A Neutral Paraquat Receptor That Uses Oriented Dipoles Produced by Dative B–N Bonds†

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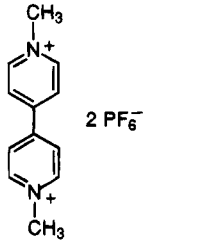
The association of paraquat dication (methylviologen) with simple neutral π-donor molecules is generally quite weak (K_{assn} < 16 M^{-1}) in polar, aprotic solvents. A new type of neutral paraquat receptor is described whose structure incorporates two dative B–N dipoles fixed in convergent orientations that are complementary with the two cationic centers of paraquat. The receptor binds paraquat bis(hexafluorophosphate) as a 1:1 complex with an association constant of 320 M^{-1} in acetone as determined by ^1H NMR titration experiments. The complex is held together by a combination of intermolecular forces: (i) ion–dipole stabilization due to the negative ends of the two dative B–N dipoles pointing directly towards the two cationic centers in paraquat, (ii) Attractive π–π stacking of the electron-rich and electron-poor biphenyls, and (iii) C–H···O hydrogen bonding between the relatively acidic paraquat methyl groups and are the basic boronate oxygens. The structurally related diquat bis(hexafluorophosphate) was bound 0.6 kcal/mol more weakly, emphasizing the directional nature of the oriented B–N dipoles.

Introduction

Neutral cation receptors that use ion–dipole interactions to bind their guests are the largest class of artificial receptors known (*e.g.*, polyethers).[1,2] A successful cation receptor must incorporate into its structure an array of preorganized dipoles arranged in spatially specific orientations such that the negative ends are pointing toward the cationic center(s). This report concerns a novel receptor for paraquat (**1**, methylviologen). Although paraquat dication forms ion-pair complexes with a range of organic and inorganic anions,[3] the associations observed with simple neutral π-donor molecules are generally quite weak (K_{assn} < 16 M^{-1}).[4] Of the more sophisticated neutral paraquat hosts,[5] the best characterized are those designed by Stoddart and co-workers.[6] For example, the macrocycle **2** forms a 1:1, face-to-face complex with paraquat in polar, aprotic solutions (K_{assn} = 730 M^{-1} in acetone) and in the solid state.[6] The complex is stabilized by ion–dipole interactions between the cationic nitrogens and the polyethylene ethers, π–π interactions (which includes electrostatic, polarization, dispersion, and charge-transfer contributions)[7], and CH···O hydrogen bonding between the polyethylene oxygens and the relatively acidic CH groups adjacent to the nitrogens.



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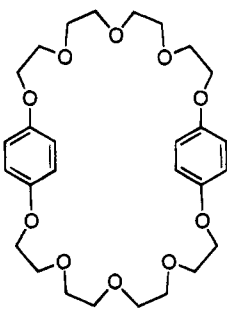

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Recently, Schmidtchen described the neutral, macrocyclic receptor **3**, which uses the convergent dipoles formed by four preorganized borane–amine adducts to selectively bind anions at its center.[8] Herein, we describe a class of neutral receptors that use the dative B–N dipole in the reverse direction, *i.e.*, the negative end of the dipole is oriented toward a cationic center.[9] Specifically, we have designed and synthesized the ditopic receptor **4** whose structure incorporates two dative B–N dipoles fixed in convergent orientations that are complementary with the two cationic centers of paraquat. We have found that receptor **4** binds paraquat much stronger than other neutral, biphenyl derivatives. We attribute this result to the Coulombic attractions produced by the oriented B–N dipoles.

† Molecular recognition with boron acids, part 10. For part 9, see: Bien, J. T.; Shang, M.; Smith, B. D. *J. Org. Chem.*, **1995**, *60*, 2147–2152.

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(7) For a recent discussion on π–π interactions, see: Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1584–1586 and references cited therein.

