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Just add tetrazole: 5-(2-Pyrrolo)tetrazoles are simple, highly potent anion recognition elements†

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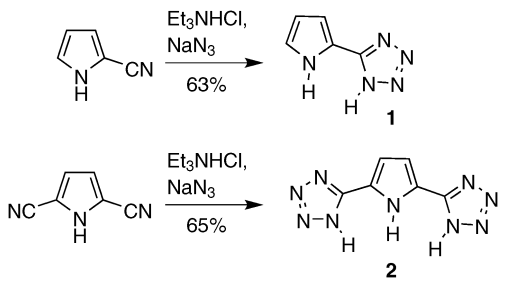
We report a novel pyrrolo-tetrazole motif that encodes anion binding orders of magnitude stronger than closely related systems and suggests the general utility of amide-tetrazole exchanges for creating simple, high-affinity anion binders.

Anion-binding molecules are increasingly being pursued for applications in waste remediation, sensing, and the treatment of disease. In spite of the introduction of anion-pi[1] and halogen bonding[2,3] interactions, hydrogen bonds remain the dominant type of weak interaction used for anion recognition. A variety of different neutral N–H hydrogen-bonding functional groups have been used for binding anions, and pyrroles are prominent examples.[4] The diversity of structures made available by combining simple N–H hydrogen-bonding elements in different ways is impressive, but the number of different groups that have been used is small. Increasing acidities by introducing multiple electron-withdrawing groups is one established route to increased potencies.[5–7] We have been seeking new, highly acidic anion-binding functional groups that might open up access to new families of inherently more potent receptors.[8,9] We report here on the invention of 5-(2-pyrrolyl)tetrazole as a simple, two-point hydrogen bonding functional group that encodes superb anion affinities and a propensity for sulfonate recognition.

Our recent identification of tetrazoles as highly acidic recognition elements[8–10] suggested to us that their combination with pyrroles might be profitable. 5-(2-pyrrolyl)tetrazole (**1**) is a nearly isosteric analog of 2,2′-bipyrrole that is readily prepared from commercially available 2-cyanopyrrole in one step by treatment with Et_3NHCl/NaN_3 (Scheme 1).[11] We synthesized pyrrole bis(tetrazole) **2** using a literature route to 2,5-dicyanopyrrole[12,13] followed by conversion to the bis(tetrazole) **2**. Control compounds pyrrole-2-carboxylic acid (**3**), simple pyrrolyl amide **4**, and 2,2′-bipyrrole (**6**)[14] were either commercially available or prepared by established routes.

Solutions of hosts **1**, **3**, **4**, and **6** in CD_3CN were titrated with Bu_4N^+ Cl^- in order to take a preliminary look at the success of this design. Chemical shift data were fit to 1 : 1 binding isotherms[15] to determine K_{assoc} values that revealed striking differences between the anion-binding potency of **1** and the control compounds (Fig. 1 and 2). We explain the difference between tetrazole-functionalized **1** (3300 M^{-1}) and carboxylic acid-functionalized **3** (125 M^{-1}; 26-fold weaker) on the basis of the stereoelectronic effects that favor the *syn* conformation of the carboxylic acid OH.[8,16] In a host like **3**, a *syn* carboxylic acid OH diverges from the binding pocket and can't cooperate with the pyrrole NH to bind a single Cl^- anion. The pyrrolyl amide **4** does not suffer from this particular conformational problem, but its Cl^- affinity is low nevertheless. Our determined value for **4**·Cl^- (K_{assoc} 75 M^{-1}) is similar to that reported for related host (**5**) published by Gale (K_{assoc} 28 M^{-1}, determined in CD_3CN containing 0.03% H_2O),[14] and both are >40-fold weaker than **1** ($\Delta\Delta G$ = 2.2 kcal mol^{-1}). These hosts differ from **1** in both conformation and acidity; calculations suggest that both factors play a role in driving stronger binding by **1** (see ESI). We examined acidity in particular by comparing **1** to its nearly isosteric, but far less acidic, analog 2,2′-bipyrrole **6**. Again, the 5-(2-pyrroyl)tetrazole **1** wins out by a significant margin, binding Cl^- more strongly than does **6** by an order of magnitude ($\Delta\Delta G$ = 1.4 kcal mol^{-1}).

