# Hydrogen Bonding in Anion Recognition: A Family of Versatile, Nonpreorganized Neutral and Acyclic Receptors

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The diamides and disulfonamides *m*-$C_6H_4(CONHAr)_2$ (Ar = Ph, **1**; *p*-*n*-$BuC_6H_4$, **2**, 2,4,6-$Me_3C_6H_2$, **3**), *m*-$C_6H_4(SO_2NHPh)_2$, **4**, and 2,6-$C_6H_3N(CONHPh)_2$, **5**, readily synthesized on a multigram scale, bind strongly to halides and acetate in organic solvents with $K_a$'s as high as $6.1 \times 10^4$ (NMR spectroscopy). The binding stoichiometry is 1:1 in solution for all cases except for the **4**·$F^-$ and **4**·$OAc^-$ complexes, where both 1:1 and 1:2 binding stoichiometries were found. The association constants in $CD_2Cl_2$ ($^1$H NMR) follow the trend $Cl^- > Br^- > I^-$ for all the receptors. $F^-$ and $OAc^-$ binding may be stronger or weaker than $Cl^-$ depending on the nature of the receptor. The presence of the pyridine nitrogen in **5** and of the more rigid amide in **1**−**3** and **5** vs the less rigid sulfonamide structure in **4** increases selectivity for smaller anions. The enthalpy and entropy of formation for **2**·$Cl^-$ were $\Delta H = -31$ kJ/mol; $\Delta S = -23$ J/(mol·K) (VT-NMR). The X-ray structure of $[PPh_4]_2$[**1**·Br][Br]·$CH_2Cl_2$, shows 1:1 complexation of $Br^-$ via two N−H···$Br^-$ hydrogen bonds and a *syn*−*syn* nonplanar binding conformation for **1**. Solution hydrogen bonding was confirmed by FT-IR and NMR spectroscopy. The receptor conformation changes on complexation. Trends in structure/binding relationships show receptor flexibility is an important factor in anion recognition.

Molecular recognition of cations[1] is long established, but anion binding has only more recently attracted interest[2] for its biomedical[3] and environmental[4] significance. Anion receptors may be useful for phase-transfer catalysis, separations,[5] and anion-selective electrodes, and several recent reviews[6] have appeared. Many such receptors bind anions tightly and selectively, but they often have elaborate structures that require multistep synthesis, and none are commercially available. Many are poorly soluble in nonpolar organic media, but very few are also easily synthesized on a large scale and therefore available for widespread use. Acyclic synthetic anion receptors are either positively charged[7] or contain Lewis acid centers.[8] In the former class, selectivity is modest owing to the dominance of nondirectional electrostatic interactions.[9]

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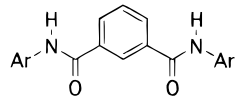
Neutral hosts that bind guests exclusively through hydrogen bonding by pyrrole,[10] urea,[9b,11] or amide groups[12] have recently been developed. Hamilton[13−15] and Still[16] have reported isophthalamide or urea derivatives as receptors for nucleotide bases,[13] barbiturates,[14] dicarboxylic acids and dicarboxylates,[15] and peptides;[16] Davis[17] reported triamide and trisulfonamide halide receptors. No halide binding properties for simple isophthalamides were reported previously.

Preorganization generally increases selectivity but limits synthetic accessibility. Here we look at a minimally preorganized system available in one step to test if two properly located amide or sulfonamide groups can give selective anion binding. We now report anion receptors that are not only efficient and selective but also easily available and soluble in organic solvents and therefore widely applicable.

As part of our studies on hydrogen bonding,[18] we recently reported the halide receptors **1** and **2** in a communication[19] and now report in full on these and on the related receptors **3**−**5**, also extending our studies to fluoride and acetate. All the receptors have a *meta* arrangement of two hydrogen-bonding groups, but they differ in the nature of the groups, in the rigidity of the skeleton, and in being alicyclic or heterocyclic. The study of anion binding properties of receptors having slightly different structures with five different anions allows us to demonstrate the importance of hydrogen bonding for anion recognition in these systems as well as to interpret the relationship between certain receptor structural features and the strength and selectivity of anion binding.

## Results and Discussion

**Synthesis of Receptors 1−5.** Compounds **1**−**5** are available in good yields from the commercially available acid dichlorides and the corresponding anilines in DMF using modified versions of reported[20] procedures. They were purified by recrystallization from benzyl alcohol (**1**), methanol (**2**, **4**, **5**), or ethanol (**3**). The new compounds **2** and **3** as well as **4**[21] were characterized by FT-IR, and $^1$H NMR, and elemental analysis or high-resolution mass spectra. The known compounds **1**[20] and **5**[22] gave spectroscopic data identical to those reported.[21b]



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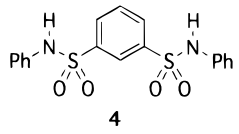
2 Ar = p-(n- Bu)C $_6$H$_4$
3 Ar = 2,4,6-Me$_3$C$_6$H$_2$



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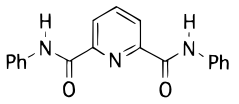

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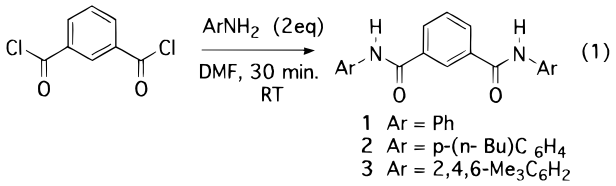

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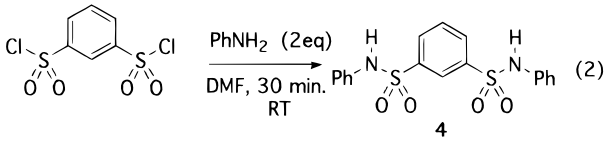
(1)



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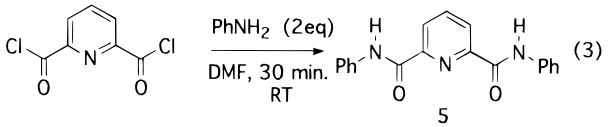

(3)

**Preliminary $^1$H NMR and $^{19}$F NMR Studies.** The less soluble compounds **1**, **2**, and **5** in a $CH_2Cl_2$ suspension are solubilized by addition of solid $Ph_4PX$ salts (X = $Cl^-$, $Br^-$, $I^-$, $OAc^-$).[23] The $^1$H NMR spectra of **1**−**5** also showed dramatic chemical shift changes upon anion addition. In particular the N−H protons involved in hydrogen bonding and the 2-C−H protons located close to the anion both give large downfield shifts (Figure 1). For the other central ring protons the shifts are smaller. For the aniline CH's the chemical shifts are also significant, particularly for the *ortho* 2-C−H, which gives a downfield shift.

The sharp $^{19}$F NMR resonance for $(n\text{-Bu})_4NF$ in $CD_2Cl_2$ at −117.0 ppm (upfield from $CFCl_3$) broadens into the baseline on addition of receptors **1**−**5** in slight excess, indicating interaction with fluoride.