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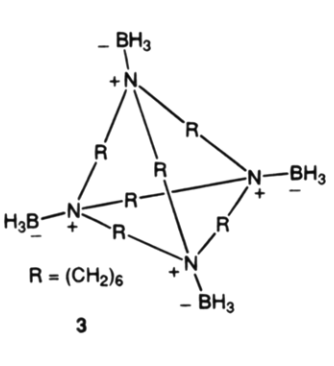

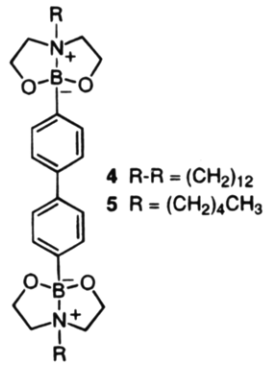

Receptor Design

There is compelling spectroscopic and X-ray crystallographic evidence that the diethanolamine esters of boronic acids form dative B–N bonds.[10,11] This Lewis acid–base interaction produces a strong dipole directed along the B–N bond.[12] In the case of arylboronic esters, steric hindrance fixes the dipole in an orientation that points away from the plane of the aryl ring (Figure 1).[10] The free energy of activation for dative bond inversion (*i.e.*, cleaving the B–N bond, flipping the 8-membered trigonal ester ring, and reforming the B–N bond on the reverse side) is around 18 kcal/mol for arylboronic acids depending on the exact system.[11c] Thus, dative bond inversion with arylboronic esters is very slow at room temperature. In relation to the rapid host–guest binding scheme described below, the tetrahedral boronate ester shown in Figure 1 can be considered as a rigid structure with hindered rotational freedom around the C–B bond.

With this knowledge in mind, receptor **4** was envisioned as having a binding shape that is complimentary to a dicationic paraquat guest. The postulated **4**:paraquat binding complex is shown in Figure 2. The complex is held together by a combination of intermolecular forces: (i) the negative ends of the two dative B–N dipoles in **4** are pointed directly toward the two cationic centers of paraquat, (ii) the electron-rich and electron-poor biphenyls produce an attractive $\pi-\pi$ stacking interaction, and (iii) C–H···O hydrogen bonding can occur between the relatively acidic paraquat methyl groups and the basic boronate oxygens.[13]

Synthesis and Characterization of Receptors

Macrocycle **4** was obtained by condensing 4,4′-biphenyldiboronic acid with *N*,*N*,*N*′,*N*′-tetrakis(2-hydroxyethyl)-1,12-dodecanediamine. The related acyclic control receptor **5** was prepared by transesterifying the known diboronate ester **6**[14] with *N*,*N*-bis(2-hydroxyethyl)-1-pentanamine. The monoboronate ester **7** was obtained by condensing 4-biphenylboronic acid with *N*,*N*-bis(2-hydroxyethyl)-1-pentanamine. All analytical and spectral data for compounds **4**–**7** were in agreement with the structures as drawn. In particular, ^{11}B NMR showed clearly that the borons in **4**, **5**, and **7** were sp^3 hybridized (^{11}B chemical shifts of 11.4, 11.3, 11.5 ppm, respectively, as referenced to $BF_3{\cdot}OEt_2$), whereas they were sp^2 hybridized in **6** (δ ^{11}B = 25.3 ppm).[11] Moreover, all ^{1}H and ^{13}C NMR spectra were sharp and well-resolved at 25 °C, indicating that dative B–N inversion, if any, was very slow compared to the NMR time scale. Upon warming to 55 °C, the ^{1}H NMR resonances for the OCH_2-CH_2N groups in **5** simplified toward apparent A_2X_2 patterns, suggestive of the onset of rapid B–N inversion.[11] The ^{1}H NMR spectrum of **4**, however, was unchanged at 55 °C, indicating that it remained locked as the datively bonded structure shown in Figure 2.

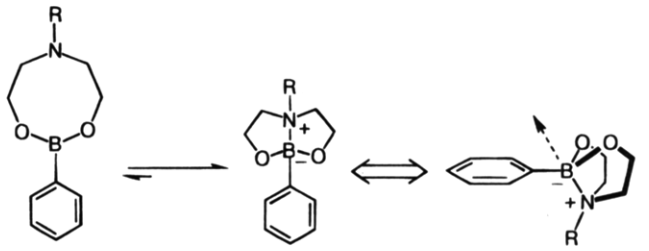

Figure 1. Structure of arylboronic acid bis(2-hydroxyethyl)-amine ester.

