A Macrobicyclic Receptor with Versatile Recognition Properties: Simultaneous Binding of an Ion Pair and Selective Complexation of Dimethylsulfoxide

Martin J. Deetz, Maoyu Shang, and Bradley D. Smith*

Contribution from the Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556-5670

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Abstract: A bicyclic receptor was synthesized and evaluated for its ability to bind alkali halide salts and polar neutral molecules in organic solvents. The receptor design is relatively straightforward in the sense that it is a combination of a dibenzo-18-crown-6 and a bridging 1,3-phenyldicarboxamide. In the presence of 1 mol equiv of metal cation, chloride affinities are enhanced in the order: K^+ (9-fold enhancement) > Na^+ (8-fold enhancement) ≫ Cs^+ (no enhancement). An X-ray crystal structure shows that the receptor binds sodium chloride as a solvent-shared ion pair. The receptor has very weak affinity for acetonitrile, nitromethane, or acetone in chloroform solvent, whereas the association constant for dimethylsulfoxide is 160 M^{-1} at 295 K. An X-ray crystal structure shows that the dimethylsulfoxide is bound deeply in the receptor cavity and forms hydrogens bonds to the receptor via a bridging water molecule. There is also evidence for CH−O interactions. Solid−liquid extraction studies show that the receptor can dissolve and associate with urea, primary amides, and primary sulfonamides in $CDCl_3$ but does not dissolve amino acids.

Introduction

An ongoing enterprise in supramolecular chemistry is the design, synthesis, and study of low-molecular weight receptor compounds with convergent functionality.[1] Such receptors exhibit a range of interesting and potentially useful molecular recognition properties. Most of the earliest examples were homoditopic receptors that contained two identical binding sites connected by a linker.[2] These compounds can chelate a structurally symmetric guest or alternatively bind two very similar guests simultaneously. More recently, attention has turned to heteroditopic receptors that contain two quite different binding sites, for example a Lewis acidic site and Lewis basic site.[1−3] These compounds are able to bind a single heteroditopic guest or simultaneously bind two non-identical guests. The invention of convergent heteroditopic hosts is a challenging problem in molecular design because the binding sites have to be incorporated into a suitably preorganized scaffold that holds them in close proximity, but not so close that the sites interact.

In this contribution we describe the design and synthesis of bicyclic receptor **1** (Figure 1), as well as an evaluation of its molecular recognition properties. The design of receptor **1** is relatively straightforward in the sense that it is a combination of two well-studied binding systems; a dibenzo-18-crown-6 (B_2-18-C-6),[4] and a bridging 1,3-phenyldicarboxamide.[5] The key structural feature that allows these binding sites to be easily incorporated into a highly preorganized bicycle is the known preference of *N*-methylanilides to adopt a *syn* conformation.[6] Although this conformational effect has been recognized for some time, it is rarely exploited by synthetic chemists as a way of producing convergent or juxtaposed binding sites.[7]

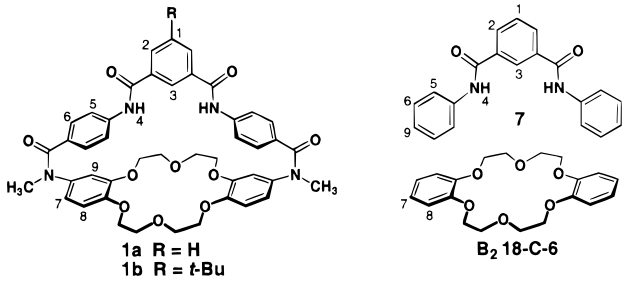

Figure 1. Macrobicyclic receptor **1** and control mixture **7**/$B_2$18-C-6 with hydrogen numbering scheme.

We find that bicycle **1** is a versatile receptor for a range of salt and neutral molecule guests. Analysis of the supramolecular complexes using solution-state NMR and X-ray crystallography shows the basis for the molecular recognition and suggests how next-generation receptors may be developed as useful molecular devices.

* Corresponding author. Telephone: 219-631-8632. Fax: 219-631-6652. E-mail: smith.115@nd.edu.

(1) (a) Schneider, H. J.; Yatsimirski, A. *Principles and Methods in Supramolecular Chemistry*; Wiley: Somerset, 2000. (b) Lehn, J. M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.

(2) For reviews of ditopic receptors for cations, see: Sutherland, I. O. In *Advances in Supramolecular Chemistry*; Gokel, G. W., Ed.; JAI Press: Greenwich, 1990; Vol. 1, 65−108. For anions, see: Sessler, J. L.; Sabsom, P. I.; Andrievsky, A.; Král, V. In *The Supramolecular Chemistry of Anions*; Bianci, A., Bowman-James, K., Carcia-Espana, E., Eds.; VCH: Weinheim, 1997; 355−420. For neutral molecules, see: Webb, T. H.; Wilcox, C. S. *Chem. Soc. Rev.* **1993**, *22*, 383−395.