**FT-IR Study.** The 1:1 bromide adduct **1**·Br was crystallized and fully characterized by X-ray diffraction (see below), and so we were interested in comparing the solution data with the solid-state material of known structure, best achieved by FT-IR spectroscopy, a tech-

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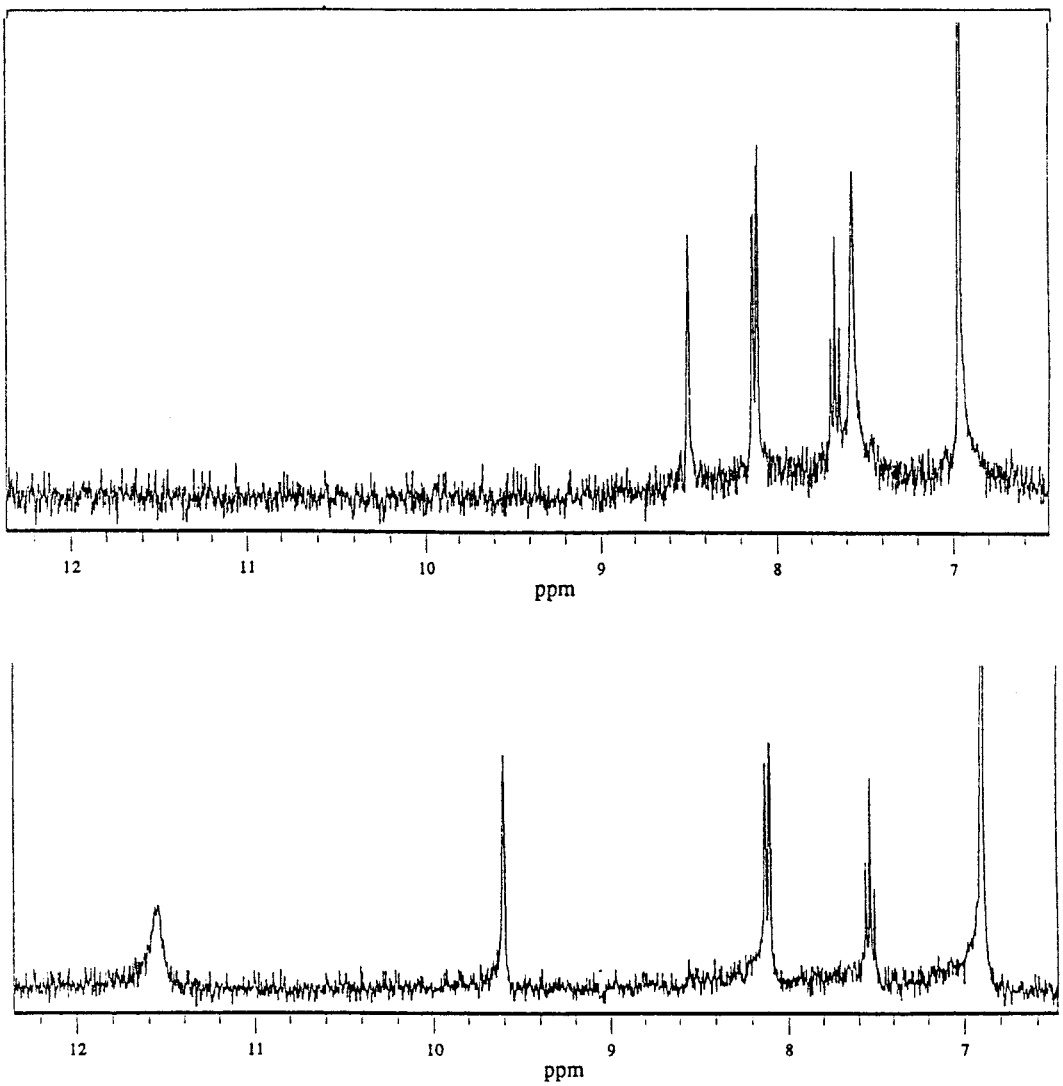
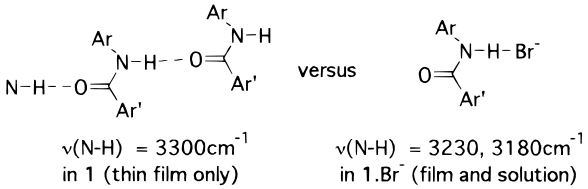



**Figure 1.** $^1$H NMR spectra of **3** before (top) and after (bottom) $Bu_4NF$ addition (10 equiv).

nique that has seen limited application in molecular recognition.[24] The solution FT-IR spectral changes of **1** and **2** in $CH_2Cl_2$ on $Br^-$ addition indicate binding. In dilute (**2**, $5 \times 10^{-4}$ M) $CH_2Cl_2$ solution **2** shows a band at 3430 $cm^{-1}$, assigned to $\nu_{NH}$ for the free amide, which, on addition of 1 equiv of $Ph_4PBr$, is replaced by bands at 3228 and 3175 $cm^{-1}$, consistent with the presence of coupled hydrogen-bonded N−H groups (Figure 2). FT-IR spectra (Table 1) for **1**, **2**, **1**·$Br^-$ and **2**·$Br^-$ were measured both in dilute $CH_2Cl_2$ solutions and in thin films, formed by evaporation of a $CH_2Cl_2$ solution. The film data proved to be a useful proxy for solid state because the IR spectra of the **1**·$Br^-$ and **2**·$Br^-$ adducts in thin film and dilute solution proved to be identical and very similar, respectively, to that of the crystalline form for **1**·$Br^-$ of known structure. The ca. 230 $cm^{-1}$ low energy shift in $\nu_{N-H}$ on going from dilute receptor solution to the adduct in thin film is consistent with N−H···Br hydrogen bonding.[24,25] Unlike the case for the adducts **1**·$Br^-$ and **2**·$Br^-$, the FT-IR spectra for pure **1** and **2** both change on moving from solution to thin film, showing only a non hydrogen bonded $\nu_{N-H}$ band at 3430 $cm^{-1}$ in dilute solution, but only a hydrogen bonded $\nu_{N-H}$ band at 3305 $cm^{-1}$ in thin film, characteristic of a self-associated amide.

These data indicate that (a) the receptors **1** and **2** are self-associated in the solid state but not in dilute $CH_2Cl_2$ solutions, probably via N−H···O=C hydrogen bonds; (b) $Br^-$ binding occurs for **1** and **2** via N−H···Br hydrogen bonding, both in the solid-state and in solution; and (c) N−H···O=C bonding is not observed in the presence of $Br^-$, either in solution or in the thin film.




**X-ray Structure of 1·Br$^-$.** The **1**·$Br^-$ adduct was successfully crystallized as $[PPh_4]_2$[**1**·Br][Br]·$CH_2Cl_2$, and the structure was determined[26] by X-ray diffraction (Table 2). The results, discussed in the communication[19] (Figure 3, Table 3,[26c] and Supporting Information) show the presence of a 1:1 complex of [**1**·Br], of an extra

