A Readily Available Non-preorganized Neutral Acyclic Halide Receptor with an Unusual Nonplanar Binding Conformation

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Although cation recognition by organic molecules is well-known,[1] anion recognition[2] has only recently attracted attention due to its biomedical[3] and environmental[4] significance. Acyclic synthetic anion receptors are either positively charged[5] or contain Lewis acid centers.[6] In acyclic positively charged receptors, selectivity is modest due to the dominance of nondirectional electrostatic interactions.[7,8] Neutral Lewis acid and macrocyclic receptors have only limited synthetic flexibility for optimizing binding selectivity.[8]

Neutral hosts that bind exclusively through hydrogen bonding via pyrrole,[9] urea,[8,10] or amide groups[11] ameliorate these disadvantages. Hamilton et al.[12−14] and Still et al.[15] have reported isopthalamide receptors for binding nucleotide bases,[12] barbiturates,[13] dicarboxylic acids,[14] and peptides;[15] however, no halide-binding properties have been reported. As part of our studies on hydrogen bonding,[16] we discovered a simple non-preorganized acyclic halide receptor available in large quantities. Binding is the result of strong N−H···Hal$^-$ hydrogen bonding seen in solution by FT-IR and ^{1}H-NMR spectroscopy and in the solid state by X-ray diffraction. Few structurally characterized N−H···Br$^-$ bonds (d(H···Br) < 2.8 Å) have been reported[17,18] for neutral organic compounds but N−H···Cl$^-$ examples are more common. We now report the crystal structure of the bromide adduct of the isophthalamide receptor **1** and the halide ion solution binding properties of the more soluble analogue **2**.

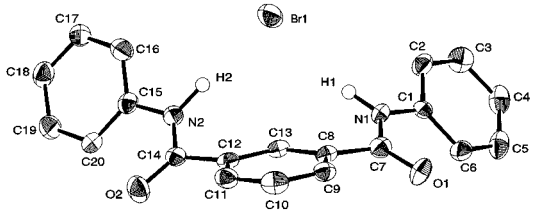
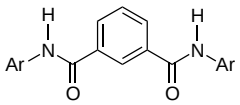


Figure 1. An ORTEP view of the crystal structure showing the [**1**·Br$^-$] unit (50% probability ellipsoids). Most of the hydrogen atoms are omitted for clarity.



1 Ar = C_6H_5
2 Ar = *p*-*n*-BuC_6H_4

Diamide **1** was synthesized as previously reported,[19] and **2** was prepared from isophthaloyl dichloride and *p*-(*n*-butyl)aniline using a modification of the previous procedure.[20]

Crystals of **1**·([PPh$_4$]Br)$_2$, grown by slow diffusion of ether into a solution of **1** and [PPh$_4$]Br in CH_2Cl_2 at 0 °C, gave a structure (X-ray diffraction)[21] that showed 1:1 complexation of Br$^-$ to **1** (Figure 1). An extra [PPh$_4$]Br and a CH_2Cl_2 are also

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(21) Colorless prismatic crystal (0.14 × 0.18 × 0.23 mm), $C_{69}H_{58}N_2O_2P_2Br_2Cl_2$, fw = 1239.89, triclinic $P\bar{1}$ (No. 2), a = 9.379(5) Å, b = 12.823(5) Å, c = 25.412(8) Å, α = 100.63(3)°, β = 94.43(4)°, γ = 101.09(4)°, V = 2927(5) Å^3, Z = 2, R (R_w) = 0.049 (0.057), GOF = 2.04.

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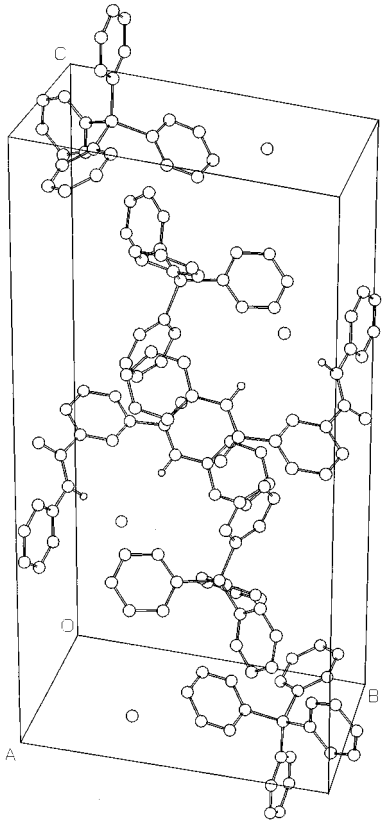


Figure 2. Three-dimensional lattice packing diagram of the $[PPh_4]_2$-[**1**·Br][Br]·CH_2Cl_2 structure. Methylene chloride has been omitted for clarity.

