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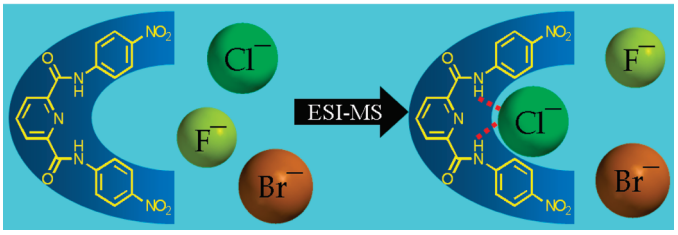
Halide Ions Complex and Deprotonate Dipicolinamides and Isophthalamides: Assessment by Mass Spectrometry and UV−Visible Spectroscopy

I. Alexandru Carasel,[⊥] Carl R. Yamnitz,[⊥] Rudolph K. Winter,[§] and George W. Gokel*[,†,‡,§]

[†]*Center for Nanoscience,* [§]*Departments of Chemistry & Biochemistry, and* [‡]*Biology, University of Missouri−Saint Louis, Saint Louis, Missouri 63121, United States, and* [⊥]*Departments of Chemistry and Developmental Biology, Washington University, St. Louis, Missouri 63130, United States*

gokelg@umsl.edu

Received September 6, 2010



The F^-, Cl^-, and Br^- binding selectivity of bis(*p*-nitroanilide)s of dipicolinic and isophthalic acids was studied by using competitive electrospray mass spectrometry and UV−Visible spectroscopy. Both hosts prefer binding Cl^- over either F^- or Br^-. Host deprotonation was observed to some extent in all experiments in which the host was exposed to halide ions. When F^- was present, host deprotonation was often the major process, whereas little deprotonation was observed by Cl^- or Br^-, which preferred complexation. A solution of either host changed color when mixed with a F^-, $H_2PO_4^-$, di- or triphenylacetate solution.

Introduction

The study of ligands, hosts, and receptors for cations and anions has been underway for a century or more.[1−8] Historically, cation complexation has received greater attention, but during recent years, the study of receptors for anions such as halides and acid anions has become an area of vigorous research effort.[9,10] Although various supramolecular interactions have proven to be significant, the most frequent binding motif for anion complexation is arguably hydrogen bonding.[11−15]

The slower development of anion sensors, compared to cation sensors, is due in part to the fact that detecting small inorganic anions is often more difficult than detecting cations. Typically, anions are larger than their isoelectronic cationic counterparts.[16] The larger size of anions lowers the charge density, which reduces the effectiveness of

* To whom correspondence should be addressed. Phone: 314-516-5321. Fax: 314-516-5342.

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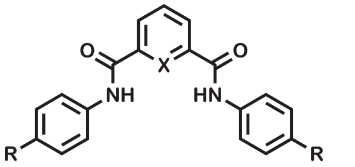
Published on Web 11/11/2010 DOI: 10.1021/jo101749a



1, X = N, R = CH_3 4, X = N, R = NO_2
2, X = N, R = H 5, X = CH, R = H
3, X = N, R = CN 6, X = CH, R = NO_2

FIGURE 1. Structures of compounds **1**−**6**.

electrostatic interactions with a potential ligand. Further, while cations are often monatomic and spherical, polyatomic inorganic anions exhibit a range of geometries with charges that are delocalized over a number of atoms. The variety of anions makes each receptor less general and requires it to incorporate individual design elements.

In many of the reported studies, anion complexation was confirmed by a solid state structure of the complex.[9−11] X-ray crystallographic studies reveal important details about complexation, but do not address issues of dynamics. This includes questions of binding strength, binding selectivities, and the overall ability of any given receptor to transport anions. Of course, dynamic studies of anion complexation and transport have also been reported.[17] These studies used various combinations of techniques to establish binding profiles including computational methods, NMR studies, optical spectroscopy, and mass spectrometric analyses.

We recently showed[18] that compounds having the general structure presented in Figure 1 can bind and transport Cl^- through phospholipid bilayer membranes. Binding and transport involving or mediated by these compounds has been investigated by using gas-phase calculations and experiments such as planar bilayer conductance studies, ion release from vesicles, fluorescence studies, and electrospray mass spectrometry (ESI-MS).