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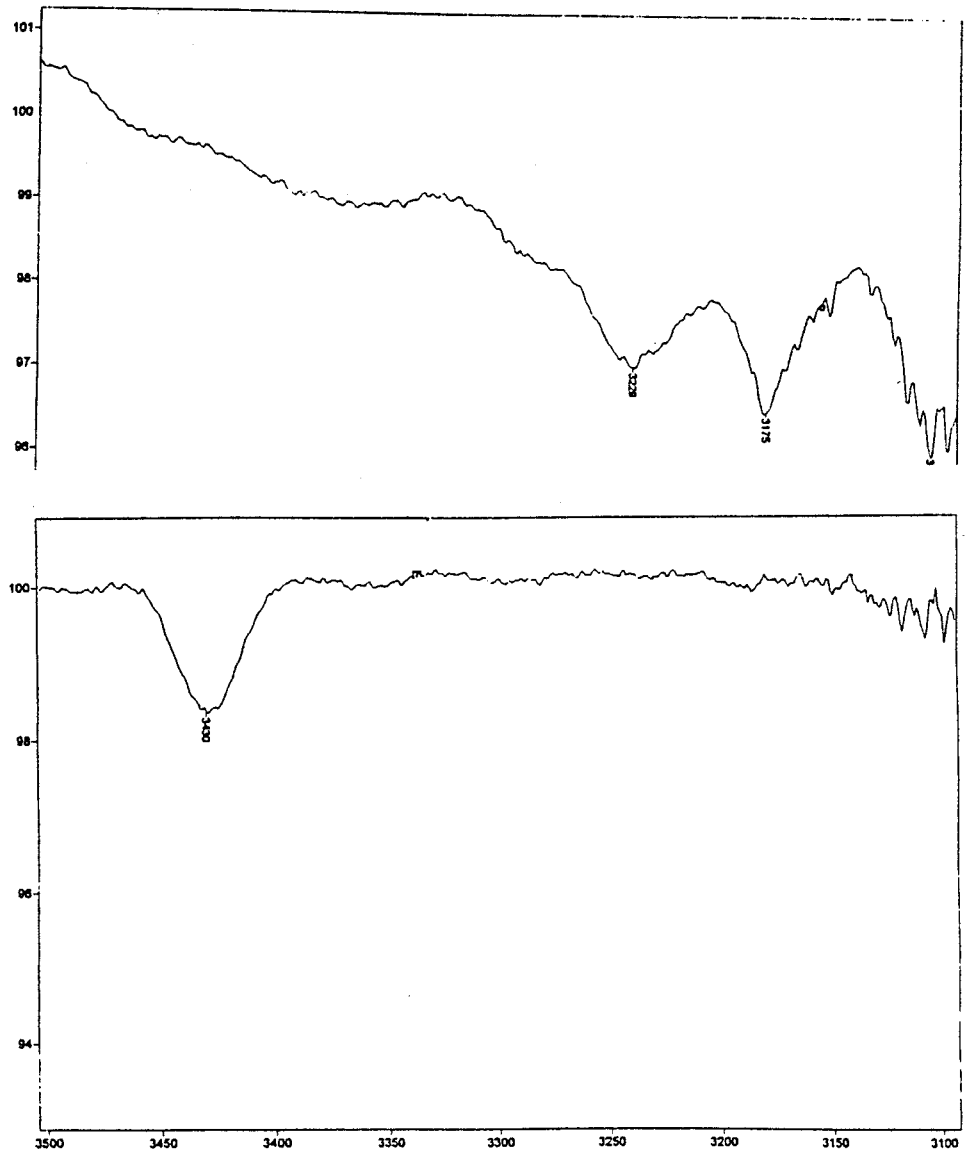



**Figure 2.** Solution FT-IR spectra of **2** after (top) and before (bottom) $Br^-$ addition.

**Table 1. N−H Stretching Frequencies for Free 1 and 2 and Their $Br^-$ Adducts**

| compound | $\nu_{N-H}$ (solution) ($cm^{-1}$) | $\nu_{N-H}$ (thin film) ($cm^{-1}$) |
|---|---|---|
| 1 | 3430 | 3302 |
| 2 | 3430 | 3281 |
| **1**·$Br^-$ | 3231 and 3184 | 3228 and 3180 |
| **2**·$Br^-$ | 3229 and 3175 | 3232 and 3171 |

formula unit of $[PPh_4]Br$, and of a molecule of $CH_2Cl_2$. The receptor adopts an unusual twisted *syn*−*syn* conformation that allows it to form two N−H···Br hydrogen bonds with one $Br^-$ ion lying out of the plane of the central arene ring. As a result, the two amide bonds are also significantly out of the central arene plane (dihedrals: 25.79° for $N_1-C_7-O_1$ and 34.88° for $N_2-C_{14}-O_2$). The bromide ion is not coordinated to any other remote groups. Electron density found in reasonable positions was tentatively assigned to the two N−H hydrogens, which were not refined. After the usual normalization

(26) (a) Full crystal data parameters are given in the Supplementary Information. (b) Instrumental details and experimental procedures are given in the Experimental Section. (c) Our previous communication[19] reported distance and angle values that were erroneously said to be normalized but were not. The values that appear here are correctly normalized.

**Table 2. Summary of Crystal Data for the $[PPh_4]_2[1·Br][Br]·CH_2Cl_2$ Structure[26]**

| | |
|---|---|
| empirical formula | $C_{69}H_{58}N_2O_2P_2Br_2Cl_2$ |
| fw (g/mol) | 1239.89 |
| cryst dimens (mm) | 0.14 × 0.18 × 0.23 |
| space group | triclinic $P\bar{1}$ (No. 2) |
| $a$ (Å) | 9.379(5) |
| $b$ (Å) | 12.823(5) |
| $c$ (Å) | 25.412(8) |
| α (deg) | 100.63(3) |
| $\beta$ (deg) | 94.43(4) |
| $\gamma$ (deg) | 101.09(4) |
| $U$ (Å$^3$) | 2927(5) |
| Z value | 2 |
| $D_{calc}$ (g $cm^{-3}$) | 1.406 |
| $F$(000) | 1272 |
| $\mu$ (Mo Kα) ($cm^{-1}$) | 15.62 |
| max 2$\theta$ (deg) | 52.6 |
| no. of reflns collected | 12619 |
| no. of ind reflns | 11865 ($R_{int}$ = 0.074) |
| obs reflns ($I > 3\sigma I$) | 6020 |
| refinement method | full-matrix least-squares |
| function mimimized | $\sum w(\|F_o\| - \|F_c\|)^2$ |
| variables | 712 |
| $R$, $R_w$ | 0.049, 0.057 |
| goodness of fit parameter | 2.04 |
| max. and min. peaks in the final difference map (e Å$^{-3}$) | 2.12 (max), −0.56 (min) |

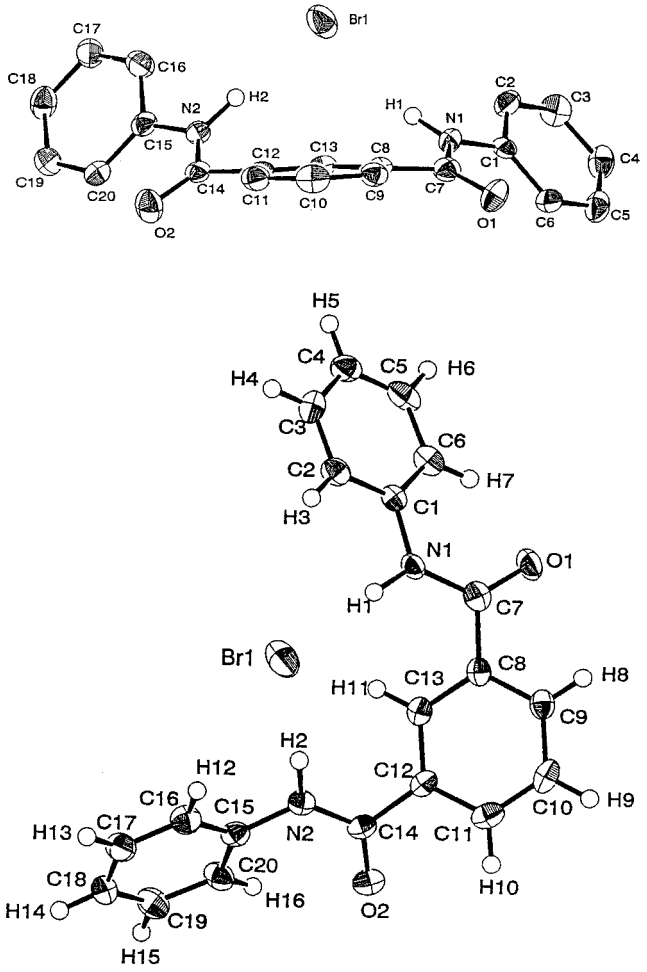



**Figure 3.** Two ORTEP views of the crystal structure showing the [**1**·$Br^-$] unit (50% probability ellipsoids). Some of the hydrogen atoms are omitted for clarity.

