JOC The Journal of Organic Chemistry

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Dissecting the Complex Recognition Interfaces of Potent Tetrazole- and Pyrrole-Based Anion Binders

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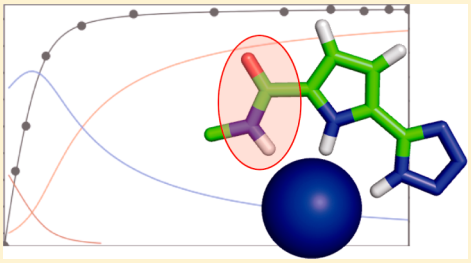
Supporting Information

ABSTRACT: Tetrazoles are potent anion binders. We report here a new family of tetrazole−pyrrole−amide hosts that arise when a tetrazole is incorporated as a new binding element alongside the well-known amidopyrrole anion-binding scaffold. In addition to reporting three new, modular synthetic routes that can be used to access these structures, we also report that the new hosts are highly potent binders of chloride. Along the way, we carried out studies of a pyrrole ester control compound that, surprisingly, bound anions almost as strongly as did the amide analogues. This led us to investigate further the relative importance of the amide NH in halide binding. We report that, despite the regular appearance of this close amide NH---Cl contact in calculated and experimental X-ray structures, the amide NH in this family of anion hosts does not hydrogen bond strongly to chloride in solution.



INTRODUCTION

Anions are ubiquitous in living organisms, where maintenance of intra- and extracellular anion concentrations is a vital control mechanism. As such, a variety of natural and synthetic ion carriers have been discovered,[1] many of which have therapeutic potential.[2−4] Synthetic anion sensors for the monitoring of ion concentrations in both biological and environmental samples are also of growing interest.[5−10]

Despite the broad importance of anion recognition, the vast majority of anion receptors are constructed by assembly of only a few different, well understood anion-binding functional groups that include amides,[10−12] sulfonamides,[13,14] and (thio)-ureas.[15−17] Pyrrole (**1**) is a dominant player in anion recognition, represented by many derivatized pyrroles[18−20] and related pyrrolic ring systems.[21−24] Triazoles, easily assembled by "click" reactions of alkynes and azides,[25,26] have recently been added to this tool kit as agents that bind anions via their electron-deficient CH group.[27,28] A related heterocycle, tetrazole, is relatively underused as a neutral binder of anions but is attractive for many reasons. Tetrazoles are easily assembled by variants of the "click" reaction that involve almost any organic nitrile being treated with NaN_3 under a variety of conditions.[29−32] Further, tetrazoles are potent anion-binding elements that operate well in a variety of structural contexts because their acidic NH bears a much larger partial positive charge than other amide-like groups and heterocycles.[33−35] In fact, a single unadorned tetrazole (**2**) is a stronger anion binder[34] than many more elaborate, multidentate hydrogen-bond-donating hosts (e.g., **3**, **4**, and **5**) (Figure 1).[35,36] One tetrazole-containing anion-binding motif that we have previously reported is represented by the pyrrole−tetrazole hybrids **6** and **7**, which are some of the most potent and simple anion recognition motifs in the pyrrole family. Monotetrazole **6** binds chloride 120-fold stronger than does analogous monoamide **4**, and bis-tetrazole **7** binds chloride almost 200-fold stronger than does its closely analogous bis-amide **8** (Figure 1).[36] We report here a new family of pyrrole-based hosts that contain both amides and tetrazoles (hosts **13** and **14**) as well as ester-functionalized host **11**. These hosts show generally high affinities for HSO_4^-, and even higher affinities for Cl^-, and allow us to dissect out energetic influences of different groups at the recognition interface. Surprisingly, we uncover evidence that the amide NH is a spectator that is not required for the very strong halide binding in these systems, in contrast to previous results reported for various amidopyrrole hosts.[37−40]

RESULTS

Synthesis. We developed multiple routes to the selective installation of both tetrazole and ester/amide functionality at the 2- and 5-positions of pyrrole (**1**). The first synthetic strategy (Scheme 1a) began with ethyl pyrrole-2-carboxylate (**9**), which was cyanated with chlorosulfonyl isocyanate to give **10**. This was followed by tetrazole formation upon treatment with NaN_3 and NH_4Cl (generating HN_3 in situ) to give ester-functionalized host **11**. Hydrolysis of the ester provided highly polar carboxylic acid **12**, and subsequent EDC-mediated coupling to *p*-toluidine or *p*-methoxybenzylamine gave amide-functionalized hosts **13** and **14**, respectively. One shortcoming in this route was the poor regioselectivity of the cyanation of **9**, where substitutions at the 4-position (undesired) and 5-position (desired) were observed at approximately a 3:2 ratio that persisted despite efforts to optimize conditions. During the