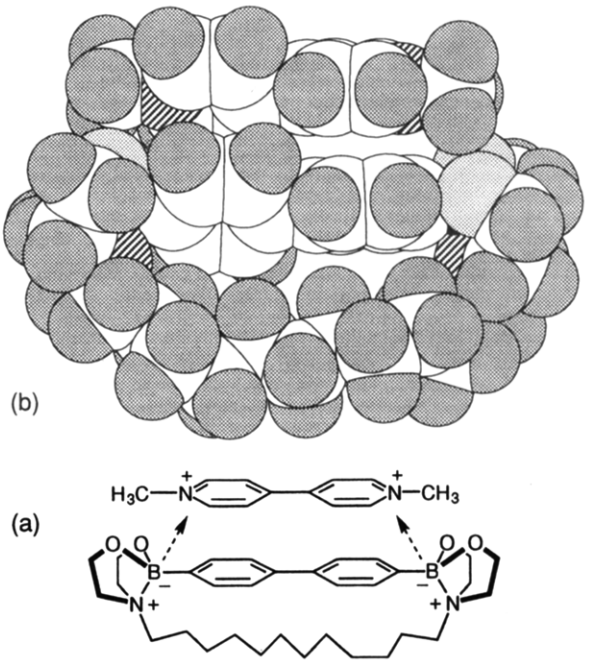

Figure 2. (a) Postulated **4**:**1** complex. (b) Computer-generated space-filling representation.

Binding Studies

The paraquat binding abilities of receptor **4** and control hosts **5**–**8** were determined in acetone. At sufficient concentrations, all host–guest solutions were yellow-orange, indicative of charge transfer interactions. However, due to the limited solubility of some of the hosts, UV–vis spectroscopy provided only a qualitative assessment of binding. Quantitative measurements were made by ^{1}H NMR titrations and subsequent iterative curve-fitting procedures.[15] Compared to the NMR time scale, the rates of host–guest association were very fast. As

(10) X-ray study of phenylboronic bis(2-hydroxyethyl)amine ester: Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1975**, *53*, 1392–1401.

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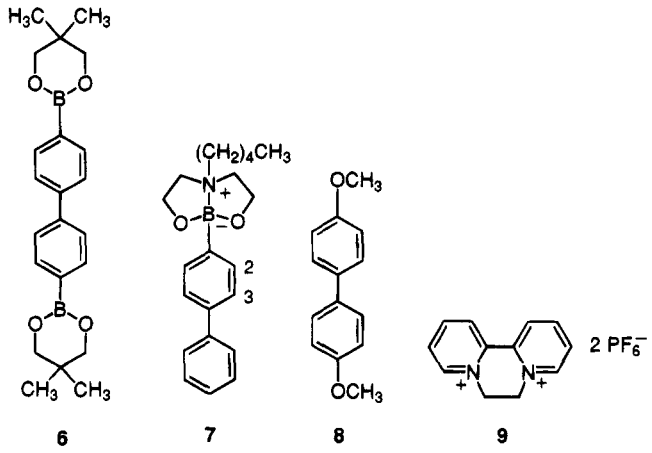
(13) Dative bonding increases the electron density on the boronate oxygens and increases their H-bonding abilities. Reetz, M. T.; Huff, J.; Goddard, R. *Tetrahedron Lett.* **1994**, *35*, 2521–2524.

(14) Coutts, I. G.; Goldschmid, H. R.; Musgrave, O. C. *J. Chem. Soc.* **1970**, 488–492.



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described in Table 1 and Figure 3, receptor **4** bound paraquat bishexafluorophosphate with an association constant of 320 ± 30 M^{-1}. Titrations curves for the H-2 and H-3 resonances in **4** fitted 1:1 binding models very well (Figure 3). A Job plot was also in favor of 1:1 binding as the dominant complex stoichiometry (Figure 4).[16] The upfield changes in chemical shifts for the aromatic signals of both host and guest are interpreted as evidence of an aromatic face-to-face orientation as the major binding structure.[17] An exactly parallel orientation, however, is not necessarily implied. As noted by others, $\pi-\pi$ stacking geometries are often characterized by tilts and displacements that optimize the out-of-plane electrostatic interactions of the participating π systems.[18] The magnitude of the complexation-induced shifts (−0.18 ppm) are significantly smaller than those observed for other paraquat binding systems such as the macrocyclic host **2** (∼−0.4 ppm).[5,6] The difference can be rationalized in terms of a "loosely bound" complex between paraquat and **4** with weak NMR shielding effects, as compared to a tighter, more oriented complex with **2** that results in stronger shielding.[19] Alternatively, the **4**:paraquat complex could be a rapidly converting mixture of face-to-face (major component) and edge-to-face (minor component) binding.[17] Unfortunately, numerous attempts at host–guest cocrystallization were unsuccessful in producing material suitable for X-ray analysis.