(3) Reetz, M. T. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Gokel, G. W., Eds.; Pergamon: Oxford, 1996; Vol. 2, 553−562.

(4) *Cation Binding by Macrocycles*; Inoue, Y., Gokel, G. W., Eds.; Marcel Dekker: New York, 1990.

(5) (a) Kavallieratos, K.; Bertao, C. M.; Crabtree, R. H. *J. Org. Chem.* **1999**, *64*, 1675−1683. (b) Hübner, G. M.; Gläser, J.; Seel, C.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 383−386. (c) Hughes, M. P.; Smith, B. D. *J. Org. Chem.* **1997**, *62*, 4492−4501. (d) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369−370.

(6) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649−10650.

(7) Krebs, F.; Larsen, M.; Jørgensen, M.; Jensen, P. R.; Bielecki, M.; Schaumburg, K. *J. Org. Chem.* **1998**, *63*, 9872−9879.

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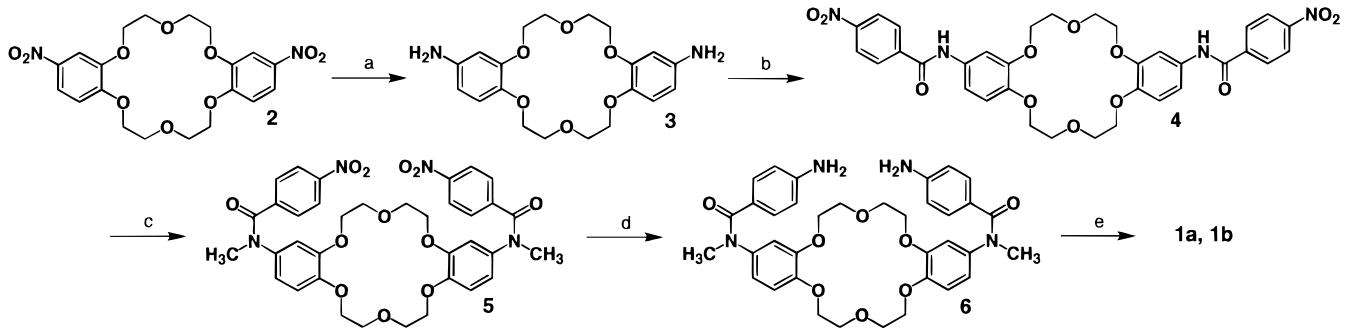
Scheme 1[a]



[a] (a) H_2 (30psi), Pd−C, DMF, 98%, (b) 4-nitrobenzoyl chloride, Et_3N, CH_2Cl_2, 99%, (c) NaH, CH_3I, DMF, 99%, (d) Fe (powder), HCl, 81%, (e) corresponding isophthaloyl dichloride, Et_3N, CH_2Cl_2, 55−75 %.

Table 1. Change in Receptor ^{1}H NMR Chemical Shifts ($\Delta\delta$) upon Guest Extraction

			$\Delta\delta$ (ppm)[a]								
receptor	guest	solvent	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1a	KCl	DMSO-d_6	−0.035	−0.085	0.020	1.028	0.353	0.008	0.038	0.066	0.149
7 + **$B_2$18-C-6**	KCl	DMSO-d_6	0.016	0.002	0.238	0.280	0.105	0.011	0.065	0.079	0.035
1b	toluenesulfonamide	$CDCl_3$	-	−0.011	−0.387	−0.206	0.066	0.072	0.040	−0.038	0.035
1b	toluamide	$CDCl_3$	-	0.064	−0.395	0.130	0.139	0.059	−0.051	−0.094	0.006
1b	urea	$CDCl_3$	-	0.032	0.177	0.498	0.126	0.000	−0.080	−0.072	0.015
1b	L-alanine	$CDCl_3$	-	0.014	0.028	0.000	0.037	0.019	−0.003	0.005	−0.010
1b	L-phenylalanine	$CDCl_3$	-	0.016	0.015	0.029	0.013	0.017	0.007	0.004	0.006

[a] See Figure 1 for hydrogen numbering scheme.

Results and Discussion

Synthesis. The syntheses of receptor analogues **1a** and **1b** are described in Scheme 1. The synthetic pathway is notable because it is short, high yielding, amenable to scale-up, and highly flexible in terms of structural modification. The pathway begins with a double nitration of dibenzo-18-crown-6. The product is an almost equal mixture of *cis* and *trans* isomers which can be readily separated by fractional crystallization.[8] For this intitial study the *cis* isomer, **2**, was chosen to continue the synthesis, however, it is anticipated that the *trans* isomer will eventually be utilized as a diastereomeric analogue. Catalytic hydrogenation of the nitro groups affords the corresponding diamine, **3**, which is subsequently coupled with 4-nitrobenzoyl chloride. *N*-Methylation is achieved in DMF using sodium hydride and iodomethane to produce **5** in excellent yield. Catalytic hydrogenation of **5** is not a clean reaction, while reduction with iron powder in HCl produces **6** in very good yield. Finally, ring closure to produce **1a** or **1b** is achieved in 55−75% yield by reaction of **6** with the appropriate isophthaloyl dichloride under dilute conditions. The success of the ring closure reaction is attributed to the highly preorganized conformation adopted by the precursor **6**.