Received: February 21, 2013
Published: April 30, 2013

dx.doi.org/10.1021/jo400372c | J. Org. Chem. 2013, 78, 4642−4648

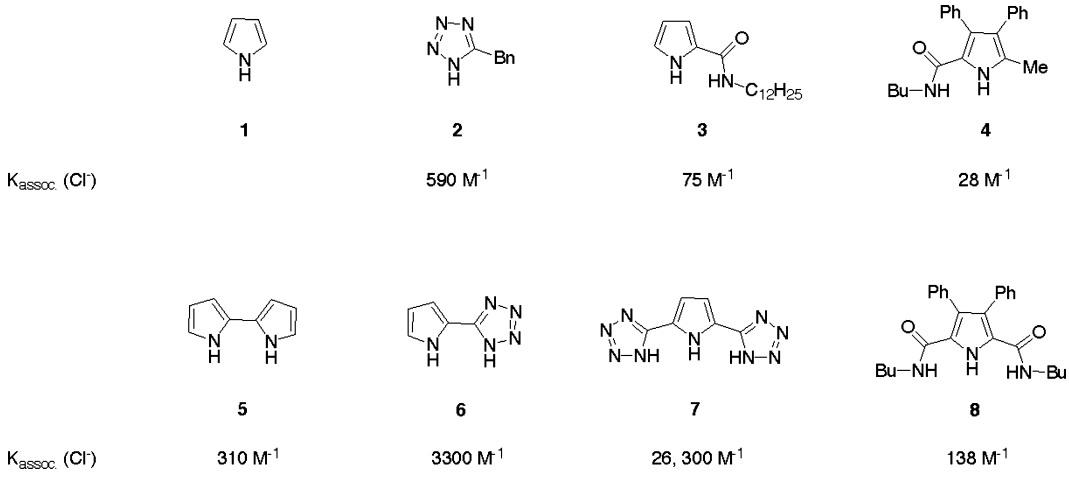
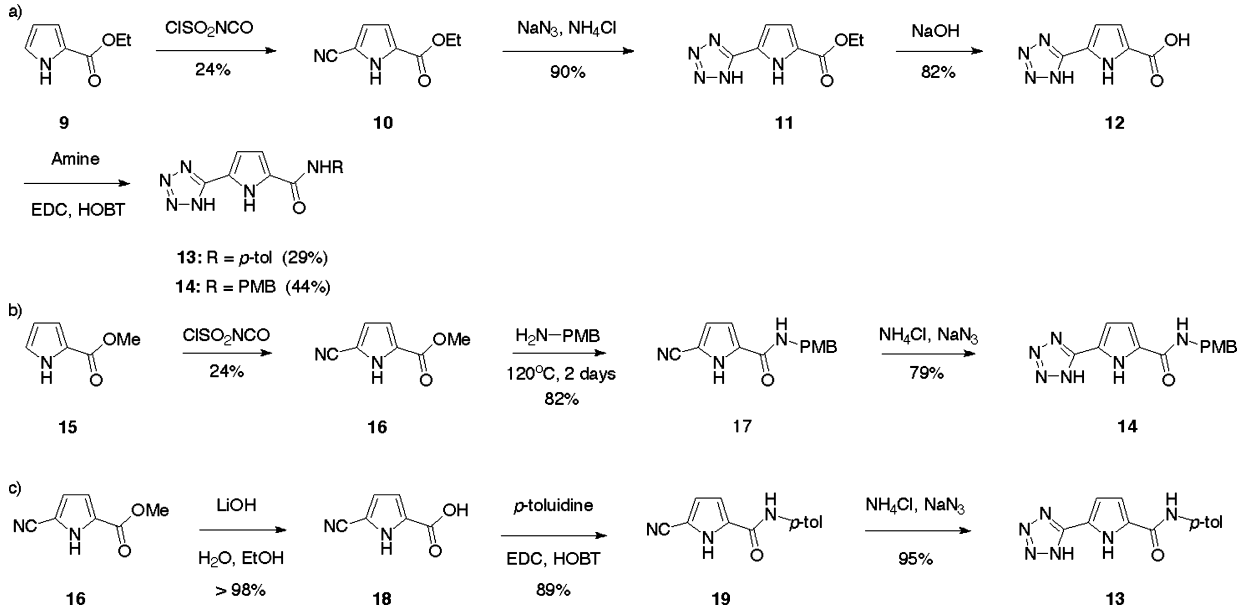


Figure 1. Structures of pyrrole (**1**) and related anion receptors **2**–**8** along with the 1:1 binding constants for the complexation of Cl^- in CD_3CN that have been previously reported in the literature (see text) (Bn = benzyl).

Scheme 1. Synthetic Approaches to Tetrazolylamidopyrroles



course of these investigations, we found the ethoxy group in **10** could be displaced directly by certain primary amines at high temperature, raising the possibility of a more direct synthetic route.