**Table 3. Selected Intermolecular Distances and Angles**

| atoms | distance (Å) |
|---|---|
| Br1−H2 | 2.41 |
| Br1−H1 | 2.63 |
| Br1−H11 | 3.01 |
| Br1−H3 | 3.34 |
| Br1−H12 | 3.08 |
| Br1−N2 | 3.44 |
| Br1−N1 | 3.64 |
| Br1−C13 | 3.58 |
| **atoms** | **angle (deg)** |
| Br1−H2−N2 | 173 |
| Br1−H1−N1 | 165 |
| Br1−H11−C13 | 119 |
| **planes** | **dih. angle (deg)** |
| C1−6, N1−C7−O1 | 29.6 |
| C15−20, N2−C14−O2 | 28.3 |
| C8−C13, N1−C7−O1 | 25.8 |
| C8−C13, N2−C14−O2 | 34.9 |

to $d_{N-H}$ =1.03 Å, Br···H distances of 2.63 and 2.41 Å and N−H···Br angles of 165° and 173° were found, consistent with hydrogen bonding.[25,26c] The much larger distance of 3.01 Å from the 2-C−H hydrogen to the Br ion as well as the 119° C−H···Br angle indicate that there is no significant C−H···$Br^-$ hydrogen bonding interaction despite the large downfield $^1$H NMR shift for this hydrogen. All the distances involving aromatic hydrogens were determined on the basis of positioning of these atoms at calculated positions ($d_{C-H}$ = 0.95 Å).

**Cambridge Structural Database and Receptor Conformation.** The Cambridge Structural Database[27] (CSD) gave few examples of structurally characterized N−H···$Br^-$ interactions ($d_{H\cdots Br}$ < 2.8 Å),[25] between a bromide ion and a neutral organic compound.[28] In contrast, many examples were found where the organic species is positively charged and the $Br^-$ acts as a counterion. Chloride cocrystallization with a neutral organic compound showing N−H···$Cl^-$ close contacts was more common than for bromide, but still rare.

The CSD also allowed comparison of the receptor conformation.[29] In the absence of a guest, isophthalamides show *syn*−*anti* or *anti*−*anti* conformations rather than the *syn*−*syn* conformation seen here. The formation of two hydrogen bonds to the same ion forces the receptor to adopt the observed conformation. A similar *syn*−*syn* conformational preference is seen for isophthalamide bound to urea[30] but not for free or self-associated isophthalamides.

The free receptor conformations for analogues of **1** and **5** have been extensively investigated by Hunter et al.,[31a] who found that the *syn*−*anti* conformation of **1** lies 22 kJ/mol lower in energy than our *syn*−*syn* conformation. If the formation of the two N−H···Br bonds induces the conformational change, the necessary energy must be supplied by hydrogen bond formation. In contrast, pyridine **5** has a *syn*−*syn* and almost planar[31b] conformation in the free state that is more stable than the *syn*−*anti* one by 25 kJ/mol[31a] and is therefore preorganized for binding. For the sulfonamide receptor **4** (for which we find both *syn*−*syn* 1:1 and *anti*−*anti* 1:2 complexation behavior with fluoride and acetate, see below), $^1$H NMR monitoring of the 2-C−H and the aniline moiety aromatic resonances suggests that the unbound sulfonamide has the *anti*−*anti* conformation, since its spectrum shows similarities in pattern to that of the *anti*−*anti* 1:2 complex but is distinctly different from that of the *syn*−*syn* 1:1 complex formed initially. A plot (Figure 4) of the 2-C−H chemical shift versus fluoride concentration shows a maximum downfield shift for the mole ratio [$F^-$]/[**4**] = 0.9. The aniline aromatic resonances in the free sulfonamide and in the 1:2 complex show a well-resolved t−t−d pattern with integration 2:1:2 for the *o*-, *m*-, and *p*-C−H arene protons. On progressive addition of $F^-$ up to a [$F^-$]/[**4**] ratio of 0.9, this pattern collapses to an unresolved multiplet. Beyond a [$F^-$]/[**4**] ratio of 1.2, the

(27) Source: Cambridge Crystallographic Database, Version 5.12. Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(28) (a) Lebioda, L.; Stadnicka, K. *Acta Crystallogr., Sect B* **1977**, *33*, 2905. (b) De Lucas L.; Einspahr, H., Bugg, C. E. *Acta Crystallogr., Sect B* **1979**, *35*, 2724. (c) Meulemans, R.; Piret, P.; Van Meersche, M. *Acta Crystallogr., Sect B* **1971**, *27*, 1187. (d) Truter, M. R.; Vickery, B. L. *Acta Crystallogr., Sect B* **1972**, *28*, 387. (e) Mak, T. C. W. *J. Inclusion Phenomena* **1990**, *8*, 199. (f) Knoch, F.; Appel, R.; Lange, J. *Z. Kristallogr.* **1994**, *209*, 914. (g) Elding-Ponten, M. *Acta Crystallogr., Sect C* **1977**, *33*, 2905.

(29) (a) Yang, J.; Fan, E.; Geib, S. G.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 5314. (b) Foresti, E.; Riva di Sanseverino, L.; Sabatino, P. *Acta Crystallogr., Sect. C.* **1986**, *42*, 220.

(30) Geib, S. G.; Vincent, C.; Fan, E.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 119.

(31) (a) Hunter, C. A.; Purvis D. A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 792. (b) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529.

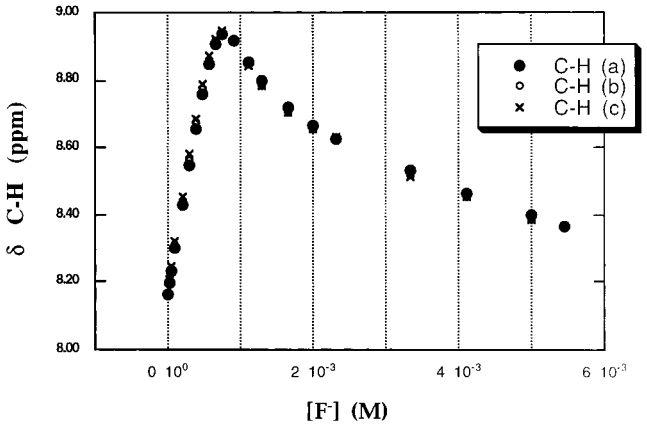
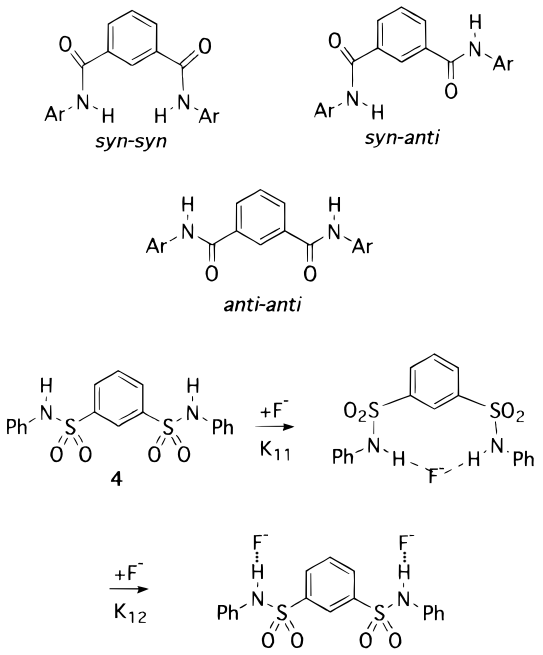