Salt Binding. [9−11] Receptor **1a** was initially examined by ^{1}H NMR for its ability to extract solid KCl into DMSO solution. The changes in receptor chemical shifts (Table 1) are consistent with formation of a rapidly exchanging receptor−salt complex. The largest change is a downfield movement of 1.03 ppm for the receptor NH protons which is indicative of hydrogen bonding with a guest chloride ion.[12] Comparison of the NH $\Delta\delta$ with the solution-state values in Table 2 indicates that receptor **1a** extracts an almost stoichiometric amount of KCl into DMSO. The solution of **1a** and extracted KCl was also analyzed by mass spectrometry. A positive ion FAB mass spectrum showed a peak at *m*/*z* 825 corresponding to the [**1a**·K]$^+$ complex, while a negative ion FAB spectrum exhibited peaks at *m*/*z* 785 [**1a**-H]$^-$, 821 [**1a**·Cl]$^-$, and 859 [**1a**·KCl−H]$^-$. No higher binding stoichiometries were observed. The solid−liquid extraction experiment was repeated using a control mixture of diamide **7**[5a] and $B_2$18-C-6 (Figure 1). The smaller changes in receptor chemical shifts (Table 1) reflect a lower extent of receptor complexation.[13] Thus, the covalently connected heteroditopic receptor **1a** is the superior salt extractant.

(8) Feigenbaum, W. M.; Michel, R. H. *J. Polym. Sci., Part A: Polym. Chem.* **1971**, 817−820.

(9) Reviews that discuss salt-binding receptors: (a) Antonisse, M. M. G.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1998**, 443−448. (b) Kimura, E.; Koike, T. *J. Chem. Soc., Chem. Commun.* **1998**, 1495−1500. (c) Stibor, I.; Hafeed, D. S. M.; Lhotak, P.; Hodacova, J.; Koca, J.; Cajan, M. *Gazz. Chim. Ital.* **1997**, *127*, 673−685. (d) Reference 3.

(10) Earlier examples of salt-binding receptors: (a) Tsukube, H. *Tetrahedron Lett.* **1981**, *22*, 3981−3985. (b) Tsukube, H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2359−2364. (c) Zinic, M.; Frkanec, L.; Skaric, V.; Trafton, J.; Gokel, G. W. *J. Chem. Soc. Chem. Commun.* **1990**, 1726−1728. (d) Olsher, U.; Frolow, F.; Dalley, N. K.; Weiming, J.; Yu, Z. Y.; Knoleoch, J. M.; Bartsch, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 6570−6574. (e) Reetz, M. T.; Niemeyer, C. M.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1474−1476. (f) Arafa, E. A.; Kinnear, K. I.; Lockhart, J. C. *J. Chem. Soc. Chem. Commun.* **1992**, 61−64. (g) Petit, W.; Iwai, Y.; Barfknecht, C. F.; Swenson, D. C. *J. Heterocycl. Chem.* **1992**, *29*, 877−881. (h) Flack, S. S.; Chaumette, J.-L.; Kilburn, J. D.; Langley, G. J.; Webster, M. *J. Chem. Soc. Chem. Commun.* **1993**, 399−400. (i) Badouche, S.; Jaquet, L.; Lobo-Recio, M. A.; Marzin, C.; Tarrago, G. *J. Inclusion Phenom.* **1993**, *138*, 16, 81−89. (j) Kinnear, K. I.; Mousley, D. P.; Arafa, E.; Lockhart, J. C. *J. Chem. Soc., Dalton Trans.* **1994**, 3637−3643. (k) Rudkevich, D. M.; Brzozka, Z.; Palys, M.; Visser, H. C.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 467−469. (l) Savage, P. B.; Holmgren, S. K.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 4069−4070. (m) Nagasaki, T. Fujishima, H.; Takeuchi, M.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1883−1888. (n) Rudkevich, D. M.; Merca-Chalmers, J. D.; Verboom, W.; Ungaro, R.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 6124−6124. (o) Kim, Y. H.; Calabrese, J. McEwen, C. *J. Am. Chem. Soc.* **1996**, *118*, 1545−1546. (p) Voyer, N.; Guérin, B. *J. Chem. Soc., Chem Commun.* **1997**, 2329−2330. (q) Nabeshima, T.; Hasiguchi, A.; Yazawa, S.; Haruyama, T.; Yano, Y. *J. Org. Chem.* **1998**, *63*, 2788−2789. (r) Beer, P. D.; Dent, S. W. *J. Chem. Soc., Chem. Commun.* **1998**, 825−826. (s) Cooper, J. B.; Beer, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 129−130. (t) Pelizzi, N.; Casnati, A.; Friggeri, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1307−1311. (u) Redman, J. E.; Beer, P. D.; Dent, S. W.; Drew, M. G. D. *J. Chem. Soc., Chem. Commun.* **1998**, 231−232. (v) Bryan, J. C.; Sachlebon, R. A.; Lavis, J. M.; Davis, M. C.; Burns, J. H.; Hay, B. P. *Inorg. Chem.* **1998**, *37*, 2749−2755.

