clear. As

Table 1 Association constants (K_1, M^{-1}) of **1** and **2** for anions in 9 : 1 CD_3CN : DMSO-d_6

	Log K_1/M^{-1}							
	Hydrophobic				Hydrophilic			
Anion	**1a**	**2a**	**1b**	**2b**	**1c**	**2c**	**1d**	**2d**
$H_2PO_4^-$	1.64	2.77	2.01	2.99	3.29	2.67	2.87	2.80
OAc^-	2.17	2.58	2.05	2.95	3.49	3.21	2.79	3.30
F^-	2.40	2.69[a]	2.43[a]	2.79	>4	>4	3.00	3.15

[a] Complicated by induction period (more prominent in **1b**).

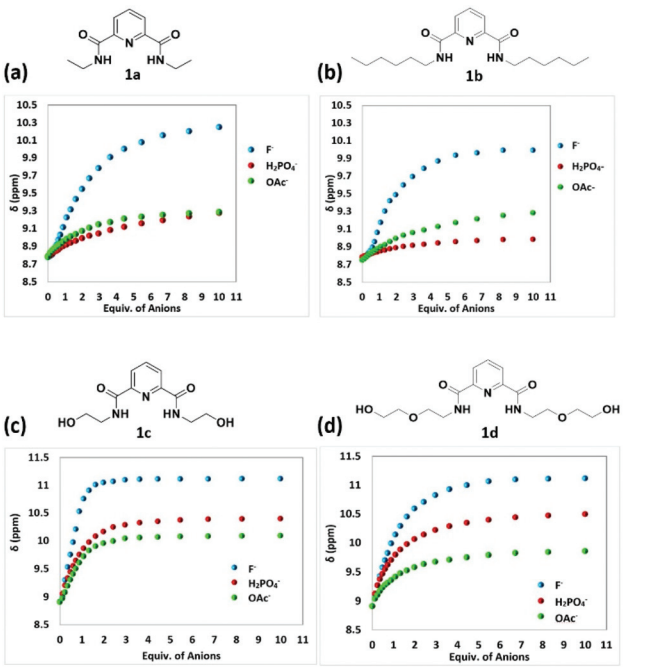


Fig. 2 Binding curves for the (a) di(Et), **1a**, (b) di(Hex), **1b**, (c) di(EtOH), **1c**, and (d) di(Gly), **1d**, hosts showing only the amide signal shifts with [nBu$_4$N$^+$][A$^-$] where A = F, OAc, H_2PO_4.

anticipated, the hydrophilic hosts, **c**, and **d**, displayed higher affinities than hydrophobic receptors. Notable was the observation that the $H_2PO_4^-$ binding curves with the hydrophobic hosts **2a** and **2b** displayed larger downfield shifts compared to those of F^- (Fig. 3(a) and (b)), the reverse of what was observed for the monotopic analogs (Fig. 2). However, considering the lack of any crystallographic data, assumptions about any direct binding between anions with host amide groups in solution should be kept at a minimum. We have noted in previous structures with dicarboxamide pincer hosts that frequently anions don't bind directly with amide NH groups, but instead through water molecules.[10] These water bridges were especially notable with phosphates, which may also be the case here.

K_{12} binding constants tended to be low for most of the ditopic hosts (Table S2†). As an example, six $\log K_{12}$s were ≤1.0. While this observation is due in part to negative cooperativity from $A^-\cdots A^-$ repulsion, determination of ditopic (or higher order) binding constants in solution is significantly more complicated. For example, as Thordarson pointed out with phenyl tetracarboxamide analogs known as pyromellitamides, one of the structural effects in ditopic binding for this class of hosts (with two pairs of adjacent carbonyls), results from carbonyl O···O repulsion of adjacent carbonyl groups. The problem arises when the amide hydrogens are aligned (or preorganized) for anion binding within the pincer cavities.[11] These relatively shorter O···O distances are observed in some of the crystal structures of the free bases discussed below.

The three exceptions to the low K_{12} values were **2a**, the tetraethyl host, with F^-, and **2c** and **d**, the hydrophilic hosts, with $H_2PO_4^-$. All three have interaction cooperativity parameters ($\alpha = 4K_{12}/K_1$) that are greater than 1.0.[11,12] Values greater than 1.0 indicate that binding of the first anion has a positive affect on the binding of the second ion. The hydrophilic hosts are by nature more complex due to the ionizable OH group, while F^- tends to have complications due to FHF^- formation. In the absence of crystallographic results showing the exact mode of binding, we don't have enough information to speculate on the exact cause of the higher $\log K_{12}$s.