Results and Discussion

Our previous work compared isophthalic acid and dipicolinic acid dianilides that had the structures shown as **1**−**6**.[18] The most interesting binding and transport properties were manifested by **3**, **4**, and **6**. Of these, the two most closely related are **4** and **6**. The former is a dipicolinic acid dianilide and the latter is the dianilide of isophthalic acid. The diacids are commercially available and the dianilides are readily prepared from the corresponding acid chlorides. The dianilides are typically high-melting solids that are quite stable.[19] The structures of **1**−**6** are shown in Figure 1.

As noted, compounds **4** and **6** were the most closely related structures that showed strong binding and transport.

TABLE 1. Halide Anion Selectivities for Pyr (4) and Iso (6)

host[a]	[host·F^{-b}]/[host·Cl^{-b}]	[host·Cl^-]/host·Br^{-b}]	[host·F^-]/[host·Br^-]
Pyr	2.9 ± 1.2	6.7 ± 0.4	11.5 ± 3
Iso	0.29 ± 0.1	6.9 ± 1	1.1 ± 0.1

[a]Stock [host] = 0.5 mM in 10% DMSO/MeOH; final [host] = 4.5 μM in 0.5% DMSO/MeOH. [b]Stock [$Bu_4N^+X^-$] = 1 mM in MeOH.

This success begged the question of ion selectivity and, indeed, selectivity in binding other types of anions. We thus chose to probe anion binding and selectivity by using **4** (**Pyr**) and **6** (**Iso**) with the series of halogen anions (F^-, Cl^-, and Br^-) as the first phase of the study.

Anion Binding Behavior of Pyr and Iso in the Presence of F^-, Cl^-, and Br^-. Electrospray mass spectrometry has been used in the past to study anion−receptor complexation[20] and we chose it to assay the binding behavior of **Pyr** and **Iso**. An inherent problem in using this technique with these two hosts is that their molecular weights are 406.09 and 407.09, respectively. The isotope distributions differ, but not enough to readily distinguish the two compounds. Absent any obvious means of distinction, direct host comparisons were difficult. To confirm that the behavior of **Pyr** and **Iso** was similar enough for the ESI-MS method to be valid, a mixture of **Pyr** and **Iso** was sprayed with 10 equiv of Cl^-. The observed chloride adduct peak ratio ([**Iso**·Cl^-]:[**Pyr**·Cl^-]) was determined by laborious analysis to be ∼1.3:1. Thus, the behavior of the hosts in an electrospray environment is similar, but not identical. When selectivities observed in subsequent experiments differed by only 30%, they were interpreted as being the same within experimental error. However, most selectivity or partition ratios were well outside a 30% difference.

Table 1 shows the results of competition experiments in which either **Pyr** or **Iso** and $Bu_4N^+F^-$, $Bu_4N^+Cl^-$, and $Bu_4N^+Br^-$ were present in a molar ratio of 1:10:10 in a DMSO/MeOH solvent mixture (see the Experimental Section). The salts were present in excess so the experiment would not be limited by the host's access to either anion. On the basis of their electronegativities and charge densities, the binding order was expected to be $F^- > Cl^- > Br^-$. The ratios recorded in column 3 of the table show that both **Pyr** and **Iso** were selective for Cl^- over Br^- by about 7 to 1. As noted above, this is the anticipated result. The situation is different, however, when F^- and Cl^- were the competing anions: **Iso** preferred Cl^- over F^- by ∼3 to 1, while in the case of **Pyr**, F^- was the preferred anion by a ratio of ∼3 to 1.

The data shown in the first line of Table 1, i.e., the binding ratios for **Pyr**, meet the intuitive expectation that complexation will be in the order $F^- > Cl^- > Br^-$. Fluoride is preferred over chloride by ∼3:1, chloride is preferred over bromide by ∼7:1, and fluoride is preferred over bromide by ∼12:1.

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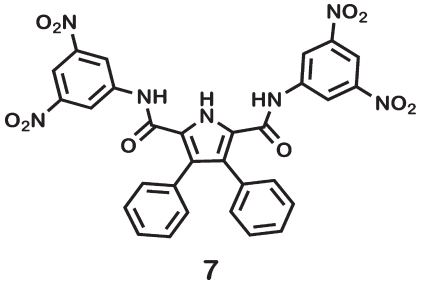
TABLE 2. Base Peak and Selectivity Ratios for Pyr at Various Anion Molar Ratios

molar ratio **Pyr**[a]:Cl^{-b}:F^{-b}	[**Pyr**·Cl^-]/[**Pyr**·F^-]	base peak *m*/*z*	base peak identity
1:1:1	4.3 ± 1.1	441 [**Pyr**·Cl^-]	chloride adduct
1:3:3	1.8 ± 0.7	405 [**Pyr**-H]$^-$	deprotonated host
1:5:5	1.2 ± 0.3	405 [**Pyr**-H]$^-$	deprotonated host
1:10:10	0.4 ± 0.1	405 [**Pyr**-H]$^-$	deprotonated host

[a]Stock [host] = 0.5 mM in 10% DMSO/MeOH; final [host] = 4.5 μM in 0.5% DMSO/MeOH. [b]Stock [$Bu_4N^+X^-$] = 1 mM in MeOH.