Table 2. Anion Association Constants (M^{-1}) and NH $\Delta\delta_{Max}$ (ppm)[a]

anion[b]	**1a**	**1a** + Na^{+c}	**1a** + K^{+c}	**1a** + Cs^{+c}
Cl^-	50 (0.93)	410 (1.16)	470 (1.28)	60 (0.95)
Br^-	9 (0.18)		27 (0.38)	
I^-	$\ll$1 (<0.01)		11 (0.03)	

[a] T = 295 K, [**1a**] = 10 mM in DMSO-d_6/CD_3CN (3:1) in the presence or absence of 1 mol equiv of metal cation. Association constants are the average of all receptor protons which exhibited significant complexation-induced shifts; uncertainty ±15%. The $\Delta\delta_{max}$ values are in parentheses and represent the change in NH chemical shift after 10 equiv of added anion. [b] As tetrabutylammonium salt. [c] As tetraphenylborate salt.

A solution-phase complexation study was undertaken to determine if receptor **1a** exhibits binding cooperativity. Experimentally, this was achieved by measuring the effect of alkali cations on the receptor binding affinities for halide anions. Anion binding constants were determined using standard ^{1}H NMR titration methods.[14] First, solutions of **1a** in DMSO-d_6/CD_3CN (3:1) were titrated with the tetrabutylammonium salts of Cl^-, Br^-, and I^-. The tetrabutylammonium cation is a highly diffuse cation and does not bind to crown ethers.[4] Thus, the binding constants observed with the tetrabutylammonium salts are reflective of receptor/anion affinity. As expected, the receptor amide NH signal underwent large downfield changes in chemical shift upon anion complexation. Other receptor protons also exhibited significant complexation-induced shifts. The resulting titration isotherms fitted nicely to a 1:1 binding model using established iterative curve-fitting methods.[5c,14,15] As described in Table 2, the order of anion binding constants for host **1a** is $Cl^- > Br^- \gg I^-$, a trend that is consistent with that observed by previous workers using simpler 1,3-phenyldicarboxamide hosts.[5,12] The titrations were repeated in the presence of 1 mol equiv of either Na^+, K^+, or Cs^+ tetraphenylborate. The NH titration curves generated upon addition of tetrabutylammonium chloride to solutions of **1a** in the presence and absence of potassium tetraphenylborate are shown in Figure 2.

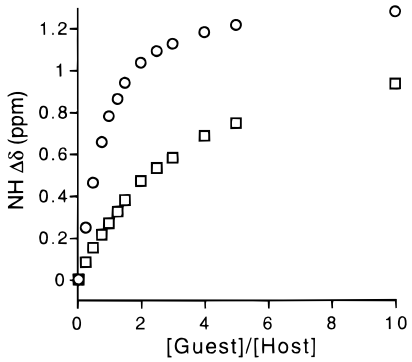


Figure 2. Change in NH chemical shift (NH $\Delta\delta$) for receptor **1a** (10 mM) in DMSO-d_6/CD_3CN (3:1) at 295 K as a function of increasing amounts of tetrabutylammonium chloride: (□) absence of potassium tetraphenylborate; (○) presence of 10 mM potassium tetraphenylborate.

In the presence of 1 mol equiv of metal cation, the chloride affinities were enhanced in the following order: K^+ (9-fold enhancement) > Na^+ (8-fold enhancement) ≫ Cs^+ (no enhancement) (Table 2). The enhancement in Cl^- binding constant induced by the presence of K^+ is almost the same as that induced by Na^+ which reflects the fact that in polar aprotic solvents such as DMSO and acetonitrile, dibenzo-18-crown-6 derivatives have about the same affinity for these two metal cations.[16,17] The largest cooperative effect occurs when K^+ is present during the titration with I^- (Table 2). This agrees with a trend that cation-induced cooperative effects increase as the anion becomes less basic.[10t,11a,18] A rationalization of this correlation will be provided elsewhere.[18]