We isolated crystal structures of all four free base hosts, one of which has been reported,[6] however, no structures with anions have been obtained despite numerous efforts. Even so, it is interesting to compare the structures of the uncomplexed hydrophilic and hydrophobic, short and long chain hosts, especially with consideration for possible preorganization for anion binding.

The structures of the short chain hosts are relatively unremarkable. The previously reported ethyl host **2a** di(Et) shows no significant intramolecular hydrogen bond except the anticipated inward oriented amide NH groups with the pyrazine nitrogen atoms (Fig. 3(a)). The planar pyrazine with adjacent carboxamide groups is ideal for promoting stacking, which is indeed the case for **2a**. In the crystal structure, the hydrophobic host stacks in columns of 11 crystallographically independent pyrazine pincers, each slightly offset from the one below and one above.[6] The intramolecular carbonyl O···O distances the averaged over the 11 independent molecules is 3.195(3) Å.

The hydrophilic tetrahydroxyethyl host **2c**, tetra(EtOH), shows some similarities with the tetraethyl analog **2a**, tetra(Et), as seen in the overhead views (Fig. 4(a) and (b)). The intramolecular carbonyl O···O distances are closer (3.007 and 3.015 Å) compared to >3.10 Å observed for **2a**. While **2c** also packs in columnar arrays, each pincer is distinctly more offset, with intervening water molecules providing linkages between the hosts, as shown in a trimeric slice of the stack (Fig. 4(c) and (d)).

The longer chain hosts are, as anticipated, more complex crystallographically. The tetrahexyl chains in **2b** possess an especially

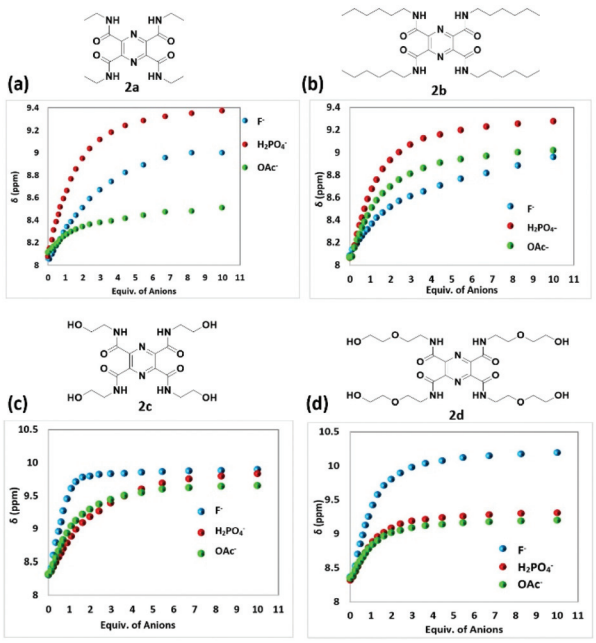


Fig. 3 Binding curves for the (a) tetra(Et), **1a**, (b) tetra(Hex), **1b**, (c) tetra (EtOH), **1c**, and (d) tetra(Gly), **1d**, hosts showing only the amide signal shifts with $[n\mathrm{Bu_4N^+}][A^-]$ where A = F, OAc, H_2PO_4.

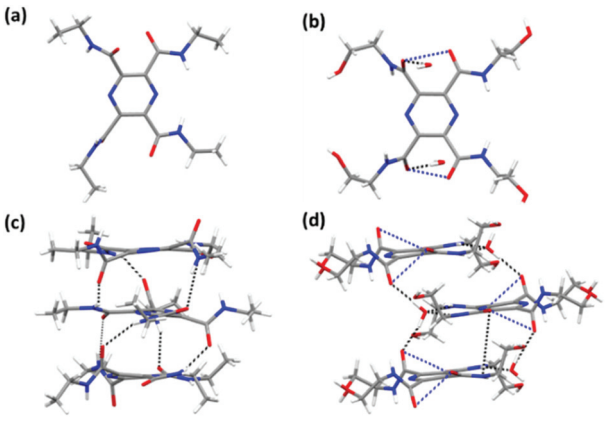


Fig. 4 Crystal structure perspective views of the short-chain pyrazine tetracarboxamides including overhead views of (a) **2a** (Et) and (b) **2c** (EtOH) hosts; and trimer arrays of the side views of (c) **2a** and (d) **2c**. Hydrogen bonds are shown in black and close interactions in blue.