To take advantage of the higher reactivity for methyl esters in direct ester-to-amide conversions, we switched to a route starting with methyl-2-pyrrole carboxylate **15** and cyanated as before to give **16** (Scheme 1b). Direct displacement of the methoxy group was achieved by stirring **16** in neat *p*-methoxybenzylamine at 120 °C for 2 days, which cleanly provided amide **17** in >80% yield. Standard tetrazole-forming conditions gave the final product **14** in only three steps from commercially available material **15**. Attempting synthesis of host **13** via the direct amidation met with disappointing results, as stirring precursor **16** in molten *p*-toluidine even at temperatures in excess of 150 °C for several days resulted only in recovery of starting material **16**. In a general sense, our studies have taught us that the tetrazole formation is best left as the last step when possible, as tetrazole-containing intermediates such as **12** can be difficult to purify and/or dissolve for subsequent reactions. We used this information to develop a simple alternative route to **13** (Scheme 1c), which avoids the formation of problematic intermediate **12.** Hydrolysis of **16** gave the cyano-acid **18**, and EDC coupling of **18** with *p*-toluidine was followed by tetrazole formation as described above to complete an efficient synthesis of **13**. This pathway proved superior to our original strategy providing easier to handle intermediates and higher yields.

NMR-Based Binding Studies. ^1H NMR titrations were used to determine the anion-binding capabilities of hosts **11**, **13**, and **14**. Studies were carried out in CD_3CN, as this solvent allows comparisons to the broadest set of values for other pyrrole-containing hosts reported in the literature. Briefly, anionic guests were added as their Bu_4N^+ salts, and the resulting host chemical shift changes were fitted to 1:1 or 2:1 (H:G) binding isotherms using HypNMR (Protonic Software, 2008). Binding stoichiometries under these conditions were cleanly 1:1 for all complexes except those of host **14** and Cl^- (the strongest complexation pair observed in this study), which showed a small contribution from 2:1 (H_2G) complex

dx.doi.org/10.1021/jo400372c | J. Org. Chem. 2013, 78, 4642–4648

Table 1. Binding Constants for the Hosts Studied Obtained via ^{1}H NMR Titrations in CD_3CN[a]

host	Cl^-	Br^-	I^-	HSO_4^-	OTs^-	NO_3^-
11	18000 ± 2300	1700 ± 260	85 ± 21	130 ± 13	950 ± 7	440 ± 35
13	31000 ± 4600	1800 ± 100	71 ± 11	1500 ± 230	3000 ± 98	750 ± 85
14	K_{11} = 23000 ± 4700	1300 ± 700	150 ± 23	1200 ± 58	770 ± 49	1120 ± 12
	K_{21} = 820 ± 11					

[a]All values are for K_{11} unless otherwise noted. All titrations were done in duplicate or triplicate, and the errors reported are standard deviations. Host solutions of 0.5−1 mM were first prepared, and then also used as solvent to make the titrant solution (containing 8−15 mM of each guest). The guest solutions were titrated into the host until a point of saturation was reached. See the Supporting Information for details.