Table 1. Intermolecular Br^- Distances and Angles

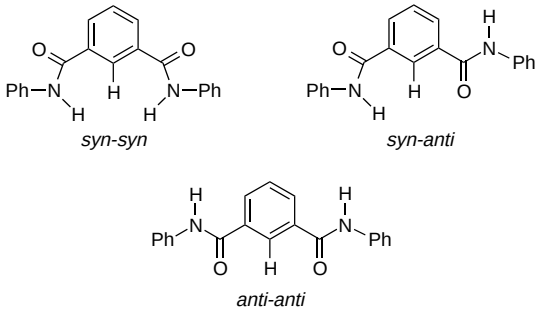
atoms	distance (Å)	atoms	angle (deg)
Br1−H2	2.39	Br1−H2−N2	166
Br1−H1	2.68	Br1−H1−N1	172
Br1−H11	3.01	Br1−H11−C13	117
Br1−H3	3.34		
Br1−H12	3.08	planes	dihedral angle (deg)
Br1−N2	3.44	C1−6, N1−C7−O1	29.6
Br1−N1	3.64	C15−20, N2−C14−O2	28.3
Br1−C13	3.58	C8−C13, N1−C7−O1	25.8
		C8−C13, N2−C14−O2	34.9

present, but are not involved in hydrogen bonding (Figure 2). The very unusual twisted *syn-syn* conformation allows **1** to form two N−H···Br hydrogen bonds with one bromide ion. The two amidic bonds are significantly out of the central ring plane (dihedral angles of 25.8° for the $N_1-C_7-O_1$ plane and 34.9° for the $N_2-C_{14}-O_2$ plane), presumably due to the large size of the Br^-. The bromide ion is not coordinated to any other groups on the receptor.[22] Electron density found in reasonable positions was assigned to the two N−H hydrogens. After normalization (to N−H = 1.03 Å), Br···H distances of 2.39 and 2.68 Å and N−H···Br angles of 166° and 172° were found, consistent with hydrogen bonding.[23] Selected intermolecular distances and angles are summarized in Table 1.

Comparison with free isophthalamides[24] suggests that N−H···Br^- hydrogen bonding forces the receptor to adopt the unfavorable *syn-syn* conformation rather than *syn-anti* or *anti-anti*, as also seen by Hamilton et al.[25]

Table 2. N−H Stretching Frequencies

compound	ν (solution) (cm^{-1})	ν (thin film) (cm^{-1})
1	3430	3302
2	3430	3281
1·Br^-	3231, 3184	3228, 3180
2·Br^-	3229, 3175	3232, 3171



The N−H···Br^- hydrogen bonding in solution was evident from an FT-IR comparison (Table 2) of **1** and **2**, in both dilute CH_2Cl_2 solutions and in thin films and in the presence or absence of Br^-. The 228 cm^{-1} (av) low-energy shift of ν(N−H) in dilute solution is consistent with strong N−H···Br^- hydrogen bonding.[23] The IR data in the solid state (thin evaporated film) differ from those in solution for **1** and **2**, but are similar for the adducts, suggesting extensive self-association for the free receptor in the solid state but not in dilute solution.

Compound **1** has very low solubility in CD_2Cl_2, presumably due to extended self-association. Addition of $[PPh_4]Br$ caused immediate solubilization,[26] and the ^{1}H-NMR spectrum showed significant downfield shifts of the N−H and aromatic 2-C−H resonances. Solubility limitations, however, required the use of the more soluble derivative **2** for determining the association constant, K_a. ^{1}H-NMR data for the complex between **2** and $[PPh_4]Br$ in CD_2Cl_2 again showed a significant downfield concentration-dependent shift for both the N−H ($\Delta\delta$ max of 2.80 ppm) and the aromatic 2-C−H resonances ($\Delta\delta$ max of 0.74 ppm), suggesting that these protons are close to the Br^- anion in solution, as seen in the crystal structure.

The K_a for the **2**·Hal^- complex in CD_2Cl_2 was determined by NMR titration,[27] monitoring δ N−H and δ 2-C−H, in a dilute receptor solution in the concentration range of $2.0-5.0 \times 10^{-4}$ M, with the addition of 1.0×10^{-2} and 1.0×10^{-1} M solutions of $[PPh_4]Hal$ in the same receptor concentration, followed by nonlinear regression analysis.[28] The K_a values at 19.2 °C (errors ca. 12%, Cl^-, 3%, Br^-; 7%, I^-) were 6.1×10^4 M^{-1} (Cl^-), 7.1×10^3 M^{-1} (Br^-), and 4.6×10^2 M^{-1} (I^-), equivalent to $\Delta G_f°$ values of −26.8 kJ/mol (Cl^-), −21.6 kJ/mol (Br^-), and −14.9 kJ/mol (I^-). Job plots[29] indicated 1:1 complexation.

We have shown that a strong halide binding can be achieved with a simple non-preorganized isophthalamide, synthetically available on a multigram scale.

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Supporting Information Available: Crystallographic X-ray structural data, NMR titration, Job plots, and text including a brief description of experimental methods with characterization data (29 pages). See any current masthead page for ordering and Internet access instructions.

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