The less preorganized control receptor **5** was found to be a poorer paraquat binder with an association constant of 230 ± 20 M^{-1} (Figure 5). A Job plot (not shown) supported 1:1 binding.[16] Receptor **5** of course suffers because it can adopt either of the two low-energy conformations shown in Scheme 1: a high-affinity *syn* conformation with convergent dipoles or a low-affinity *anti* conformation with divergent dipoles.[20] Assuming no interaction between the two boronate groups, both con-

Table 1. Association Constants and $\Delta\delta_{max}$ Values from ^{1}H NMR Titrations in Acetone at 296 K

host	guest	K_{assn} (M^{-1})[a]	ΔG_{296} (kcal/mol)	$\Delta\delta_{max}$ (ppm)[b]
4	**1**	320	−3.4	−0.16,[c] −0.18[d]
5	**1**	230	−3.2	−0.15,[c] −0.14[d]
6	**1**	<5	>−1	
7	**1**	25	−1.9	−0.13,[c] −0.13[d]
8	**1**	<5	>−1	
4	**9**	120	−2.8	−0.11[c]
5	**9**	85	−2.6	−0.10[c]

[a] In most cases, K_{assn} is the average of values obtained from host H-2 and H-3 titration curves. All duplicate runs were within ±10%. [b] Derived for fully saturated host. [c] Host resonance H-2. [d] Host resonance H-3.

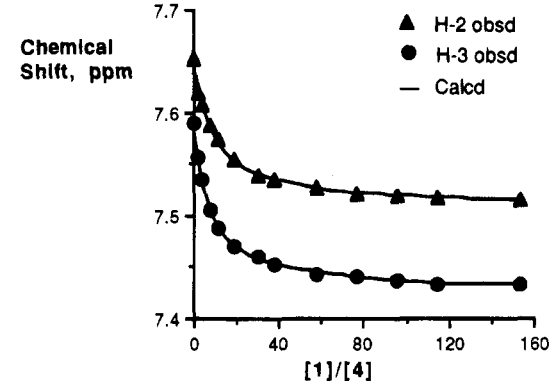


Figure 3. Chemical shifts for the H-2 and H-3 resonances of **4** as a function of added paraquat, **1**.

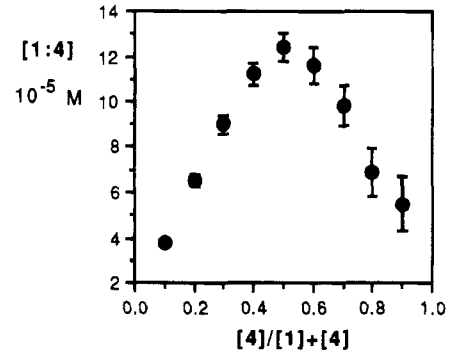


Figure 4. Job plot: [**1**:**4**] versus [**4**]/[[**1**] + [**4**]] at constant [**1**] + [**4**].

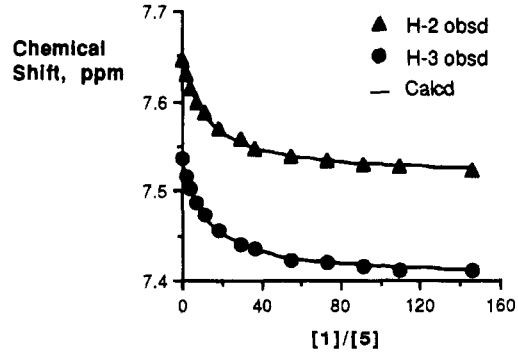


Figure 5. Chemical shifts for the H-2 and H-3 resonances of **5** as a function of added paraquat, **1**.

(15) (a) Conners, K. A. *Binding Constants, The Measurement of Molecular Complex Stability*; Wiley: New York, 1987. (b) Gil, V. M. S.; Olivera, N. C. *J. Chem. Ed.* **1990**, *67*, 472–478. (c) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: Weinham, 1991; pp 123–143.