**Figure 4.** Titration curve for sulfonamide **4** and $Bu_4NF$ in $CD_2Cl_2$ (2-C−H proton resonance), showing the maximum downfield shift for $[F^-]/[\mathbf{4}] = 0.9$.

spectrum gradually reverts to a pattern similar to that of the unbound receptor as the *anti*−*anti* 1:2 complex is formed.




**$^1$H NMR Titrations.**[32] To determine the association constants, $K_a$, for the anion receptor interaction of **1**−**5** with $Cl^-$, $Br^-$, $I^-$, $F^-$, and $OAc^-$ in $CD_2Cl_2$ solution, we used the standard NMR titration method[32] with monitoring of $\Delta\delta$ N−H and $\Delta\delta$ 2-C−H, in a dilute receptor $CD_2Cl_2$ solution in the concentration range $(0.5-1) \times 10^{-3}$ M, with the addition of $1.0 \times 10^{-2}$ to $1.0 \times 10^{-1}$ M $CD_2Cl_2$ solutions of the corresponding anion salt in the same receptor concentration, followed by analysis with a nonlinear regression method. A typical binding curve is shown in Figure 5.

A 1:1 stoichiometry was found in all cases except for the sulfonamide **4**, with fluoride and acetate, in which both 1:1 and 1:2 binding stoichiometries were found (Figure 4). Receptors **2**−**5** with $Ph_4PX$ (X = $Cl^-$, $Br^-$, $I^-$) or $(n\text{-Bu})_4NX$ (X = $F^-$, $OAc^-$) and receptor **4** with $Ph_4PX$

(32) Connors, K. A. *Binding Constants*, 1st ed.; John Wiley & Sons: New York, 1987; pp 189−215.

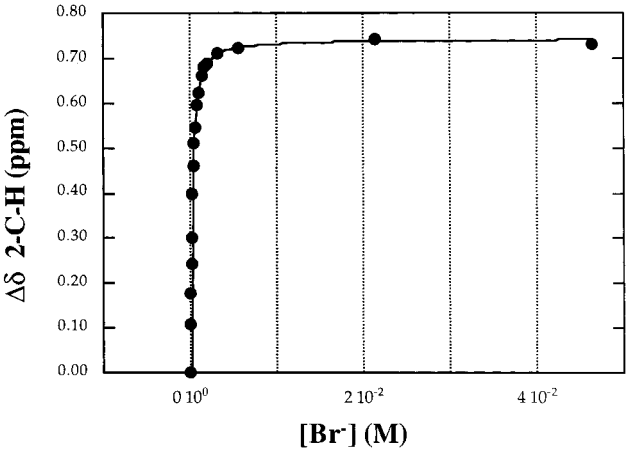



**Figure 5.** 2-C−H titration plot for receptor **2** and $Ph_4PCl$ in $CD_2Cl_2$.

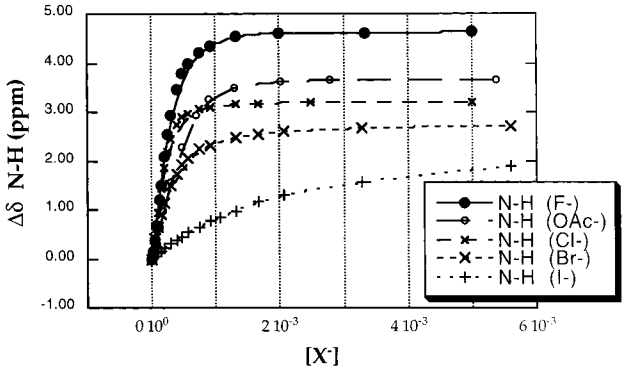



**Figure 6.** N−H titration plots for **2** + $X^-$ ($X^-$ = $Cl^-$, $Br^-$, $I^-$, $F^-$, $OAc^-$).

(X = $Cl^-$, $Br^-$, $I^-$) gave 1:1 binding isotherms for both the N−H and the 2-C−H resonances (Figure 6). The 2-C−H resonance was generally sharper and therefore allowed more accurate determination of $\Delta\delta$. The N−H and C−H titration curves for each of the receptors **2** and **3** were very similar, and the analysis gave the same $K_a$'s within experimental error. Receptor **1** was not studied because of its limited solubility. An accurate number could not be obtained for **5** + $I^-$ because of the low $K_a$ and limited solubility of $Ph_4PI$ in sufficiently high concentrations. Figure 6 shows all five different titration N−H curves obtained for **2** with $Cl^-$, $Br^-$, $I^-$, $F^-$, and $OAc^-$.

**Determination of Binding Stoichiometry by Job Plots.**[33] The complexation stoichiometries indicated by the titration curves were also confirmed by the continuous variation method (Job plots) (Figure 7). $[RX^-]$ is the supramolecular complex concentration as determined by the ratio of chemical shift change $\Delta\delta/\Delta\delta_{max}$ for the corresponding N−H and C−H protons. For all the 1:1 cases, bell-shaped Job plots were obtained with maxima for mole ratio $[\mathbf{R}]_t/[\mathbf{R}]_t + [X^-]_t$ of 0.5 or $[\mathbf{R}]_t/[X^-]_t$ of 1. One exception was the **5** + $OAc^-$ case, which gave a maximum at $[\mathbf{5}]_t/[\mathbf{5}]_t + [X^-]_t$ of 0.55, probably suggesting a small contribution from 2:1 complexation. Figure 7 shows comparable Job plots for **2** with different anions but from the same stock receptor solution, giving a qualitative picture of the observed selectivity for each receptor.

**Data Analysis: Association Constants.**[32] A 1:1 binding isotherm gave a satisfactory fit in all cases except

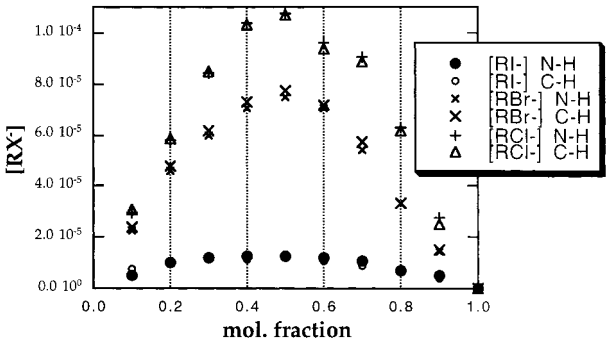



**Figure 7.** Job plots for **2** (using a $3.5 \times 10^{-4}$ M stock solution) and $Ph_4PX$ ($X = Cl^-$, $Br^-$, $I^-$).