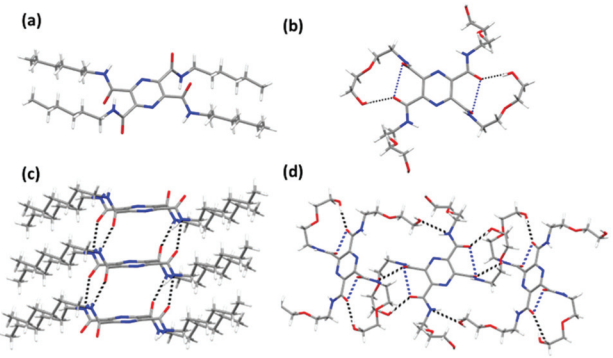


Fig. 5 Crystal structure perspective views of the long-chain pyrazine tetracarboxamides including overhead views of the (a) **2b** (hexyl) and (b) **2d** (hydroxyethyl ethyl ether) hosts; and trimer arrays of the side views of (c) **2b** and (d) **2d**. Hydrogen bonds are shown in black and close interactions between the adjacent carbonyl groups in blue dotted lines.

elegant, slightly offset stacking motif due to extended inter- and intra-molecular hydrophobic interactions between the long alkyl chains. Intra-molecular C–C distances in the chains are as short as 4.07 Å, with *ortho* substituted chains pointed along the same directions (Fig. 5(a)). The closest approaches are found between pyrazine heterocycles, from the pyrazine nitrogen atoms to adjacent carbon atoms at 3.950(6) Å. Stacking is promoted by the orientation of the amide groups. Adjacent carbonyls are pointed in the same direction, upward on one side of the pyrazine and downward on the other, leading to strong intermolecular hydrogen bond-held stacking interactions between the hydrophobic hosts (Fig. 5(c)). The weaker anion binding interactions with both the pyridine and pyrazine hydrophobic **a** and **b** hosts could be due to the stronger hydrophobic intramolecular and intermolecular interactions between the chains. The tetrahexyl derivative **2b** readily forms gels, which will be reported elsewhere.

As in the hydroxyethyl (EtOH) host, the tetracarboxamides of the ethyl hydroxyethyl ether (Gly) receptor contain additional hydrogen binding sites given the presence of the terminal hydroxide. This undoubtedly plays a significant role in its organization in the solid state. We obtained two structures from two different batches of host. Both were almost identical in the solid state. Again, the pyrazine group acts in an organizational fashion, and the adjacent carbonyl groups are relatively close at 2.998(3) Å. The molecule does not show ordered stacking as seen in the tetraethyl-substituted duplex. However, the hydroxyl group of two *trans* pyrazine chains curl around to form intramolecular hydrogen bonds with the carbonyl group of adjacent chains (OH···O = 2.765(3) Å). These hydroxyl groups also form intermolecular hydrogen bonds with those of adjacent molecules. In total, twelve intermolecular hydrogen bonds link each molecule to surrounding neighbours.

Conclusions

In summary, we have designed and synthesized a series of "bare bones" monotopic and ditopic pincers adorned with hydrophobic and hydrophilic chains. Our aim was to explore hydrophobic and hydrophilic effects on anion binding as well as monotopic *vs.* ditopic binding for coordination sites on the same heterocycle. As expected, all hosts displayed, in general, relatively low binding, with monotopic pincers exhibiting slightly lower affinities compared to their extended ditopic analogs in 9 : 1 CD_3CN : DMSO-d_6. Both mono-and ditopic hydrophilic pincers displayed higher anion compared to the hydrophobic hosts, possibly attributed to the additional OH···A^- binding, as well as the more inviting nature of the hydrophilic pincer cavity. Cooperative binding of the second anion was not observed to a significant extent, with the exception of the $H_2PO_4^-$ anions for the hydrophilic hosts **2c** and **2d**, and F^- with the tetraethyl host **2a**. The lack of significant ditopic interactions may be due to the proximity of the anion binding sites, as well as distortion of the binding cavities due to repulsion between adjacent carbonyl groups. The results of this study may lead to more complex synergistic binding and solubility control in supramolecular ligand designs.

Author contributions

J. L. did the characterization and binding studies. H. T. did the original synthesis and characterization of the pincers. S. P. refined the synthesis of several pincers and repeated some of the binding studies. J. L., H. T., and S. K. did the crystallizations. K. B. J. designed the project. J. L. wrote the preliminary draft of the paper, and K. B. J. and S. P. finalized the paper. V. W. D. performed the crystal structures and assisted in the writing of the paper.

Conflicts of interest

There are no conflicts to declare.

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