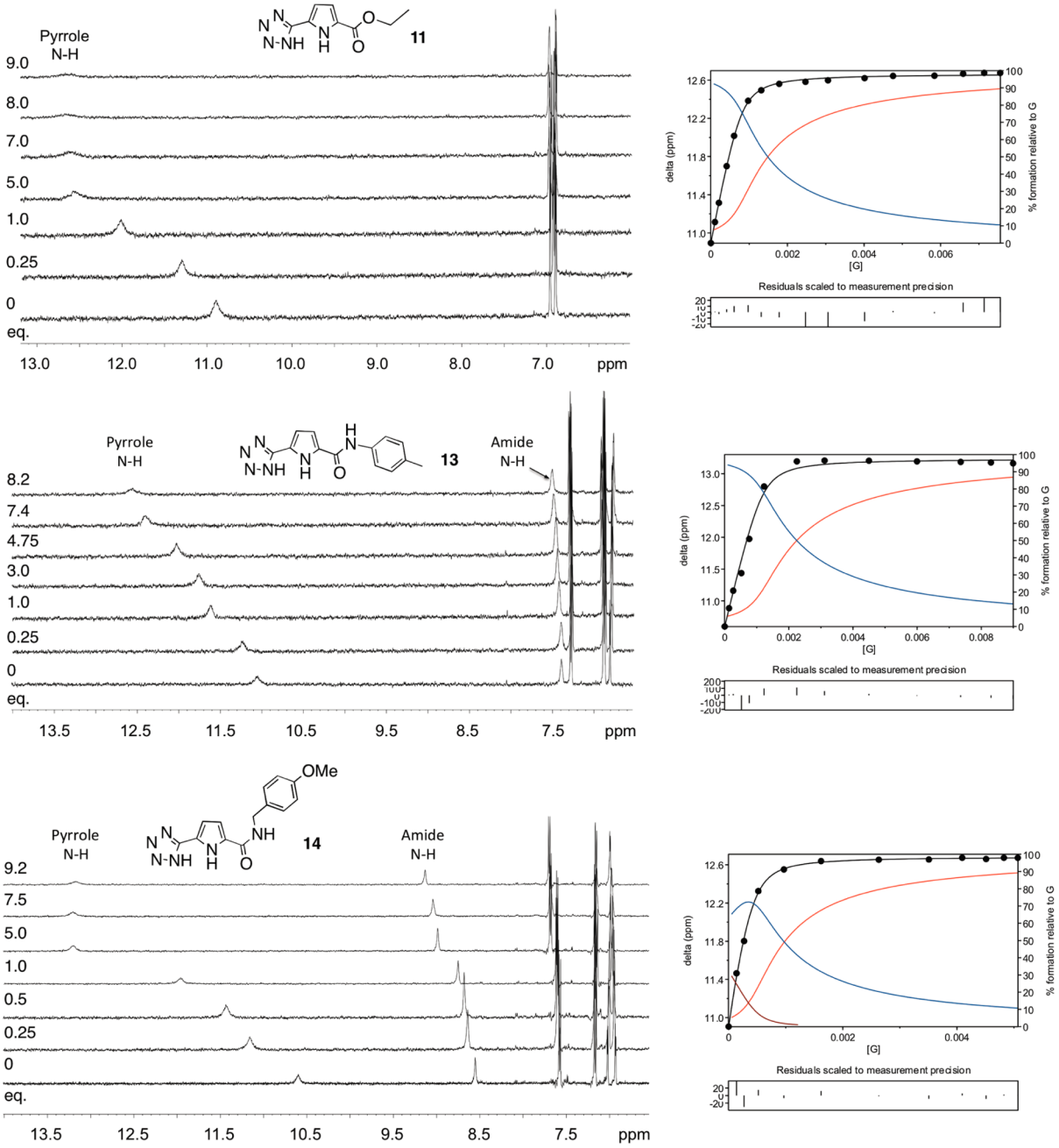


Figure 2. (Left) Excerpts of stacked ^{1}H NMR plots following pyrrole (downfield singlet) and amide (upfield singlet) signals for each host in this study. Titrations in these examples were performed in CD_3CN with $Bu_4N^+Cl^-$ as the guest (see the Experimental Section for details). (Right) Representative binding curves following the pyrrole N−H and speciation plots (see text) (black points = experimental chemical shift data, black line = fitted chemical shift data, red line = [1:1 complex], blue line = [free host], brown line = [2:1 host/guest complex]).

formation. Our choices of binding stoichiometries for curve fitting were confirmed by Job plot[42] data for all three hosts with Cl^- and for hosts **11** and **14** additionally with Br^- and HSO_4^- (Supporting Information). The resulting association constants