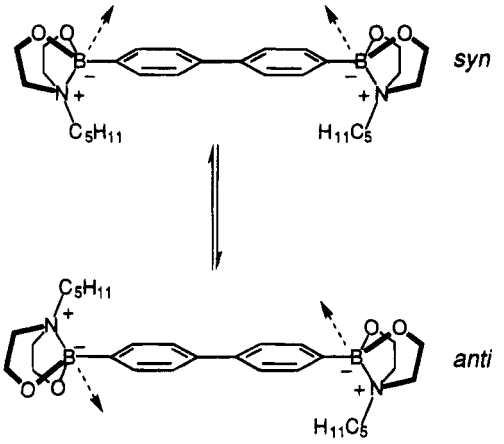
(16) All Job plots supported 1:1 binding; however, the associated error bars were quite large (due to the inherent uncertainties in measuring small changes in chemical shifts) and reflect the difficulty in applying Job's method to weakly bound complexes. Nowick, J. S.; Chen, J. S.; Noronha, G. *J. Am. Chem. Soc.* **1993**, *115*, 7636–7644.

(17) Face-to-edge binding can be ruled out as the major complex structure due to the absence of downfield shifts in one of the binding partners. For a discussion, see: Schneider, H. J.; Schiestel, T.; Zimmerman, P. *J. Am. Chem. Soc.* **1992**, *114*, 7698–7703. Hunter, C. A. *J. Am. Chem. Soc.* **1992**, *114*, 5303–5311. Hunter, C. A. *J. Chem. Soc., Chem. Commun.* **1991**, 749–751.

(18) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534.

(19) A reviewer has suggested that the weaker association of paraquat with **4** may be due to the fact that the boronate oxygens necessarily protrude above the plane of the aromatic rings (Figure 2), whereas the more flexible crown oxygens in **2** can allow closer aromatic ring approach.

Scheme 1



formations will be equally populated. This problem is eliminated in receptor **4** because the macrocycle enforces the convergent *syn* dipole relationship. ^{11}B NMR of receptors **4** and **5** in the presence of excess paraquat showed no guest-induced change in boron hybridization.

To probe the relative importance of the various contributors to host–guest binding, association constants were determined for a number of other control hosts. As summarized in Table 1, the trigonal diboronate ester **6** exhibited a very weak affinity for paraquat ($K_{assn} < 5$ M^{-1}). A similar association was obtained with the electron-rich 4,4′-dimethoxybiphenyl **8**. These results are in accord with previous studies that have found weak associations with simple electron-rich π-donors. For example, $K_{assn} \sim 0.5$ M^{-1} was recently reported for paraquat and 1,4-dimethoxybenzene in acetonitrile.[21] Thus the electrostatic components associated with the B–N dative bonds in **4** appear to have a major effect on host–guest binding. The importance of the ditopic nature of receptor **4** is highlighted by the much lower association ($K_{assn} = 25$ M^{-1}) obtained with the monotopic receptor **7**.[22] The guest selectivities of ditopic receptors **4** and **5** were probed by comparing their paraquat binding affinities with those for the structurally related diquat **9** (Table 1). In both cases, binding selectivities of 0.6 kcal/mol in favor of paraquat were obtained, emphasizing the directional nature of the oriented B–N dipoles.

In conclusion, a new type of neutral paraquat receptor has been described that takes advantage of the strong dipoles generated by dative B–N bonds. Although oriented dipoles are thought to play an important role in enzyme catalysis,[23] it is only recently that biomimetic chemists have begun to incorporate them within the structures of artificial catalysts.[24] Also, there have been some interesting recent reports of neutral anion receptors that utilize oriented dipoles.[8,25] Continued advances in these two research areas can be expected in the near future.

(20) The small decrease in binding energy accured upon moving to the less preorganized receptor is difficult to analyze with the data in hand. For a discussion on preorganization and enthalpy–entropy compensation in π-donor receptors, see: Zimmerman, S. C.; Mrksich, M.; Baloga, M. *J. Am. Chem. Soc.* **1989**, *111*, 8528–8530.

(21) Benniston, A. C.; Harriman, A. *J. Am. Chem. Soc.* **1994**, *116*, 11531–11537.

(22) For a discussion on bonding additivity in supramolecular chemistry, see: Schneider, H.-J. *Chem. Soc. Rev.* **1994**, *23*, 227–234.

(23) Fan, C.; Moews, P. C.; Walsh, C. T.; Knox, J. R. *Science* **1994**, *266*, 439–443. Lodi, P. J.; Knowles, J. R. *Biochemistry* **1993**, *32*, 4338–4343.

(24) Smith, P. J.; Kim, E.; Wilcox, C. S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1648–1650.