Additional information concerning the receptor binding behavior is gained from the solid-state structure of a **1a**·NaCl complex (Figure 3). Single crystals were obtained from a solution of **1a**, tetrabutylammonium chloride, and sodium tetraphenylborate in chloroform/methanol/water solvent. X-ray analysis shows that a Na^+ is complexed within the dibenzo-18-crown-6 with average Na−O distances of 2.67 Å. The Na^+ is also coordinated by an axial water molecule. A Cl^- is hydrogen-bonded to the two receptor NH residues (Cl−N distances are 3.34 and 3.31 Å; N−H−Cl angles are 152° and 177°) on the *exo* face of the bridging 1,3-phenyldicarboxamide such that the distance between the complexed Na^+ and Cl^- ions is 7.31 Å. The central cavity of the macrocycle contains either a chloroform molecule (62% relative occupancy), or two water molecules (38% relative occupancy) that are not shown. The molecular dipole of the chloroform is aligned with the dipole generated by the **1a**·NaCl complex. Thus, in the solid-state, receptor **1a** prefers to bind NaCl as a solvent-shared ion pair.[19] It is worth noting that Moyer and co-workers recently described a tetrabenzo-24-crown-8 host that binds cesium nitrate as a solvent-separated ion pair.[11m] It is possible that many salt-binding systems work this way, and it may be useful to consider this feature in future receptor designs.

Neutral Molecule Binding. During the above NMR titration studies, we noticed that receptor **1a** appeared to associate

(11) Recent examples of salt-binding receptors: (a) Beer, P. D.; Hopkins, P. K.; McKinney, J. D. *J. Chem. Soc., Chem. Commun.* **1999**, 1253−1254. (b) Kubik, S. *J. Am. Chem. Soc.* **1999**, *121*, 5846−5855. (c) Barboiu, M. D.; Hovnanian, N. D.; Luca, C.; Cot, L. *Tetrahedron* **1999**, *55*, 9221−9232. (d) Chrisstoffels, L. A. J.; De Jong, F.; Reinhoudt, D. N.; Sivelli, S.; Gazzola, L.; Casnati, A.; Ungaro, R. *J. Am. Chem. Soc.* **1999**, *121*, 10142−10151. (e) White, D. J.; Laing, N.; Miller, H.; Parsons, S.; Coles, S.; Tasker, P. A. *J. Chem. Soc., Chem. Commun.* **1999**, 2077−2078. (f) Lutzen, A.; Rebslo, A. R.; Schalley, C. A.; O'Leary, B. M.; Rebek, J. *J. Am. Chem. Soc.* **1999**, *121*, 7455−7456. (g) Kubik, S.; Goddard, R. *J. Org. Chem.* **1999**, *64*, 9475−9486. (h) De Wall, S.; Barbour, L. J.; Gokel, G. W.; *J. Am. Chem. Soc.* **1999**, *121*, 8405−8406. (i) Meadows, E. S.; De Wall, S. L.; Barbour, L. J.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.* **1999**, 1557−1558. (j) Bartoli, S.; Roelens, S. *J. Am. Chem. Soc.* **1999**, *121*, 11908−11909. (k) Teramae, N.; Shigemori, K.; Nishizawa, S. *Chem. Lett.* **1999**, 1185−1186. (l) Andrisano, V.; Gottarelli, G.; Masiero, S.; Heijne, E. H.; Pieraccini, S.; Spada, G. P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2386-2388. (m) Levitskaia, T. G.; Bryan, J. C.; Saclebon, R. A.; Lamb, J. D.; Moyer, B. A. *J. Am. Chem. Soc.* **2000**, *122*, 554−562. (n) Kavallieratos, K.; Sachleben, R. A.; Van Berkel, G. J.; Moyer, B. A. *J. Chem. Soc., Chem. Commun.* **2000**, 187−188.

(12) The fact that **1b** is a selective receptor for DMSO explains a couple of curious observations concerning its anion binding ability. First the anion association constants determined for **1a** in DMSO (Table 2) are unusually low.[5] This is because the DMSO is more than just a polar solvent, it directly competes for the receptor binding site. This also explains why the NH $\Delta\delta$ values upon anion binding are also relatively small;[5a] the binding of anion to **1a** in DMSO involves displacement of a hydrogen-bonded DMSO molecule, and thus the receptor NH chemical shift is not greatly changed.

(13) A control titration of **7** with $N(Bu)_4Cl$ in DMSO shows that the NH signal for **7** moves about 0.7 ppm downfield when it is saturated with Cl^-. Thus, the NH $\Delta\delta$ of 0.28 ppm observed upon treatment of a DMSO solution of **7**/$B_2$18-crown-6 with excess solid KCl (Table 1) indicates that the **7**/$B_2$18-crown-6 mixture extracts about 0.4 mol equiv of KCl.

(14) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072−7080.

(15) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: Weinham, 1991; 123−143.

(16) De Jong, F.; Reinhoudt, D. N. In *Advances in Physical Organic Chemistry*; Gold, V., Bethell, D., Eds.; Academic Press: London, 1980; p 307.