**5** with $I^-$, as discussed above. The expression used for the 1:1 nonlinear regression is shown in eq 5.[32,34]

$$\Delta\delta = ([\mathbf{R}]_t + [X^-]_t + K_a^{-1} - ((([\mathbf{R}]_t + [X^-]_t + K_a^{-1})^2 - 4[X^-]_t[\mathbf{R}]_t)^{1/2}))\Delta\delta_{max}/(2[\mathbf{R}]_t) \quad (5)$$

In eq 5, $[\mathbf{R}]_t$ is the total receptor concentration, $K_a$ is the association constant, and $[X^-]_t$ is the total anion concentration. $\Delta\delta$ and $\Delta\delta_{max}$ are the observed and maximum chemical shift changes for the monitored resonances. For the $F^- + \mathbf{4}$ and $OAc^- + \mathbf{4}$ cases in which both 1:1 and 1:2 binding were observed, the expression of eq 6 was used for analysis of the 2-C−H titration curve:

$$\Delta\delta = ([\mathbf{R}]_t + [X^-]_t + K_{11}^{-1} - ((([\mathbf{R}]_t + [X^-]_t + K_{11}^{-1})^2 - 4[X^-]_t[\mathbf{R}]_t)^{1/2})) \times \Delta\delta_{max}/(2[\mathbf{R}]_t) - ([\mathbf{R}]_t + [X^-]_t + K_{12}^{-1} - ((([\mathbf{R}]_t + [X^-]_t + K_{12}^{-1})^2 - 4[X^-]_t[\mathbf{R}]_t)^{1/2}))\Delta\delta_{max}/(2[\mathbf{R}]_t) \quad (6)$$

In eq 6, $K_{11}$ and $K_{12}$ are the association constants for the formation of the 1:1 and 1:2 complexes, respectively. Equation 6 assumes that $K_{11} \gg K_{12}$ and also that the 2-C−H shifts of the uncomplexed receptor and the 1:2 complexed ones are identical, so that the two consecutive steps can be treated independently in an additive way. The correctness of both assumptions were verified by the results, since we obtained fits with very high $R$ values, with $K_{11} \gg K_{12}$ and more importantly with an $[\mathbf{R}]_t$ value (which we left as a free parameter rather than defining it arbitrarily) essentially the same as the one we used in the experiment. The association constants and the corresponding $\Delta G$'s are shown in Table 4.

Table 4 shows that the $K_a$'s are unusually high for acyclic and nonpreorganized receptors, especially for the smaller and harder anions, but are also high even for the larger and softer anions, for which selective receptors are generally difficult to design. The less rigid disulfonamide **4** binds iodide with a quite impressive $K_a$ value for such a simple receptor.[35] This we ascribe to a disposition of the two hydrogen bonds that allows formation of two almost linear hydrogen bonds. No rigid or bulky groups

**Table 4. Maximum Chemical Shift Changes and Association Constants $K_a$ at 19.2 °C in $CD_2Cl_2$[a]**

| **2** + anion | Δδ max (N−H) (ppm) | Δδ max (C−H) (ppm) | $K_a$ ($M^{-1}$) | Δ$G$ (kJ/mol) |
|---|---|---|---|---|
| $F^-$ | 4.65 | 1.55 | 30000 (10%) | −25.1 |
| $Cl^-$ | 3.20 | 0.95 | 61000 (12%) | −26.8 |
| $Br^-$ | 2.80 | 0.74 | 7100 (3%) | −21.6 |
| $I^-$ | 2.57 | 0.59 | 460 (7%) | −14.9 |
| $OAc^-$ | 3.73 | 0.98 | 19800 (5%) | −24.1 |

| **3** + anion | Δδ max (N−H) (ppm) | Δδ max (C−H) (ppm) | $K_a$ ($M^{-1}$) | Δ$G$ (kJ/mol) |
|---|---|---|---|---|
| $F^-$ | 4.03 | 1.05 | 7500 (10%) | −21.7 |
| $Cl^-$ | 3.16 | 1.28 | 5300 (5%) | −20.9 |
| $Br^-$ | 2.76 | 1.11 | 1400 (8%) | −17.6 |
| $I^-$ | 2.33 | 0.91 | 220 (10%) | −13.1 |
| $OAc^-$ | 3.60 | 1.02 | 2800 (15%) | −19.3 |

| **4** + anion | Δδ max (C−H) (ppm) | stoichiometry of binding | $K_a$ ($M^{-1}$) | Δ$G$ (kJ/mol) |
|---|---|---|---|---|
| $F^-$ | 1.20 | 1:1 + 1:2 | $K_{11}$ = 55000 (25%) | −26.6 |
| | | | $K_{12}$ = 1000 (10%) | −16.8 |
| $Cl^-$ | 1.50 | 1:1 | 20000 (6%) | −24.1 |
| $Br^-$ | 1.40 | 1:1 | 4600 (4%) | −20.5 |
| $I^-$ | 1.16 | 1:1 | 1200 (15%) | −17.3 |
| $OAc^-$ | 1.74 | 1:1 + 1:2 | $K_{11}$ = 21000 (25%) | −24.2 |
| | | | $K_{12}$ = 300 (12%) | −13.9 |

| **5** + anion | Δδ max (N−H) (ppm) | $K_a$ ($M^{-1}$) | Δ$G$ (kJ/mol) |
|---|---|---|---|
| $F^-$ | 4.68 | 24000 (18%) | −24.5 |
| $Cl^-$ | 1.54 | 1500 (30%) | −17.8 |
| $Br^-$ | 1.85 | 57 (6%) | −9.8 |
| $I^-$ | 0.99 | <20 | >−7.3 |
| $Ac^-$ | 2.30 | 525 (6%) | −15.2 |

[a] Errors calculated from the deviation of three independent measurements.

are present and the host skeleton is flexible, allowing adjustment of conformation according to guest size. No repulsive lone pairs are present for receptors **1**−**4**, and this appears to be an important factor for strong binding, particularly for the bulkier anions. Receptor flexibility seems to be a favorable factor that has been largely ignored in the past[36] and appears to be more important for bulkier and softer anions (at least in these systems). Moreover the receptors are readily available in multigram quantities from inexpensive and commercially available starting materials, via a synthesis that allows easy variation of substituents.

The acidity of the N−H hydrogen has a significant influence. The less acidic hexamethyl receptor **3** shows a sharp decrease in binding constant for $Cl^-$ as compared to **2**; steric factors could also play a role, however. Sulfonamides ($pK_a \approx 9-10$) are about 5 $pK_a$ units more acidic than amides, ($pK_a \approx 14-15$),[37] a factor that would be expected to increase their H-bond donor ability and their binding constants dramatically. We find this is not generally the case, except for the $F^-$ and $OAc^-$ cases, where a mixed 1:1 and 1:2 stoichiometry may play an additional role. The cavity size of the receptors, their flexibility, and the need for the two donor groups to converge on one acceptor atom, to form the two linear hydrogen bonds—easier for **4** because of the freer rotation about the HN−C(arene) bond—are the most important

(33) Connors, K. A. *Binding Constants*, 1st ed.; John Wiley & Sons: New York, 1987; pp 24−28.
(34) Kavallieratos, K., Ph.D. Thesis, Yale University, 1998.
(35) For examples of $I^-$ complexation, see: (a) Beer, P. D.; Cooper, J. B. *J. Chem. Soc., Chem. Commun.* **1998,** 129. (b) Rohrbach, R. P.; Rodriguez, L. J.; Eyring, E. M.; Wojcik, J. F. *J. Phys. Chem.* **1977,** *81*, 944. (c) Worm, K.; Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 65.
(36) Eblinger, F.; Schneider; H.-J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 726.
(37) Andersen, K. K. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ed.; Pergamon Press: Oxford, 1979; Vol. 4, p 345.