Experimental Section

General Methods. All materials obtained from commercial sources were reagent grade and used without further purification. ^{11}B, ^{1}H, and ^{13}C NMR chemical shifts are given in ppm relative to tetramethylsilane (TMS) or external boron trifluoride etherate (BF_3·OEt_2); coupling constants are quoted to ±0.5 Hz.

Cyclic 4,4′-Biphenyldiboronate Ester 4. Diethanolamine (37.4 mmol), 1,12-dibromododecane (19.7 mmol), ground potassium carbonate (37.4 mmol), and a catalytic amount of tetrabutylammonium iodide were combined in acetonitrile (120 mL) and heated at reflux for 18 h.[26] After filtration, the solvent was evaporated to afford *N,N,N′,N′*-tetrakis(2-hydroxyethyl)-1,12-dodecanediamine: yield 96%; mp 60–62 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.61 (8H, t, J = 5.5 Hz), 3.28 (2H, bs), 2.64 (4H, t, J = 5.5 Hz), 2.51 (4H, pseudo t, J = 7.5 Hz), 1.45 (4H, m), 1.26 (16H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 59.5, 56.0, 54.8, 29.4, 27.3, 26.8 ppm; FAB HRMS calcd for $C_{20}H_{44}O_2N_2$ [MH$^+$] 377.3379, found 377.3353. 4,4′-Biphenyldiboronic acid[14] (0.20 mmol) was treated with *N,N,N′,N′*-tetrakis(2-hydroxyethyl)-1,12-dodecanediamine (0.10 mmol) in benzene (250 mL) under Dean–Stark conditions for 18 h. The solution was decanted and evaporated to afford a tan gum. The mixture was purified using C_{18} reverse phase HPLC (flow rate = 7 mL/min, t_R = 5.4 min) using methanol as the eluent. The receptor **4** was precipitated as a white solid using dichloromethane/petroleum ether: yield 33%; mp 193–195 °C; ^{11}B NMR ($CDCl_3$, 96 MHz) δ 11.4 ppm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (4H, d, J = 8.0 Hz), 7.59 (4H, d, J = 8.0 Hz), 4.21 (8H, m), 3.03 (8H, m), 2.45 (4H, m), 1.46–0.50 (20H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.5, 133.5, 125.6, 63.1, 59.7, 57.7, 29.6, 27.6, 26.7, 18.1, 14.1 ppm; FAB HRMS calcd for $C_{32}H_{48}O_4N_2B_2$ [MH$^+$] 547.3878, found 547.3873.

Acyclic 4,4′-Biphenyldiboronate Ester 5. Diethanolamine (18.7 mmol), 1-bromopentane (19.7 mmol), ground potassium carbonate (18.7 mmol), and a catalytic amount of tetrabutylammonium iodide in acetonitrile (60 mL) were heated at reflux for 18 h.[26] After filtration and evaporation, the residue was distilled to give *N,N*-bis(2-hydroxyethyl)-1-pentanamine as a clear oil: yield 80%; bp 140 °C/0.15 mmHg; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.56 (4H, t, J = 6.0 Hz), 3.41 (2H, bs), 2.60 (4H, t, J = 6.0 Hz), 2.47 (2H, t, J = 7.5 Hz), 1.40 (2H, m), 1.24 (4H, m), 0.85 (3H, t, J = 6.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 59.5, 56.0, 54.7, 29.4, 26.5, 22.5, 13.9 ppm; FAB HRMS calcd for $C_9H_{21}O_2N$ [MH$^+$] 176.1651, found 176.1644. To compound **6**[14] (2.6 mmol) in chloroform (20 mL) was added *N,N*-bis(2-hydroxyethyl)-1-pentanamine (6.6 mmol) in 2-propanol (5 mL). Ether (75 mL) was added, and the partially heterogeneous solution was vigorously stirred for 18 h, during which time compound **5** formed as a white precipitate: yield 94%; mp 250–251 °C; ^{11}B NMR ($CDCl_3$, 96 MHz) δ 11.3 ppm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (4H, d, J = 8.0 Hz), 7.59 (4H, d, J = 8.0 Hz), 4.19 (8H, m), 3.05 (8H, m), 2.36 (4H, m), 1.51 (4H, m), 1.23 (4H, m), 1.09 (4H, m), 0.82 (6H, t, J = 7.5 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.4, 133.6, 125.8, 63.1, 59.8, 57.2, 29.0, 24.6, 22.3, 13.7 ppm; FAB HRMS calcd for $C_{30}H_{46}O_4N_2B_2$ [MH$^+$] 521.3733, found 521.3741.