The results shown in the second line of the table are nearly identical for $Cl^- > Br^-$, but very different when fluoride ion is involved in the competition. The competition experiments suggest that when **Iso** is the only available host, the selectivities are $Cl^- > F^-$, $Cl^- > Br^-$, and $F^- \approx Br^-$. These results seem counterintuitive unless a process different from complexation occurs instead of, or simultaneous with, binding.

The closest work of which we are aware is a study reported by Gale, Hursthouse, and their co-workers.[21] Their receptor family was based on 2,5-dicarboxypyrrole. Several dianilides were studied and two especially interesting facts emerged. First, a solid state structure was obtained in which N^2,N^5-bis(3,5-dinitrophenyl)-3,4-diphenyl-1*H*-pyrrole-2,5-dicarboxamide (**7**, Figure 2) complexed Cl^-. In that case, close contacts were observed between Cl^-, the two amide NH bonds, and the adjacent CH bonds on the aromatic rings. The pyrrole nitrogen was not apparently in contact. Second, a titration of the bis(4-nitrophenyl) analogue of **7** (shown) with Bu_4NF was monitored by NMR. Shifts were observed for aromatic protons. They suggested that the NMR data could be accounted for by a three-step process as follows. The first equivalent of F^- coordinates to the host. The next step is deprotonation by a second equivalent of F^-. A third equivalent of F^- "is coordinated by the deprotonated receptor with the participation of the phenyl CH groups that, in this receptor, are particularly acidic because of the presence of the electron-withdrawing groups present in the phenyl ring."



7

FIGURE 2. Structures of compound **7**.

The anion selectivity profile for **Iso** differed from the results predicted by computational studies[18] as well as from a chemically intuitive order. A closer examination of the data showed that the greatest differences between prediction and observation occurred in experiments in which F^- was present. When F^- was present, the base peak often corresponded to the deprotonated host rather than to an anion adduct. To the extent that deprotonation occurred, we assumed that anion complexation would be excluded by unfavorable charge−charge interactions.

TABLE 3. Binding/Deprotonation Ratios for Iso and Pyr When Exposed to 1 or 10 Equiv of F^- or Cl^-

				% interaction	
host[a]	anion[b]	host:X^- ratios	[host·X^-]/[host-H]$^-$	% binding	% deprotonation
Pyr	F^-	1:1	2.4:1	70	30
Iso	F^-	1:1	3.1:1	75	25
Pyr	F^-	1:10	0.42:1	30	70
Iso	F^-	1:10	0.2:1	17	83
Pyr	Cl^-	1:1	17.2:1	94	6
Iso	Cl^-	1:1	21.3:1	96	4
Pyr	Cl^-	1:10	5.5:1	85	15
Iso	Cl^-	1:10	15.6:1	94	6

[a]Stock [host] = 0.5 mM in 10% DMSO/MeOH; final [host] = 4.5 μM in 0.5% DMSO/MeOH. [b]Stock [$Bu_4N^+X^-$] = 1 mM in MeOH.

To better address the question of anion selectivity for **Pyr**, a set of conditions was required that would favor binding over deprotonation. A series of ESI-MS experiments were conducted in which the molar ratios of anions to host were varied. The results that were obtained are shown in Table 2.

The data in Table 2 show that in the presence of excess F^- (high anion to host molar ratios, e.g., 10:1, 5:1, and 3:1), the base peak was the deprotonated host. At a molar ratio of **Pyr**:Cl^-:F^- = 1:1:1 the base peak was the chloride adduct showing that most of the host was involved in binding events rather than being deprotonated. When equimolar concentrations of host, F^-, and Cl^- were present, the ESI-MS experiment showed that the complexation profile for **Pyr** was $Cl^- > F^- > Br^-$, similar to that observed for **Iso**.