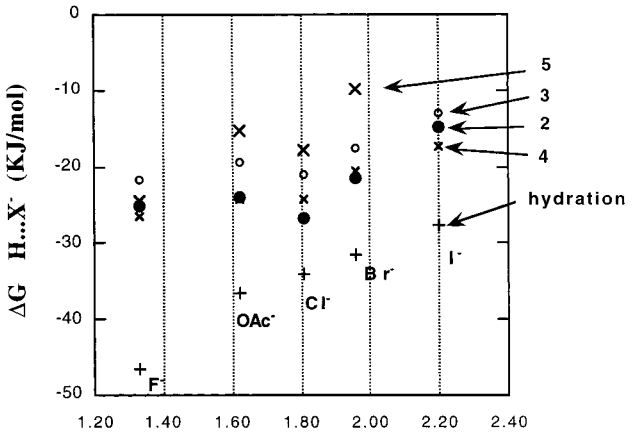



**Figure 8.** Plot of $\Delta G$ vs ionic radius. Experimental hydration free enthalpies (scaled) and ionic radii are taken from ref 39.

factors, particularly in the series $Cl^-$, $Br^-$, $I^-$. For instance, the bulky iodide is preferred for the more flexible disulfonamide group versus the less flexible amide one. For chloride, in contrast, the $K_a$ is unusually high for the rigid amide **2** presumably because of size compatibility. We were not able to obtain a crystal of the chloride adduct to confirm this assumption. However for similar metal-containing macrocyclic systems recently reported by Beer et al.,[2p] a much more planar structure was obtained for chloride versus bromide. For the hard and small fluoride and acetate ions, the higher acidity may be the predominant factor giving sulfonamide its very high $K_a$'s. From the results for **2**−**4** and **5** with $Cl^-$, $Br^-$, and $I^-$, we see that increased receptor rigidity (in the order **4** < **3** < **2** < **5**) leads to enhanced binding of the smaller halides. Table 4 shows that **5**, with its nitrogen lone pair close to the anion binding site, prefers binding the smaller halides. Such a lone pair is known to be sterically more bulky than an aromatic C−H bond,[38] and electrostatic repulsion between the negatively charged anions and the lone pair is expected to decrease the binding strength. This effect is more pronounced for the larger $I^-$ and $Br^-$ and much smaller for $F^-$, giving receptor **5** the highest selectivity for smaller anions.

Figure 8 summarizes the results of Table 4 in a form that makes the observed relative trends more obvious. The inclusion of scaled ($10^{-1}$) free enthalpies of hydration[39] in the graph provides a comparison and confirms that smaller, harder anions are better H-bond acceptors than larger and softer ones. The right-hand part of the graph includes the larger anions $Cl^-$, $Br^-$, and $I^-$ and shows nearly straight lines for the different receptors, and the different slopes show the various size selectivities of the receptors. The less rigid sulfonamide **4** has the smallest slope, only marginally different from the trend in hydration enthalpy, suggesting that the receptor prefers $Cl^-$ over $I^-$ mainly because the NH···$Cl^-$ H-bonds are stronger. This does not appear to be the case for the more rigid receptor **2**, however, because the slope is three times larger. The presence of an N lone pair instead of a C−H in the pyridine receptor **5** results in an even larger increase in the slope and therefore in the selectivity.

**$\Delta H$ and $\Delta S$ of Interaction: VT NMR Data.** A variable-temperature NMR titration study allowed us to determine the $K_a$ at different temperatures for the **2** + $Cl^-$ case. A van't Hoff plot (Supporting Information) gives a $\Delta H$ of −31 kJ/mol and a $\Delta S$ of −23 J/(mol·K), as expected for a 1:1 interaction of two molecules in an organic solvent.[40]

## Conclusion

Strong and selective anion binding can be achieved with simple nonpreorganized *m*-diamides or disulfonamides, which are synthetically obtainable on a multigram scale. The importance of hydrogen bonding for anion recognition in these systems was demonstrated by a crystal structure of **1**·Br that shows a *syn*−*syn* nonplanar binding conformation. The study of anion binding properties of receptors having slightly different structures with five different anions allowed us to demonstrate the importance of hydrogen bonding for anion recognition in these systems as well as to interpret the relationship between certain receptor structural features and the strength and selectivity of anion binding.

Trends in structure/binding relationships show receptor flexibility is an important factor in anion recognition. Applications of these and other flexible receptors with simple structure to various areas of interest can be anticipated.

## Experimental Section

**General Comments.** All solvents were of analytical grade and were used without further purification. Isophthaloyl dichloride, aniline, *p*-*n*-butylaniline, and 2,4,6-trimethylaniline (Aldrich) were used as received. $^1$H NMR spectra (GE-Omega 300 MHz) were referenced to residual solvent resonances. FT-IR spectra were recorded on a MIDAC M1200 FT-IR spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc. Norcross, GA, or Robertson Microlit Laboratories Inc., Madison, NJ. Fast atom bombardment (FAB) high-resolution mass spectra were obtained at the laboratories of Dr. Stephen Mullen at the University of Illinois at Urbana−Champaign.

**1,3-Benzenedicarboxamide-*N*,*N*′-bis(4-butylphenyl) (2).** The compound was synthesized by a modification of the previously published method for **1**.[20] To dimethylformamide (DMF, ca. 75 mL) in a 250 mL flask was added *p*-*n*-butylaniline (9.25 g, 0.062 mol) with magnetic stirring. Isophthaloyl dichloride (6.33 g, 0.031 mol) was added gradually, and the reaction mixture was stirred at room temperature for ca. 30 min and then poured into water (300 mL). The product was precipitated as a white powder, which was washed three times with water. The diamide was air-dried and subsequently recrystallized from ethanol/benzyl alcohol. The colorless crystals were washed with methanol and dried in vacuo at 90 °C for 4 h. Yield: 10.62 g (80%). $^1$H NMR ($CD_2Cl_2$, 19.2 °C): $\delta$ (ppm) 8.38 (s br, 1H), 8.05 (dd, 2H, $J$ = 7.8 Hz, 1.9 Hz), 7.98 (s, br, 2H), 7.64 (t, 1H, $J$ = 7.8 Hz), 7.56 (d, 4H, $J$ = 8.2 Hz), 7.21 (d, 4H, $J$ = 8.2 Hz), 2.61 (t, 4H, $J$ = 7.7 Hz), 1.60 (m, 4H), 1.36 (m 4H), 0.94 (t, 6H, $J$ = 7.2 Hz). FT-IR ($CH_2Cl_2$, thin film − $cm^{-1}$): 3281 (br $\nu_{N-H}$), 1650, 1523, 1410, 1324, 1104, 927, 824, 714, 703. FT-IR (dil. solution, $cm^{-1}$): $\nu_{N-H}$ 3430. Elemental anal. Calcd for $C_{28}H_{32}N_2O_2$: C, 78.5; H, 7.53; N, 6.54. Found: C, 77.37; H, 7.26; N, 6.25. High-resolution mass spectrometry (FAB): Calcd for ($MH^+$) 429.254 204, found 429.254 000.