In order to examine the scope of anion binding by this new motif, we carried out NMR studies of **1** with a variety of halides and oxyanions, both in anhydrous CD_3CN and in CD_3CN containing 1% (v/v) H_2O. Addition of BzO^- to tetrazole-containing **1** gave rise to curves that could not be fit to 1 : 1, 2 : 1, or 1 : 2 binding isotherms, along with disappearance of the tetrazole NH when ~2 equivalents of BzO^- had been added. Job plots were complex (*i.e.* had multiple extrema) and not supportive of any n : m binding stoichiometry (Fig. S23†). These data are in line with those reported by other groups for other combinations of acidic hosts and carboxylate anions, in which initial (strong) binding is followed by proton transfer from



Scheme 1

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† Electronic supplementary information (ESI) available: synthesis and characterization data, experimental details, computational results. See DOI: 10.1039/c1cc15875a

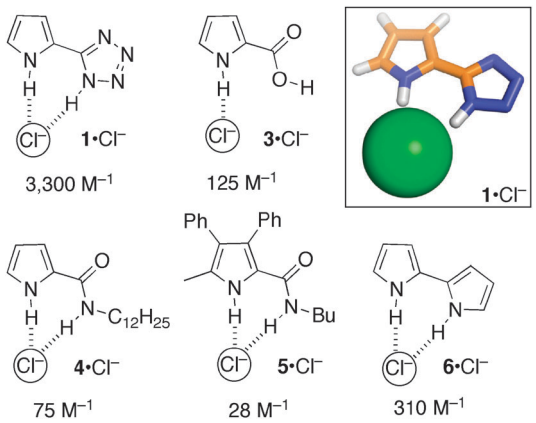

Fig. 1 Pyrrole-based hosts and their K_{assoc} values for Cl^- determined in CD_3CN. Inset: calculated structure of **1**·Cl^- (HF/6-311+G**). Data for **5** taken from ref. 14.

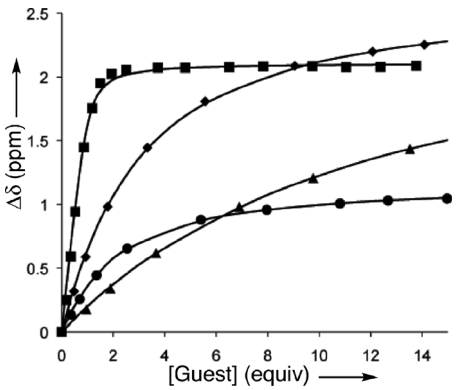

Fig. 2 Chemical shift data (points) and fitted 1 : 1 binding isotherms (lines) that arise upon titration of Bu_4N^+ Cl^- into CD_3CN solutions of hosts **1** (■), **3** (●), **4** (▲), and **6** (◆). See ESI for experimental details.†

host to guest that is partially driven by the formation of a strong $RCOO^-\cdots HOOCR$ complex.[5,17–20] All other (less basic) anions studied produced NMR titration data that fit well to 1 : 1 binding isotherms to give K_{assoc} values (Table 1). To evaluate better the potency of **1**, we also studied 2,2′-bipyrrole (**6**) with the complete set of anions because it has a nearly identical hydrogen bonding geometry to **1**. Chemical shift data for bipyrrole **6** fit well to 1 : 1 binding isotherms to give K_{assoc} values for all anions tested (Table 1), with no evidence of proton transfer to BzO^- (as expected). A 1 : 1 stoichiometry of complexation was confirmed by Job plots for Cl^- and BzO^- (see ESI†). Comparison of these two hosts' K_{assoc} values reveals that the increased acidity of the tetrazole in **1** gives rise to significantly higher affinities for all anions than **6**, with a maximum difference of ~25-fold observed for TsO^- in both solvent systems.