dx.doi.org/10.1021/jo400372c | J. Org. Chem. 2013, 78, 4642−4648

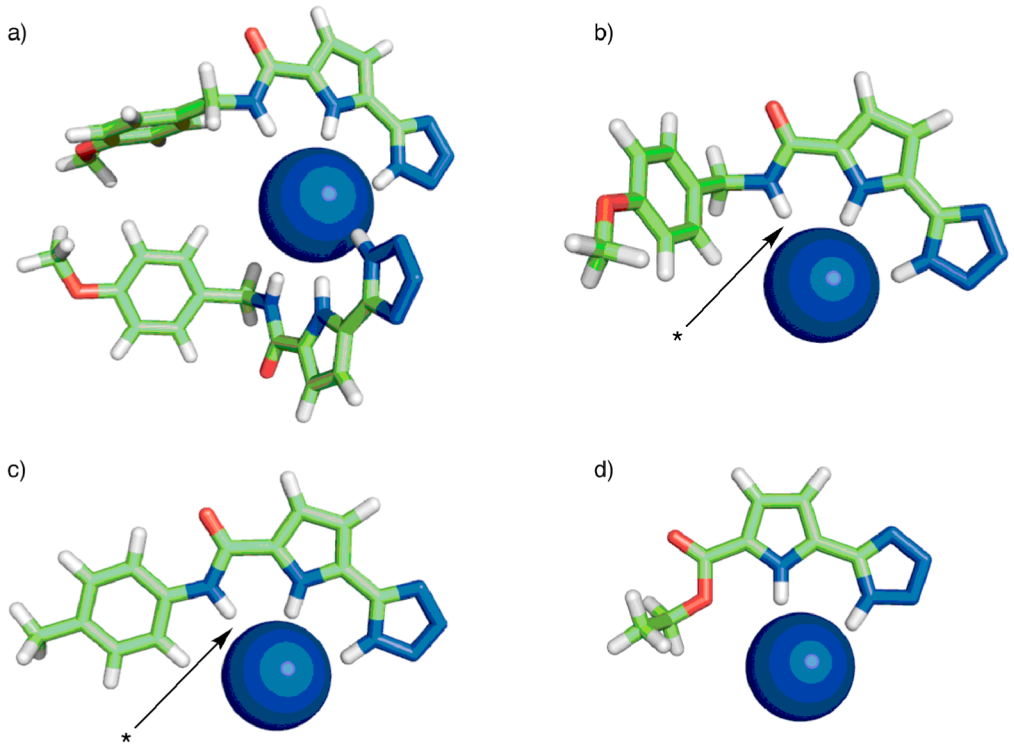


Figure 3. Local minima identified for the host–guest complexes with Cl^- by calculations at the HF/6-31+G* level of theory: (a) 2:1 complex observed between host **14** and chloride; (b) 1:1 complex between host **14** and chloride; (c, d) 1:1 complexes of the other two hosts with chloride. Hydrogen bonds that are suggested by calculated structures but whose energetic importance is refuted (or diminished) by solution-phase data are marked with an asterisk (*).

between the hosts studied and various anionic guests are given in Table 1. Representative stacked plots and binding curves are shown in Figure 2.

DISCUSSION

Halide Binding. All hosts showed similar high affinities for chloride and lowest affinities for iodide. The ability of **11** to bind Cl^- and Br^- as well as do amides **13** and **14** was unexpected, as its ester oxygen atom lone pairs must be in close proximity to anions engaged by the central pyrrole NH. Even more surprising, when picturing a repulsive, close O---Cl^- contact, is that **11** is 5.5-fold more potent than its unsubstituted parent compound **6**.[35] The best interpretations of these data are that (a) the O---Cl^- contact for **11** is long enough not to destabilize the complex significantly and (b) the electron-withdrawing nature of the ester acidifies the pyrrole NH and thereby increases the strength of pyrrole NH---Cl^- hydrogen bond. The pyrrole NH in free **11** is 0.8 ppm downfield of the chemical shift of the same NH in parent host **6**, giving further support to this line of reasoning.

So what are the amide NH's in **13** and **14** in fact doing in the exceptionally stable 1:1 complexes of each host with Cl^-? Comparison to host **11**, which has no amide NHs but has similar Cl^- affinity, would suggest that they are not strongly involved in hydrogen bonding to the anion. Upon binding Cl^- the amide NHs in **13** and **14** shift downfield by only 0.5 and 0.2 ppm, respectively, as fitted $\Delta\delta_{max}$ values; host **13** in particular shows a barely detectable experimental downfield shift (Figure 2). Much larger downfield shifts of ~2 ppm are normally observed upon formation of NH---Cl^- hydrogen bonds. The answer then, would seem to be that the amides serve mainly as electron withdrawing groups that increase the strength of pyrrole NH---Cl^- hydrogen bonding in a manner analogous to the ester in host **11**. Given the similarity of the amidopyrrole motifs in **13** and **14** with the large number of previously published amidopyrrole hosts in the literature, we wondered if this lesson could tell us something about this broader set of hosts. Literature hosts **3**,[35] **4**,[36] and **8**[36] bind Cl^- with affinities of 28–138 M^{-1} in CD_3CN. Some substantial parts of these affinities are routinely attributed to amide NH---Cl^- hydrogen bonds. Close contacts between amide NH and anionic guest are always observed in calculated host–guest structures, and are sometimes also observed in X-ray cocrystal structures of the host–guest complexes.[40] To understand these motifs better, we carried out control titrations that revealed that even unsubstituted pyrrole (**1**) and ethyl 2-pyrrolecarboxylate (**9**) bind to Cl^- with significant affinity ($K_{assoc} \geq 10$ M^{-1}, Supporting Information). More importantly, the pyrrole N–H signals in compounds **1** and **9** experience downfield shifts of ≥2 ppm when saturated with chloride, while smaller shifts are observed for amide protons in **3**, **4**, or **8** that resemble more the small shifts we detect for **13** and **14**. When considering all lines of evidence, it is clear that the amides in **13** and **14** do not contribute strong H-bonds to halide guests and that a similar interpretation is probably justified for most of the many amidopyrrole hosts that have been reported.[39,40]

Oxyanion Binding. But the amides do not always remain innocent... Host **13** shows moderately strong binding for the oxyanions HSO_4^-, TsO^- (tosylate), and NO_3^- that is stronger in each case than that of ester-functionalized host **11**. Host **13** shows 4-fold stronger binding for TsO^- than NO_3^-. Conversely, **14** displayed an approximately 1.5-fold weaker binding for TsO^- than NO_3^-. In a general sense, amides **13** and **14** show better aptitude for engaging the varied geometries of