**1,3-Benzenedicarboxamide-*N*,*N*′-bis(2,4,6-trimethylphenyl) (3).** Isophthaloyl dichloride (2.11 g, 10.3 mmol) was added gradually to a solution of 2,4,6-trimethylaniline (2.81 g, 20.8 mmol) in DMF (25 mL) and was allowed to react for 15 min. The solution was added to excess water (200 mL), resulting

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in the formation of a thick, white precipitate, which was filtered through a coarse-fritted glass funnel, washed multiple times with water, and air-dried. Recrystallization from ethanol gave the pure product that was dried at 80 °C in vacuo. Yield: 1.77 g (43%). $^1$H NMR ($CD_2Cl_2$, 19.2 °C): $\delta$ (ppm) 8.51 (s, 1H), 8.12 (dd, 2H, $J$ = 7.8 Hz, 1.9 Hz), 7.73 (t, 1H, $J$ = 7.7 Hz), 7.61 (br s, 2H), 7.02 (s, 4H), 2.41 (s, 6H), 2.18. (s, 12H). FT-IR: (film) ($cm^{-1}$) 3234 ($\nu_{N-H}$), 1635, 1516, 1429, 1304, 1256, 844, 735. Elemental anal. Calcd for $C_{26}H_{30}N_2O_2$: C, 77.6; H, 7.51; N, 6.96. Found: C, 77.80; H, 7.14; N, 6.74.

**1,3-Benzenedisulfonamide-*N*,*N*′-bis(diphenyl) (4).** The compound was synthesized by a modification of the previously published method for **1**.[21a] 1,3-Benzenesulfonyl chloride (4.27 g, 15.5 mmol) was added gradually to a solution of aniline (2.89 g, 31 mmol) in DMF (40 mL) and was allowed to react for 30 min. The solution was added to excess water (150 mL), and a crystalline white solid was precipitated, filtered through a coarse fritted glass funnel, washed many times with water, and air-dried. Recrystallization from methanol/water gave the pure product, which was dried in vacuo for 8 h at 60 °C. Yield: 2.51 g (42%). $^1$H NMR ($CD_2Cl_2$, 19.2 °C): $\delta$ (ppm) 8.33 (t br, 1H, $J$ = 1.7 Hz), 7.82 (dd, 2H, $J$ = 7.9 Hz, 1.9 Hz), 7.48 (t, 1H, $J$ = 8.0 Hz), 7.25 (td, 4H, $J$ = 7.9 Hz, 1.6 Hz), 7.16 (tt, 2H, $J$ = 7.5 Hz), 7.02 (dt, 4H, $J$ = 8.1 Hz, 1.5 Hz), 6.92 (s, br, 2H). FT-IR ($CH_2Cl_2$, thin film, $cm^{-1}$): 3264 (br $\nu_{N-H}$), 3072, 1598, 1495, 1415, 1343, 1177, 1154, 924. Elemental anal. Calcd for $C_{18}H_{16}N_2S_2O_4$: C, 55.7; H, 4.15; N, 7.21; S, 16.5. Found: C, 55.72; H, 4.24; N, 7.20; S, 16.44.

**Crystallography.** Crystal data and data collection parameters are summarized in Table 2.2.[26a] A colorless prismatic crystal (0.14 × 0.18 × 0.23 mm) of $C_{69}H_{58}N_2O_2P_2Br_2Cl_2$ was mounted on a glass fiber. All measurements were carried out on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Mo Kα radiation. The data were collected at a temperature of −90 ± 1 °C using the $\omega-2\theta$ scan technique to a maximum $2\theta$ value of 52.6°. The structure was solved by the Patterson method.[41] The non-hydrogen atoms were refined anisotropically. The hydrogen atoms, except for the N−H hydrogen atoms, were included in calculated positions. The N−H hydrogen atoms were located in the difference map, but not refined.

All calculations were performed using the TEXSAN[42] crystallographic software package of the Molecular Structure Corporation.

**$^1$H NMR Titrations.** Solutions of receptor **R** in $CD_2Cl_2$ (dried under activated 4 Å molecular sieves) were prepared in the concentration range $2.0 \times 10^{-4}$ to $1.0 \times 10^{-3}$ M. One milliliter of these solutions was titrated in NMR tubes with $1.0 \times 10^{-2}$ to $1.0 \times 10^{-1}$ M solutions of $Ph_4PX$ salts (for $Cl^-$, $Br^-$, and $I^-$) or $Bu_4NX$ salts (for $OAc^-$ or $F^-$), which also contained receptor in the same concentration as the titrated solutions. A 1 M solution in THF was used as tetrabutylammonium fluoride source. Solution transfers were performed by syringe and septa techniques. The resonances assigned to the N−H protons and the aromatic 2-C−H protons were monitored as a function of the anion concentration up to the point where the chemical shift change reached saturation. The association constant $K_a$ was calculated from the obtained curves ($\Delta\delta$ N−H vs [$X^-$] and $\Delta\delta$ C−H vs [$X^-$]) via nonlinear regression analysis carried out with the Kaleidagraph program[43] and using the curve fit for simple 1:1 binding (eq 5).[32] In the cases where both a 1:1 and 1:2 stoichiometry occurred (**4** + $F^-$ or $OAc^-$), the analysis was carried out using the more complex eq 6. All the runs were carried out for three independent samples, and the values obtained for $K_a$ agreed within <5%. The concentration of the receptor solution was set as a free parameter for fitting, and the value obtained was found to agree within 10% with the concentration value actually used. The values obtained for the $K_a$ from the aromatic 2-C−H and the N−H protons were found within the same range. In all cases more than 10 equiv of anion was added before the titration was terminated. All measurements were carried out in triplicate using independent samples.

**Continuous Variation Method (Job plots).** Stock solutions of the receptor ($3.5 \times 10^{-4}$ M for **2**, $1.0 \times 10^{-3}$ M for **3**−**5**) and the corresponding anion salt ($3.5 \times 10^{-4}$ or $1.0 \times 10^{-3}$ M, respectively) in $CD_2Cl_2$ were prepared. Ten NMR tubes were filled with 500 mL solutions of the host and guest in the following volume ratios (in mL): 50:450, 100:400, 150:350, 200:300, 250:250, 300:200, 350:150, 400:100, 450:50, 500:0. $^1$H NMR spectra were recorded, and the concentration of the complex was calculated as follows: $[\text{complex}] = ([\mathbf{R}]_t) \times (\delta_{obs} - \delta_o)/(\delta_c - \delta_o)$ (3), where $[\mathbf{R}]_t$ is the total concentration of the receptor in the solution, $\delta_{obs}$ is the observed chemical shift for the N−H or any 2-C−H protons, $\delta_o$ is the chemical shift for the free host, and $\delta_c$ is the chemical shift of the N−H or the 2-C−H protons in the complex. Job plot curve maxima at mol fraction of 0.5 were observed for host:guest molar ratios of 1:1 and were confirmed for both N−H and 2-C−H resonances when applicable.

**Solution and Thin Film FT-IR.** Solutions of the receptors and $PPh_4$ halide salts of similar concentrations were prepared in $CH_2Cl_2$. The two solutions were mixed in equal amounts, and the spectrum of the new solution was obtained in a NaCl, FT-IR cell. Right after the collection the same solution was layered on a NaCl plate in order to form a thin film (via slow evaporation), and the spectrum was obtained. The same procedure was applied for the solutions of the free receptors.

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**Supporting Information Available:** Tables of crystallographic data for the adduct of **1** with $PPh_4Br$ are available, as well as Job and van't Hoff plots for the receptors. This material is available free of charge via the Internet at http://pubs.acs.org.

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