(17) Hofmanova, A.; Koryta, J.; Brezina, M.; Mittal, M. L. *Inorg. Chim. Acta* **1978**, *28*, 73−80.

(18) Shukla, R.; Kida, T.; Smith, B. D. Unpublished results.

(19) Muller, P. *Pure Appl. Chem.* **1994**, *66*, 1077−1184.

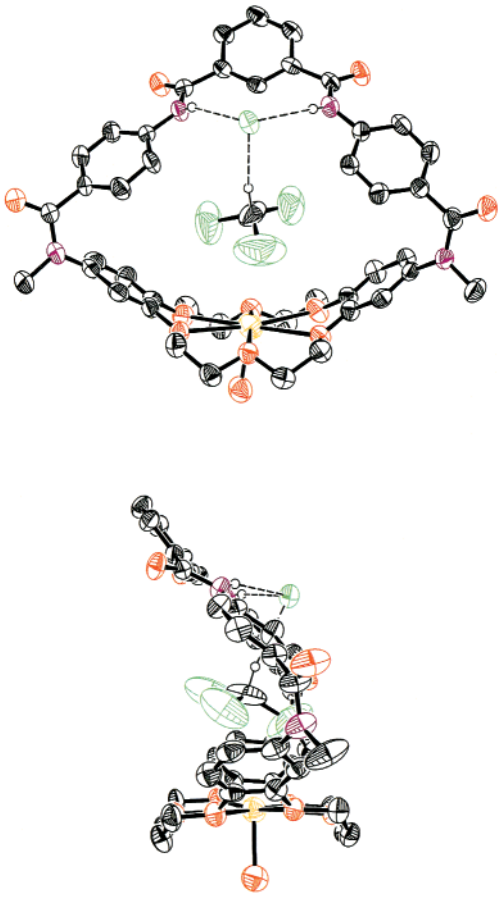


Figure 3. Front and side views of the X-ray crystal structure of [**1a**·Na^+·$CHCl_3$·Cl^-] showing 50% probability ellipsoids. Absent are disordered solvent molecules found in the lattice voids away from the macrocyclic cavity.

strongly with the DMSO cosolvent.[12] Although the literature contains a number of crystal structures of compounds complexed with DMSO,[20] to the best of our knowledge there is no example of a receptor that selectively binds DMSO in organic solution.[21] Therefore, the chloroform-soluble analogue **1b** was prepared and examined by ^{1}H NMR for its ability to associate with polar aprotic guests. Titration isotherms were generated and fitted to a 1:1 binding model using iterative curve fitting methods.[5c,14,15] As reflected by Figure 4, receptor **1b** is unusually selective for DMSO in $CDCl_3$ solution. Crown ethers typically have a higher affinity for acetonitrile and nitromethane than for DMSO,[22] but in this case the trend is strongly reversed (Table 3). The complexation-induced shifts indicate deep inclusion of the DMSO into the receptor cavity. For example, the NH signal for **1b** moves 0.38 ppm downfield upon saturation with DMSO guest, and conversely, the DMSO methyl signal is 0.21 ppm upfield

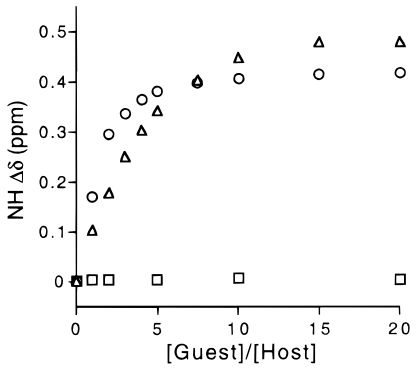


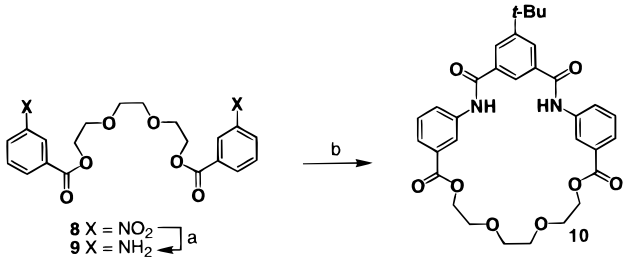
Figure 4. Change in NH chemical shift (NH $\Delta\delta$) for receptor **1b** (10 mM) in $CDCl_3$ at 295 K as a function of increasing amounts of: (○) DMSO; (□) acetone; (△) methylphenylsulfoxide.