dx.doi.org/10.1021/jo400372c | J. Org. Chem. 2013, 78, 4642–4648

oxyanions than does ester **11**. The amide NH chemical shifts inform us on the possible formation of NH---O hydrogen bonds in these various host-oxyanion complexes. The largest complexation-induced shifts of the amide NH are seen for TsO^-, while insignificant shifts are seen for NO_3^-. These shifts offer direct experimental evidence of amide NH---anion hydrogen bonding (or lack thereof), but we cannot draw simple connections between observed affinities and the presence or absence of the aforementioned hydrogen bonds. Again, these results raise questions about the roles of amide NH's in oxyanion binding by previously reported amido-pyrrole hosts. An X-ray crystal structure of a bis-amidopyrrole (**8**) in complex with benzoate reveals all H-bond donors engaging the guest. In this complex, one benzoate oxygen is engaged by both the pyrrole N−H and one amide N−H. The remaining amide N−H and guest oxygen are separated by a distance virtually identical to the pyrrole-guest bond length demonstrating that each H-bond donor contributes nearly equally to guest stabilization. In an indole-based system that included both pendant urea and amide groups, a weak participation of the amide N−H in guest binding that is reminiscent of the behavior of hosts **13** and **14** was also observed.[41] The binding constants of **8** with chloride and benzoate were determined to be 138 and 2500 M^{-1}, respectively. Conversely, monoamide **4** shows affinities of 28 and 202 M^{-1}, respectively, for the same two guests, a clear indication that a third hydrogen bond donor is necessary for strong binding of oxyanions.

2:1 Complexation by 14. The **14**·Cl^- complex, indicated by Job plot to be a 2:1 host/guest binding event, was fit to a 2:1 (H_2G) binding isotherm using HypNMR. The results show a K_{11} value of 2×10^4 M^{-1}, similar to those seen for **11**·Cl^- and **13**·Cl^-, and a K_{21} value ~2 orders of magnitude weaker. No other titration data collected in this study could be fit well to any analogous 2:1 isotherm. The 2:1 complex only exists when a large excess of host is present, and only about 2% of it is present in solution after 1 equiv of guest is added (Figure 2).

Molecular Modeling. Molecular modeling was conducted to further investigate the conclusions drawn from solution phase data (Figure 3). Local minimum energy structures were identified for the chloride complexes of **11**, **13**, and **14**, including the H_2G complex posited for **14**. All structures have reasonable bond lengths and angles, and notably, all complexes of amide-containing hosts have local minima with amide NH groups forming hydrogen bonds to Cl^-. Heavy atom (N---Cl) separations with respect to guest and tetrazole NH were 3.35 and 3.32 Å for hosts **13** and **14**, respectively; guest and pyrrole nitrogen were observed to be 3.21 and 3.18 Å for hosts **13** and **14**, respectively; guest and amide nitrogen were observed to be 3.55 and 3.58 Å for hosts **13** and **14**, respectively. As with many other previously reported amidopyrrole examples,[39,40] the calculated N---Cl contacts for amides, while moderately long, would suggest an energetically favorable contact between these groups that the NMR data tell us must not exist in solution.

Modeling the H_2G complex for **14** revealed a local minimum in which two of the benzylamide-functionalized hosts (**14**) bound chloride in their hydrogen bond donating clefts orthogonally to one another, but this structure could not be identified as a local minimum for the other hosts. It can be seen in the model (Figure 3a) that an edge-to-face interaction between the two aromatic rings is occurring. The methylene linker in **14** allows for an extra degree of rotational freedom relative to the more rigid host **13**. It is possible that this additional aromatic−aromatic contact is the reason why **14** forms weak, but measurable, 2:1 complexes with Cl^- while **13** does not, but the data in hand do not definitively rule out other explanations.

■ CONCLUSION

We have synthesized a new class of anion recognition elements containing tetrazole and amide functionalities at the 2- and 5-positions of pyrrole. These compounds were able to outperform common bis-amidopyrroles such as **8** in chloride recognition by a wide margin. Further, a 2:1 host/guest complex was observed between **14** and chloride due to a key edge-to-face interaction between the appended *p*-methoxybenzyl moieties. Of particular importance, we found that an extra amide-type hydrogen bond donor does not increase halide affinity significantly in this family of hosts and probably does not make strong hydrogen bonds to halides in solution. Previous studies have shown this to be true in similar systems such as indole analogues of amidopyrroles.[41] Also to our surprise, we observed that the association constants of hosts **11**, **13**, and **14** for chloride are relatively comparable and also similar to that of bis-tetrazole **7**. These data suggest that adding a third H-bond donor does not significantly affect the stability of the complex, but that it is the electron withdrawing nature of tetrazole, ester, or amide functionalities at the 2-position of a pyrrole that can have a profound, favorable influence on binding affinities. In any case, the introduction of tetrazoles clearly produces some of the most potent halide-binding hosts in the pyrrole family. In other areas of the chemical sciences, authors extol the virtues of tetrazoles' high stability in biological systems and high degree of usefulness as pharmacological agents.[29] We continue to explore the possibility that tetrazoles might find utility as anion-binding therapeutic and/or sensing agents in biological settings.