Binding/Deprotonation Equilibrium of Pyr and Iso in the Presence of $Bu_4N^+F^-$ and $Bu_4N^+Cl^-$. Bromide anion seemed to follow the predicted behavior: it is the least desirable guest for both hosts, most likely due to higher ionic radii and lower charge density. The balance between binding and deprotonation is a greater issue for chloride and fluoride anions. Thus, **Pyr** or **Iso** was sprayed with either F^- or Cl^- (1 or 10 equiv). The results are shown in Table 3.

The deprotonation reaction is clearly undesirable in terms of complexation. First, deprotonation depletes the pool of host available for binding. Second, a deprotonated host has a negative charge in the anion binding cleft. A negative charge attracts a cation but repels an anion.

The data in Table 3 show that anion binding by both **Pyr** and **Iso** is preferred over deprotonation for Cl^-. Relatively little deprotonation occurs if Cl^- is present in a 1:1 ratio (94−96% binding) or even in 10-fold excess (85−94% binding). The greater deprotonation that is observed with **Pyr** when Cl^- is in excess may result from the higher acidity of its amidic protons. The difference between **Pyr** and **Iso** in the presence of a single equivalent of Cl^- is within experimental error. In contrast, even when a single equivalent of F^- is present, 25−30% deprotonation is observed. Deprotonation becomes the dominant process (70−83%) when the ratio of host:F^- is 1:10. Because deprotonation by F^- is greater than for Cl^-, we infer that most, if not all, deprotonation will be caused by fluoride in any competition between F^- and Cl^-.

The results of competition between F^- and Cl^- are recorded in Table 2 (above). When **Pyr** and equimolar concentrations of F^- and Cl^- were present, Cl^- complexation was the dominant process. When excess F^- was present, even when an equivalent

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amount of Cl^- was also present, deprotonation dominated. We conclude that the anticipated complexation order of $F^- > Cl^- > Br^-$ is subverted by a second process (deprotonation) that is prevalent with F^- but is less prominent or absent for Cl^- or Br^-.

Fabbrizzi and co-workers investigated the anion binding ability of a chromogenic anion receptor, 1-(7-nitrobenzo[*c*]-[1,2,5]oxadiazol-4-yl)-3-(4-nitrophenyl)urea, to react with various anions including fluoride.[22] They had previously demonstrated[23] that the cationic species 1-benzyl-3-(toluene-4-sulfonylamino)pyridinium and 2-benzyl-9H-*b*-carbolin-2-ium both undergo deprotonation in the presence of F^- but do not do so in the presence of Cl^-, Br^-, or other such anions and nitrate. The three compounds noted in these two reports represent a class of compounds, i.e., ureas, carbazoles, and sulfonamides, rather than the diamides reported herein. Nevertheless, the parallel chemical behavior is obvious. It is particularly interesting that deprotonation of the oxadiazolylurea was confirmed by an X-ray crystal structure of the tetrabutylammonium salt. Deprotonation was also characterized by optical spectroscopy, as we have done for the present system.

An attempt was made to completely convert receptors **Iso** and **Pyr** to their fully deprotonated forms. The deprotonation reaction was attempted with both tetrabutylammonium hydroxide in DMSO and dimsyl sodium in DMSO. In both cases, rapid precipitation occurred and characterization of the products proved ambiguous.

UV−Visible Spectroscopy Studies. When **Pyr** was titrated with Bu_4NF (TBAF) in EtOAc, the curves shown in Figure 3 were obtained. The maximum absorption shifted from 322 nm when TBAF was absent (yellow trace) to 343 nm when TBAF was present in large excess (**Pyr**:TBAF 1:10 blue trace). An isosbestic point is observed at 331 nm. The last curve that intersects the isosbestic point (green) is the trace corresponding to 1:2 **Pyr**:TBAF. We infer that balance of complexation and deprotonation remains constant over this concentration range. The fact that λ_{max} for the data points corresponding to mixtures with 0−2 equiv of F^- are close to λ_{max} in the experiment using 10 equiv Cl^- (data shown in the Supporting Information) indicates that binding predominates. At higher F^- concentrations, the increase in λ_{max} is in concert with the predominance of deprotonation.

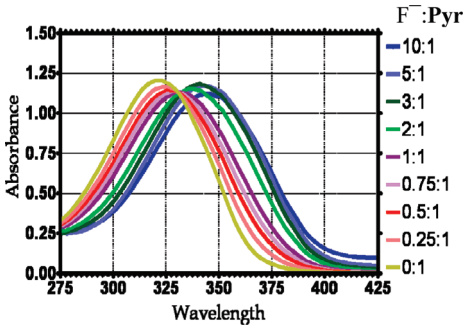

FIGURE 3. Titration of **Pyr** with 0−10 equiv of Bu_4NF in EtOAc.