Table 3. Association Constants, K_a, and NH $\Delta\delta_{max}$

receptor/guest	K_a (M^{-1})[a]	$\Delta\delta_{max}$ (ppm)[b]
1b/DMSO (1.3 mM H_2O)	160	0.38
1b/DMSO (5 mM H_2O)	160	0.38
1b/DMSO (15 mM H_2O)	150	0.38
1b/methylphenyl sulfoxide	30	0.48
1b/dimethyl sulfone	9	−0.29
1b/acetonitrile	2	−0.17
1b/nitromethane	<1	<−0.1
1b/acetone	≪1	<0.01
1b/malononitrile	*c*	*c*
10/DMSO	70	0.23

[a] In $CDCl_3$, T = 295 K, [receptor] = 10 mM. Association constants are the average of all receptor protons which exhibited significant complexation-induced shifts; uncertainty ±20%. [b] The change in chemical shift of the NH protons after 20 equiv of added guest. [c] Precipitate formed.

Scheme 2[a]



[a] (a) H_2 (30psi), Pd−C, THF, 100%, (b) 5-*tert*-butylisophthaloyl dichloride, Et_3N, THF, 59%.

when it is saturated with receptor. Further evidence in favor of a heteroditopic interaction is the observation that control macrocycle **10** (Scheme 2) binds DMSO with less than half of the affinity of **1b** (Table 3). In this case, the DMSO methyl signal is essentially unchanged when it is saturated with receptor **10**.

Additional binding information was gained from an X-ray crystal structure of the **1a**·DMSO complex (Figure 5). The structure shows that the DMSO is located at a definite position inside the receptor cavity, but the sulfur atom is disordered between two sites on either side of the triangle formed by the oxygen and the two carbon atoms. The DMSO oxygen is hydrogen-bonded to a water molecule (O−O distance of 2.64 Å) that in turn is hydrogen-bonded to the host NH residues (O−N distances are 3.08 and 2.98 Å; N−H−O angles are both 177°). One of the DMSO methyl groups is bonded to the crown ether through a set of C−H−O interactions (average C−O distances of 3.41 Å)[20a] and resides in the shielding cone of the crown benzo groups, while the other methyl points away from the host cavity.

(20) (a) Wijaya, K.; Moers, O.; Blaschette, A.; Jones, P. G. *Acta Crystallogr.*, **1998**, *C54*, 1707−1710. (b) Bhattacharyya, P.; Slawin, A. M. Z.; Smith, M. B.; Williams, D. J.; Woollins, J. D. *J. Chem. Soc., Dalton Trans.* **1996**, 3647−3651. (c) Helgeson, R. C.; Paek, K.; Knobler, C. B.; Maverick, E. F.; Cram, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5590−5604. (d) Daitch, C. E.; Hampton, P. D.; Duesler, E. N. *Inorg. Chem.* **1995**, *34*, 5641−5645. (e) Reichwein, A. M.; Verboom, W.; Harkema, S.; Spek, A. L.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1167−1172. (f) Furphy, B. M.; Harrowfield, H. J. M.; Ogden, M. I.; Skelton, B. W.; White, A. H.; Wilner, F. R. *J. Chem. Soc., Dalton Trans.* **1989**, 2217−2221. (g) Harata, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1644−1648.

(21) Binding of DMSO in *aqueous* solvent has been reported: Fujimoto, T.; Yanagihara, R.; Kobayashi, K.; Aoyama, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2113−2124.

(22) (a) Izatt, R. M.; Bradshaw, J. S.; Pawlak, K.; Bruening, R. L.; Tarbet, B. J. *Chem. Rev.* **1992**, *92*, 1261−1354. (b) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1995**, *95*, 2529−2586.

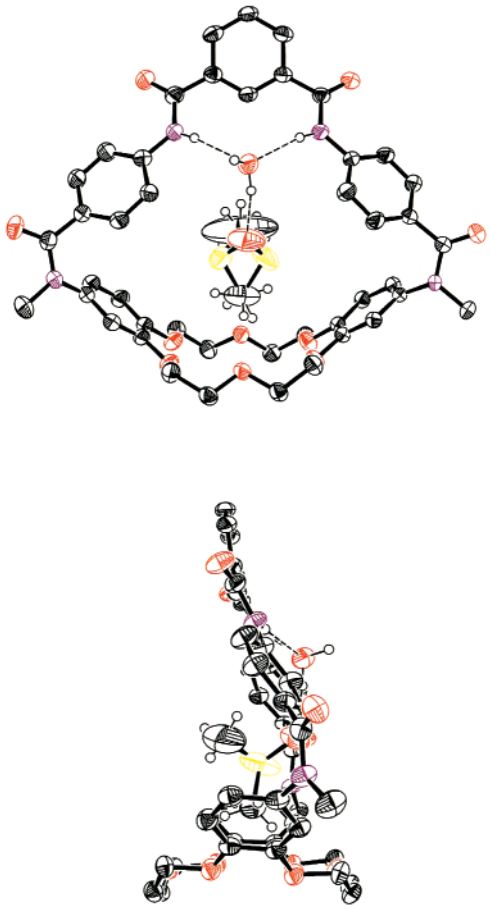


Figure 5. Front and side views of the X-ray crystal structure of [**1a**·DMSO·H_2O] showing 50% probability ellipsoids. The front view shows how the included DMSO is disordered.