■ EXPERIMENTAL SECTION

Proton (^1H) NMR spectra were recorded on 500, 360, or 300 MHz spectrometers, as indicated in each case. Carbon (^{13}C) NMR spectra were recorded at 125, 90, or 75 MHz as indicated in each case. All NMR binding studies were performed on a 500 MHz spectrometer. HR-ESI-MS was obtained at the UVic Genome BC Proteomics Centre on a LTQ Orbitrap in positive ionization mode unless otherwise indicated. Melting points are uncorrected. All molecular modeling was performed using Spartan '04 or Spartan '06 (Wavefunction, Inc.) at the HF/6-31+G* level of theory. Microwave reactions were carried out in a Biotage Initiator 2.5 microwave reactor at the temperatures indicated.

General Procedure for Pyrrole Cyanation. *Ethyl 5-Cyano-1H-pyrrole-2-carboxylate (**10**).* Ethyl 1*H*-pyrrole-2-carboxylate (500 mg, 3.6 mmol) dissolved in 10 mL/7 mL anhydrous MeCN/DMF was cooled (−40 °C). Chlorosulfonyl isocyanate (0.94 mL, 10.8 mmol) was added dropwise and the reaction mixture allowed to warm to ambient temperature. After 24 h, the mixture was poured over ca. 100 g of ice containing 20 mL of 2 M NaOH. The ice was allowed to melt and the aqueous layer extracted with DCM (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude brown solid was purified (SiO_2, 2:1 hexanes/EtOAc) yielding 126 mg of **10** (0.77 mmol, 21%) as a pale brown solid: mp 82−84 °C; IR (KBr, thin film) 3349s, 3132w, 2990w, 2921w, 2233s, 1689s, 1568s, 1270s, 1205w, 1107; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (t, 3H, J = 7.11 Hz), 4.35 (q, 2H, J = 7.11 Hz), 7.12 (m, 1H), 7.42 (m, 2H), 10.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 61.6, 95.2, 115.5, 117.8, 124.4, 129.2, 160.6; HR-ESI-MS 187.04810 (MNa^+, $C_8H_8N_2O_2Na^+$, calcd 187.04781).

*Methyl 5-Cyano-1H-pyrrole-2-carboxylate (**16**).* The general procedure for pyrrole cyanation was applied to methyl 1*H*-pyrrole-2-carboxylate (**15**): mp 140−142 °C; IR (KBr, thin film) 3300s, 3100w,

dx.doi.org/10.1021/jo400372c | J. Org. Chem. 2013, 78, 4642−4648

2990w, 2325w, 2150s, 1701s, 1568s, 1495s, 1270s, 1205w, 750s; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.90 (s, 3H), 7.12 (dd, J = 2.52 Hz, 1.50 Hz, 1H), 7.41 (dd, J = 3.21 Hz, 1.46 Hz, 1H), 9.57 (s, 1H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 52.1, 95.3, 116.0, 118.0, 125.1, 130.9, 160.7; HR-ESI-MS 173.03222 (MNa^+, $C_7H_6N_2O_2Na^+$, calcd 173.03211).

5-Cyano-N-(4-methoxybenzyl)-1H-pyrrole-2-carboxamide (17). A mixture of compound **10** (50 mg) dissolved in *p*-methoxybenzylamine (3 mL) was heated to 120 °C and stirred for 2 days. The reaction was allowed to cool, and 20 mL of EtOAc was added. The organic phase was washed with 1 M HCl (5 × 15 mL), dried ($MgSO_4$), and concentrated leaving pure **17** (45 mg, 89%) as a pale brown solid: mp 235 °C (dec); IR (KBr, thin film) 3370m, 3174s, br, 2225s, 1634s, 1538w, 1512m, 1436w, 1253m, 1150w; ^{1}H NMR (DMSO-d_6) δ 3.69 (s, 3H), 4.33 (d, J = 6.01 Hz, 2H), 6.85 (d, J = 6.84 Hz, 2H), 7.14 (d, J = 1.19 Hz, 1H), 7.17 (d, J = 7.17 Hz, 2H), 7.64 (d, J = 1.11 Hz, 1H), 8.72 (t, J = 5.95 Hz, 1H), 12.43 (s, 1H); ^{13}C (DMSO-d_6) 41.5, 55.1, 91.9, 112.3, 113.7, 116.5, 127.9, 128.6, 129.1, 131.3, 158.3, 159.2; HR-ESI-MS (−ve): 254.09353 (M − H, $C_{14}H_{12}N_3O_2^-$, calcd 254.09359)