The Deprotonation and Binding Processes. Both mass spectrometry and UV−vis spectroscopy confirm the occurrence of binding and deprotonation by F^- for these host molecules. As reported for **7**,[21] the initial interaction between **Pyr** and F^- must be coordination. Although deprotonation occurs simultaneous with complexation, it is not until a significant excess of fluoride ion is present that the former process dominates. When deprotonation predominates, the combination of the pyridine nitrogen lone pair and a deprotonated amide must certainly repel F^- or any other anion.

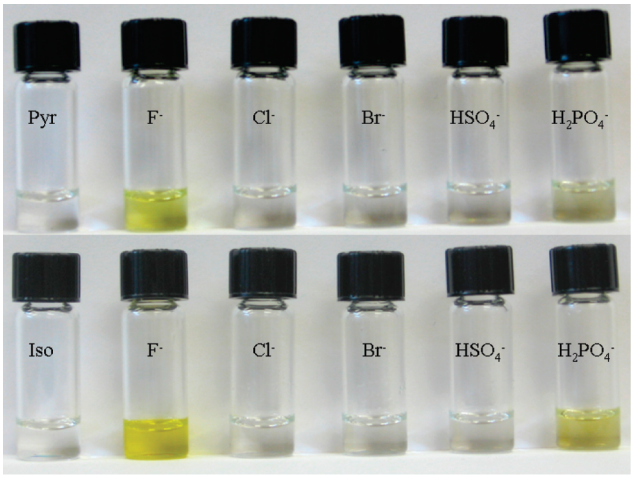

FIGURE 4. Color change for DMSO solutions of **Pyr** and **Iso** upon addition of 1 equiv of various anions.

Colorimetric Behavior of Pyr and Iso. It was noted that solutions of **Pyr** and **Iso** changed color when certain anions were added. This color change is both concentration and anion dependent. The color change was assumed at first to result from the deprotonation event that occurs when F^- reacts with the host. Subsequently, it was noted that color changes occurred when anions such as $H_2PO_4^-$ (DHP) and acetate were present. Figure 4 shows each receptor alone and in the presence of one of five anions. They are, from left to right in Figure 4, F^-, Cl^-, Br^-, HSO_4^-, and $H_2PO_4^-$.

Confirmation of host binding to $H_2PO_4^-$ (DHP) and acetic acid anion derivatives (diphenyl- and triphenylacetic acids, not shown) was obtained by ESI-MS experiments similar to those described in detail for the halides. Both **Iso** and **Pyr** hosts were titrated separately with DHP (in ethyl acetate) and the UV−Vis absorption spectra were recorded. When **Iso** was the host, diminishing intensity for the peak centered at 330 nm was noted along with the development of a second peak in the region 400−500 nm (see Figure 5). The intensity of the secondary peak is directly proportional with the amount of DHP added. This spectroscopic behavior and visible color change have been reported to occur between anions and other receptors featuring amidic hydrogens.[24−31] Several authors reported that such interactions can be useful for the selective detection of anions in complex mixtures. No effort was made to develop a

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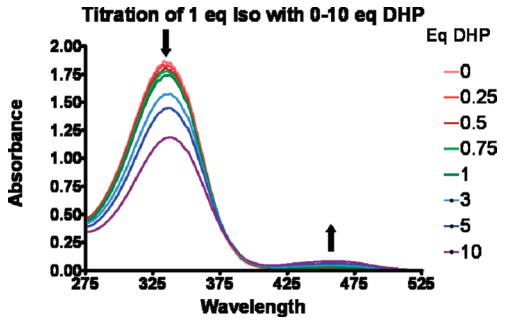

FIGURE 5. UV−Vis titration of **Pyr** with dihydrogenphosphate (DHP).

colorimetric sensor based on these hosts but the structural simplicity of the hosts reported here suggests that they could be economical scaffolds in such an application.