4-Biphenylboronate Ester 8. Butyllithium (2.5 M, 5 mmol) was added dropwise at −78 °C to a solution of 4-bromobiphenyl (3.4 mmol) in THF. After 7 h at −78 °C, the solution was treated with trimethyl borate (10 mmol) and allowed to warm to room temperature over 18 h. The reaction was quenched with 20% HCl (5 mL) and partitioned between ethyl acetate (40 mL) and 10% NaOH (40 mL). Acidification of the aqueous layer provided the 4-biphenylboronic acid as a white precipitate: yield 58%; mp 254–260 °C; ^{1}H NMR (DMSO-d_6/10% D_2O, 500 MHz) δ 7.86 (2H, d, J = 8.0 Hz), 7.66

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(2H, d, J = 8.0 Hz), 7.62 (2H, d, J = 8.0 Hz), 7.45 (2H, t, J = 7.5 Hz), 7.53 (1H, t, J = 7.5 Hz) ppm; ^{13}C NMR (DMSO-d_6/10% D_2O, 125 MHz) δ 141.8, 140.2, 134.9, 129.1, 127.7, 126.8, 125.8 ppm; FAB HRMS (glycerol matrix) calcd for $C_{15}H_{16}O_3B$ [MH^+ + glycerol] 255.1195, found 255.1175. Treatment of 4-biphenylboronic acid (0.16 mmol) with *N,N*-bis(2-hydroxyethyl)-1-pentanamine (0.16 mmol) in benzene (70 mL) under Dean–Stark conditions for 18 h yielded boronate ester **8**: yield >95%; mp 126–127 °C; ^{11}B NMR ($CDCl_3$, 96 MHz) δ 11.5 ppm; ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.67 (2H, d, J = 8.0 Hz), 7.63 (2H, d, J = 8.0 Hz), 7.50 (2H, d, J = 8.0 Hz), 7.419 (2H, t, J = 7.5 Hz), 7.29 (1H, t, J = 7.5 Hz), 4.04 (4H, m), 3.20 (4H, m), 2.36 (2H, m), 1.61 (2H, m), 1.18 (2H, m), 1.03 (2H, m), 0.77 (3H, t, J = 7.5 Hz) ppm; ^{13}C NMR (acetone-d_6, 125 MHz) δ 142.6, 140.1, 135.0, 129.5, 127.6, 127.4, 126.0, 63.8, 61.1, 58.2, 25.1, 22.9, 14.0 ppm; FAB HRMS calcd for $C_{21}H_{28}O_2NB$ [MH^+] 338.2291, found 338.2289.

Paraquat and Diquat Bis(hexafluorophosphate) Salts. The organic soluble bis(hexafluorophosphate) salts of paraquat **1** and diquat **9** were prepared from the corresponding chloride and bromide salts according to the procedure of Elliot and Hershenhart.[27]

Binding Studies. ^{1}H NMR Titrations.[15] Twelve to fifteen aliquots of a 60 mM stock guest solution (bis(hexafluorophosphate) salts of paraquat or diquat in acetone) were added to 700 μL of acetone solution of 0.35 mM host in a 5 mm NMR tube. By the end of the titration, the guest:host ratio was around 150. The chemical shifts of the host aryl protons were monitored, relative to TMS, as a function of added guest. The determinations were repeated using independent stock solutions, and several titrations were performed with each stock solution. All titration curves were well-fit by 1:1 binding isotherms produced by nonlinear curve-fitting procedures.[15c] In all cases, K_{assn} and $\Delta\delta_{max}$ could be reproduced to within ±10%.

Job Plots.[15,16] To nine 5 mm NMR tubes were added aliquots of 1 mM host and guest stock acetone solutions in the following ratios, such that the total volume always equaled 1 mL: 1.0:0.0, 0.9:0.1, 0.8:0.2, 0.7:0.3, 0.6:0.5, 0.5:0.5, 0.4:0.6, 0.3:0.7, 0.2:0.8, and 0.1:0.9. The changes in chemical shifts for the host and guest aryl protons were monitored relative to TMS.

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Supporting Information Available: ^{1}H NMR spectra of **4** and **5** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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