General Procedure for Tetrazole Formation. *Ethyl 5-(5′-Tetrazolyl)-1H-pyrrole-2-carboxylate (11).* Ethyl 5-cyano-1*H*-pyrrole-2-carboxylate **10** (25 mg, 0.15 mmol), NaN_3 (19.2 mg, 3.2 mmol), NH_4Cl (17.1 mg, 3.2 mmol), and anhydrous DMF (1 mL) were added to a microwave vial. The vessel was purged with argon, sealed, vortexed at maximum speed for 1 min, and placed in a microwave reactor at 110 °C for 1 h. The mixture was transferred to a separatory funnel with 30 mL of saturated $NaHCO_3$, and the aqueous layer washed with 30 mL of EtOAc and subsequently acidified to pH < 1 with concd HCl. The aqueous layer was then extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude brown solid was triturated in $CHCl_3$, and the insolubles were filtered and air-dried yielding 28 mg (90%) of **11** as a pale brown solid: mp 220 °C dec; IR (KBr, thin film) 3279m, 2993w, 2981w, 1722s, 1611w, 1475w, 1290m, 1503m, 1763m; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (t, 3H, J = 7.11 Hz), 4.36 (q, 2H, J = 7.11 Hz), 6.86 (d, 1H, J = 4.05 Hz), 6.98 (d, 1H, J = 4.11 Hz); ^{13}C NMR (MeOD, 90 MHz) δ 14.7, 61.8, 113.0, 117.2, 121.9, 127.7, 151.4, 162.0; HR-ESI-MS 208.08278 (MH^+, $C_8H_9N_5O_2H^+$, calcd 208.08287).

Compound 14. The general procedure for tetrazole formation was applied to compound **17**: mp 235 °C (dec); IR (KBr, thin film) 3291s, br, 2932w, 1615s, 1514s, 1568m, 1249m; ^{1}H NMR (MeOD, 300 MHz) δ 3.78 (s, 3H), 4.49 (s, 2H), 6.83−6.98 (m, 4H), 7.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 43.5, 66.7, 102.9, 112.9, 113.2, 114.9, 120.4, 129.9, 131.0, 132.0, 160.5, 162.4; HR-ESI-MS 321.10692 (MNa^+, $C_{14}H_{14}N_6O_2Na^+$, calcd 321.10701).

Compound 13. The general procedure for tetrazole formation was applied to compound **19**: mp 190 °C (dec); IR (KBr, thin film) 3180s, br, 1654s, 1625s, 1602s, 1535s, 1449m, 1332m, 815m; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.28 (s, 3H), 7.15 (d, J = 8.40 Hz, 2H), 7.50−7.79 (m, 4H), 10.00 (s, 1H), 12.30 (s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 20.5, 108.2, 109.6, 120.0, 122.6, 128.1, 129.1, 132.3, 136.5, 151.1, 158.4; HR-ESI-MS 291.09652 (MNa^+, $C_{13}H_{12}N_6ONa^+$, calcd 291.09651).

5-Carboxy-1*H*-pyrrole-2-carbonitrile (18). To a mixture of compound **16** (50 mg, 0.4 mmol) in H_2O/EtOH (1 mL/2 mL) was added LiOH (47.9 mg, 2 mmol). The mixture was heated at reflux with stirring for 2 h and then cooled to room temperature. EtOAc (10 mL) was added and the organic layer washed with 1 M HCl (3 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated leaving pure **18** in quantitative yield: mp 185 °C dec; IR(KBr, thin film) 3239s, br, 3131s, 2920m, 2236s, 1674s, 1454m, 1121s; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.11 (s, 1H), 7.77 (s, 1H), 12.67 (s, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 93.7, 115.5, 117.3, 125.2, 129.7, 161.5; HR-ESI-MS 135.02021 (M − H^-, $C_6H_3N_2O_2^-$, calcd 135.01945).

5-Cyano-*N*-(*p*-tolyl)-1*H*-pyrrole-2-carboxamide (19). Compound **18** (40 mg, 0.29 mmol), EDC·HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl) (90 mg, 0.58 mmol), HOBT (hydroxybenzotriazole) (60 mg, 0.44 mmol), and *p*-toluidine (38 mg, 0.35 mmol) were dissolved in anhydrous DMF (5 mL) and stirred at room temperature for 18 h. Ethyl acetate (15 mL) was added and the organic phase washed with 1 M HCl (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated. The product was purified (SiO_2, 2:1 EtOAc/Hex) yielding 58 mg (89%) of **19** as a brown solid: mp 185 dec; IR (KBr, thin film) 3239s, br, 3131s, 2920m, 2236s, 1674s, 1454m, 1121s; ^{1}H NMR (acetone-d_6, 300 MHz) δ 2.29 (s, 3H), 7.15 (m, 2H), 7.30 (m, 2H), 7.62 (m, 2H), 7.72 (m, 2H), 9.34 (s, 1H), 11.64 (s, 1H); ^{13}C NMR (acetone-d_6, 920 MHz) δ 20.0, 93.9, 112.5, 115.5, 120.1, 128.4, 129.0, 129.2, 136.4, 157.7; HR-ESI-MS 226.09748 (MH^+, $C_{13}H_{11}N_3OH^+$, calcd 226.09748).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Supplementary NMR titration data and Job plots; NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by NSERC and the University of Victoria. F.H. is a Canada Research Chair and Michael Smith Foundation for Health Research Scholar.

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