Finally, we carried out NMR studies of pyrrole bis(tetrazole) **2**. NMR studies in 1% H_2O/CD_3CN and in pure CD_3CN show the formation of 1 : 1 complexes with significantly increased association constants relative to host **1** for all anions (Table 2), demonstrating that both tetrazole NH's and the central pyrrole NH can cooperate to bind complementary anions as suggested by models (Fig. 3). Titration with BzO^- again gave rise to data suggesting binding followed by proton transfer (Fig. S15).

Table 1 Affinities of 5-(2-pyrrolo)tetrazole (**1**) and 2,2′-bipyrrole (**6**) for various anions[a]

Guest	K_{assoc} for **1** in CD_3CN (M^{-1})	K_{assoc} for **6** in CD_3CN (M^{-1})	K_{assoc} for **1** in 1% H_2O/CD_3CN (M^{-1})	K_{assoc} for **6** in 1% H_2O/CD_3CN (M^{-1})
Cl^-	3300 ± 1200	310 ± 10	890 ± 100	71 ± 5
Br^-	450 ± 50	50 ± 3	110 ± 15	21 ± 2
I^-	17 ± 3	3 ± 1	<3	<3
TsO^-	900 ± 50	37 ± 4	420 ± 120	16 ± 1
NO_3^-	160 ± 20	19 ± 1	60 ± 9	7 ± 1
BzO^-	p.t.[b]	1500 ± 200	p.t.[b]	260 ± 30

[a] Guests were titrated as their Bu_4N^+ salts into solutions of hosts in the stated solvent system. Chemical shift data for all nuclei that displayed significant chemical shifts were fit to 1 : 1 binding isotherms to arrive at K_{assoc} values. Experiments were done in duplicate or triplicate. Values reported are averages of all nuclei from all experiments. Errors reported are standard deviations. [b] p.t. = evidence of proton transfer between host and guest; see text.

Table 2 Affinities of bis(tetrazole) **2** for various anions[a]

Guest	K_{assoc} for **2** in CD_3CN (M^{-1})	K_{assoc} for **2** in 1% H_2O/CD_3CN (M^{-1})
Cl^-	K_{11} 26 300 ± 2300 K_{12} 780 ± 120	6500 ± 500
Br^-	1500 ± 430	1100 ± 50
I^-	1100 ± 130	650 ± 50
TsO^-	34 000 ± 3500	3000 ± 1000
NO_3^-	1600 ± 300	900 ± 300
BzO^-	p.t.[b]	p.t.[b]

[a] All values are for K_{11} unless otherwise indicated. See also footnotes for Table 1.

In pure CD_3CN, titrations with Cl^- gave rise to data that indicated mixed 1 : 1 and 1 : 2 (H : G) complex formation. The simple titration data was best fit to binding isotherms including both the formation of 1 : 1 and 1 : 2 complexes, with the expected strong 1 : 1 complex formation (K_{11} = 26 300 M^{-1})

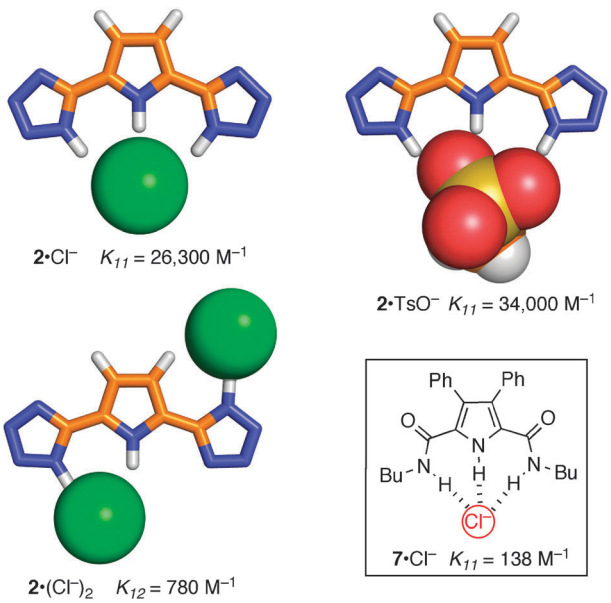

Fig. 3 Calculated structures and stepwise binding constants for complexes of **2** with Cl^- and TsO^- (truncated as methanesulfonate for calculations). Inset: structure and K_{11} value for reference host **7**.[21]