Differences between Isophthalic Acid and Dipicolinic Dianilides. The work presented here emphasizes dipicolinic acid derivatives. The isophthalic and dipicolinic acid analogues have been pioneered by Crabtree and co-workers,[32] with the former being studied,[32,33] mimicked, and incorporated into other receptor systems[34] to a greater extent. Binding data obtained from a ^{1}H NMR study of unsubstituted dipicolinamide and alkyl-substituted isophthalamides[32] predicts stronger binding interactions with F^- and Cl^- as opposed to Br^- and I^- or OAc^-, which is in general agreement with the data presented here. Notwithstanding, the behavior of **Pyr** and **Iso** are surprisingly different. A solid state structure of N^1,N^3-diphenylisophthalamide (**5**, see Figure 1) complexing Br^- shows the bromide ion well above the plane of isophthalic acid and remote from all three aromatic rings. When the aromatic rings are nitrated, they may serve as π-acids to help stabilize the halide anion. As noted by Gale and co-workers,[21] the aromatic C−H groups may also serve as H-bond donors.

When F^- deprotonates one of the amide N−H residues, the remaining lone pair will want to minimize dipolar interactions with the adjacent lone pair present on the pyridyl nitrogen. This may lead to a conformation in which additional F^- is bound by a combination of H-bonding by the amide and anion−Lewis acid π-stacking.[35] This is, of course, a speculative suggestion, but it seems unreasonable to think that an electron-rich environment would favor direct anion binding. A possible conformational difference between the two receptors may also account for the differences observed in binding selectivity profiles, revealed in the mass spectrometric studies.

Conclusions

The initial goal of this work was to assess the binding interactions of dipicolinamides and isophthalamides with various halogen anions. We found that **Iso** as well as **Pyr** successfully bound the three halogenated anions studied: F^-, Cl^-, and Br^-. Basing our predictions on ionic radii, charge density, and the computational studies performed on these hosts and hosts−anion pairs, the complexation order should be $F^- > Cl^- > Br^-$. Surprisingly though, competitive ESI-MS studies showed that in both cases the preferred anion was Cl^- followed by F^- and Br^-. While Br^- was expected to be the least preferred guest due to its higher ionic radius and lower charge density, F^- ranked second mostly because of its propensity for deprotonation rather than binding. In our ESI-MS control experiments we observed that F^- deprotonates the host more than the other anions (Cl^- or Br^-). Even though the host anion binding interaction is expected to be stronger for F^- than for Cl^- or Br^-, this cannot be realistically quantified within our experimental set of conditions due to the competition from the deprotonation process.

The second finding is that anion binding is always accompanied by host deprotonation and vice versa. While there were previous reports documenting fluoride anion's propensity for host deprotonation, we have shown that deprotonation and binding are present for all three anions, albeit in various ratios. What differentiates the anions is the degree to which these two competing processes occur: F^- always favors deprotonation over binding due to its higher basicity and higher charge density, while adduct formation dominates in the case of Cl^- and Br^-.

The two hosts show changes in color when F^-, $H_2PO_4^-$, or acetate is added to their solutions. Although phosphate ions are usually determined in medical applications as total phosphate, this change in color may be useful as a detection method for these anions in other contexts.

Experimental Section

Compounds **4** and **6** have previously been reported.[18]

Electrospray Mass Spectrometry Experiments. Stock solutions (1 mM) of tetrabutylammonium salts were prepared in MeOH. Stock solutions of hosts (500 μM) were prepared in 10% (v/v) DMSO/MeOH. In a typical experiment 20 μL of host stock solution and 100 μL of stock anion(s) solution were added to 2 mL of MeOH. The resulting solution was filtered and then injected into the ESI-MS instrument. In all competition experiments, hosts were present in equimolar concentrations if more than one was present. In anion competition experiments, competing anions were present in equimolar concentrations (45 μM) and the host concentration(s) were 4.5 μM. The selectivity ratios shown in tables and text were calculated from the total integration of relevant m/z peaks for all host·A^- adducts. Errors shown are the calculated standard deviations of ratios from at least three replicates.

UV−Visible Spectroscopy Experiments. Solutions of the host (1 mM) and tetrabutylammonium salt (1 mM) of the anions were prepared in DMSO. In a typical experiment, 0.1 mL of host, DMSO stock solution was added to EtOAc (2 mL) and the resulting mixture was titrated with aliquots of the stock anion solution, added to yield the desired molar ratios. The final concentrations of host and guest in the 1:1 experiment were 0.045 mM. UV−Visible spectroscopy experiments were performed with EtOAc as a solvent. Each of the traces reported is the average of at least three replicates.

Acknowledgment. We thank Joseph Kramer for assistance in obtaining mass spectrometric results. We thank the NIH for a grant (GM 36262) that partially supported this work.

Supporting Information Available: Representative ESI-MS and UV−vis spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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