followed by a much weaker binding of a second equivalent of Cl^- (K_{12} = 780 M^{-1}). Job plot analysis also indicated mixed complex formation, but in an unconventional way: the Job plot tracking the chemical shift of the pyrrolic NH had its maximum at 0.5, indicating 1 : 1 binding, while the plot tracking the pyrrolic CH had a maximum at 0.3, indicating 1 : 2 binding (Fig. S24†). Mixed Job plot results of this type must be interpreted with caution. In this case, our hypothesis is that the pyrrolic NH reports largely on the formation of the 1 : 1 complex while the chemical shift of the CH arises largely due to the binding of the second equivalent of Cl^-. This theory is consistent with the calculated structures for **2**·Cl^- and **2**·$(Cl^-)_2$ (Fig. 3), as are the relative magnitudes of the experimentally determined values of K_{11} and K_{12}.

Host **2** also displays an altered guest-binding preference relative to **1** in pure CD_3CN, showing its highest affinity for the oxyanion TsO^- (K_{assoc} = 34 000 M^{-1}) instead of Cl^-. Molecular models (HF/6-311 + G**) suggest that Cl^- can't hydrogen bond to the peripheral tetrazole NH's of **2** as effectively as does the larger TsO^- anion (Fig. 3). In **2**·Cl^- the distance between the tetrazole NH donor and Cl^- acceptor is d_{N-Cl} = 3.41 Å, or 0.11 Å *longer* than the sum of van der Waals radii;[22] in **2**·TsO^- the equivalent hydrogen bonding distances are d_{N-O} = 2.813 and 2.815 Å, which are 0.25 Å *shorter* than the sum of van der Waals radii. With that said, the "normal" selectivity of Cl^- over TsO^- is observed in 1% H_2O/CD_3CN, making it incautious to interpret these selectivities exclusively in terms of host–guest contacts observed in gas-phase calculations.[23] Whatever the details of host–guest complexation, stoichiometries, and geometries, it is clear that the addition of tetrazoles has a consistently strong and favorable influence on the anion binding properties of the pyrrole scaffold. The potency of the 5-(2-pyrrolyl)tetrazole motif in this setting is most clearly demonstrated by a simple comparison of the K_{11} of **2** for Cl^- in CD_3CN (26 300 M^{-1}) to the reported value for the closely related pyrrole bis(amide) **7** (138 M^{-1}),[21] a *nearly 200-fold increase* in affinity that arises from a simple tetrazole-for-amide swap.

Pyrroles offer a richness of photochemical and electrochemical properties, as well as diverse possibilities for synthetic derivatization, that have driven researchers to incorporate them into myriad anion hosts and sensors.[4,24,25] Yet the potencies of simple, acyclic pyrrole-based anion receptors can be orders of magnitude weaker than their urea, squaramide, and indolocarbazole counterparts.[26–28] Tetrazoles are prized as metabolically stable carboxylic acid bioisosteres in medicinal chemistry[29] and have shown promise as organocatalysts,[30] but their favorable recognition properties have been ignored with few exceptions.[8–10,31–34] Like other acidic recognition elements, tetrazoles are inherently limited to moderately basic anions. But the tradeoff for this limited scope is the ability to create potent receptors quickly and easily without complex synthetic steps like macrocyclizations and strapping reactions. Host **1** is derived from host **5** *via* a tetrazole-for-amide swap, as host **2** is derived from host **7**. We envision that this conservative modification could be applied as a general and synthetically simple improvement that will provide orders-of-magnitude affinity enhancements for a large number of other amide and urea-based anion-binding hosts.

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