Although a bridging water molecule is observed in the solid-state it does not appear to be present or necessary for solution-phase complexation for two reasons. (i) Receptor **1b** has a weak affinity for water in $CDCl_3$. For example, addition of 15 mM of water induces essentially no change in the receptor NH chemical shift. (ii) The observed DMSO/**1b** association constant in $CDCl_3$ is unchanged when the water/**1b** ratio is systematically changed from 0.13 to 1.5 (Table 3).[23] The solid-state structure in Figure 5 indicates that if receptor **1b** maintains the same conformation in solution then, in the absence of water, an included DMSO molecule would be unable to simultaneously contact the NH resides at the top of the **1b** cavity and the crown ether oxygens at the bottom.[24] This suggests that in chloroform solution, the bound DMSO is disordered within the **1b** cavity. The titration isotherms for the different receptor protons are within experimental error; thus, there is no evidence that the DMSO prefers to associate with one part of the receptor cavity over another.[25] A corollary of this solution-state binding model is that bicycle **1b** may be a good receptor for slightly larger heteroditopic guests. Thus, **1b** was examined for its ability to associate with other types of neutral polar compounds. Solid−liquid extraction studies (Table 1) show that **1b** can dissolve and strongly bind urea, primary amides, and primary sulfonamides in $CDCl_3$, but not dissolve amino acids. The changes in host ^{1}H NMR chemical shifts indicate that the extracted guests are deeply included in the host cavity, although it appears that the host−guest orientations vary (e.g., compare toluenesulfonamide to toluamide in Table 1).

Future Studies. The syntheses of analogues **1a** and **1b** from precursor **2** demonstrate how easily the receptor bridging unit can be modified to produce receptors for a range of neutral and salt guests. In addition, a number of chiral dibenzocrown ethers are known,[26] and thus there appears to be a variety of ways of modifying the scaffold and building enantioselective receptors. For example, efforts are underway to produce an enantioselective methyl sulfoxide receptor which can be used as a resolving agent. Examination of the X-ray crystal structures in Figures 3 and 5 suggests that it should be possible to use bicycle **1** as a "wheel" to generate novel rotaxanes. An attractive approach is the trapping method using anionic templates, described recently by Seel and Vögtle.[27,28] As salt-binding receptors, bicycle **1** and its later-generation derivatives should be useful in a range of applications such as selective extraction, membrane transport, chemosensing, homogeneous catalysis, and phase-transfer catalysis.[1]

Experimental Section

Materials. All salts and NMR solvents were purchased from Aldrich and, after being checked for purity, were used as supplied. $K(BPh)_4$ was synthesized according to a literature procedure.[29]

***cis*-Di(nitrobenzo)-18-crown-6, 2.**[8] Dibenzo-18-crown-6 (5.19 g, 14.4 mmol) was dissolved in $CHCl_3$ (104 mL). Acetic acid (78 mL) was added to the solution over 10 min, which was then stirred at room temperature for an additional 5 min. A solution of HNO_3 (3.6 mL) in acetic acid (10.4 mL) was added via dropping funnel over 15−20 min. The solution was stirred at room temperature for 1 h and then heated to reflux for 3 h whereupon a precipitate formed. The solution was cooled, and the precipitate (predominantly the *trans* isomer) was filtered (2.85 g, 6.33 mmol, 44%, mp 237−242 °C, lit.[8] 247−252 °C). Upon sitting for a further 48 h, the *cis* isomer precipitated from the mother liquor (2.56 g, 5.69 mmol, 40%, mp 203−205 °C, lit.[8] 206−232 °C). Each compound was isolated as a pale yellow solid. The combined yield was 84%. Residual acetic acid was removed by dissolving the sample in DMF followed by addition of water to precipitate pure **2**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.85 (m, 8H), 4.21(m, 8H), 7.15 (d, 2H, J = 9 Hz), 7.72 (d, 2H, J = 2.7 Hz), 7.89 (dd, 2H, J = 9, 2.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.8, 147.7, 140.6, 117.6, 111.3, 106.6, 68.4, 68.0. IR (KBr) (ν, cm^{-1}) 3638.7, 3435.2, 3093.1, 2954.9, 2886.6, 1591.2, 1502.0, 1336.2, 1230.9, 1129.5, 1055.9, 807.6, 744.8. MS (FAB$^+$) exact mass calcd for $C_{20}H_{22}N_2O_{10}$ [M + H]$^+$ 451.1353, found 451.1333.

***cis*-Di(aminobenzo)-18-crown-6, 3.** *cis*-Di(nitrobenzo)-18-crown-6, **2**, (0.78 g, 1.73 mmol) was dissolved in hot DMF (70 mL). The solution was degassed using argon, then 10% Pd/C (0.156 g) was added and the flask placed in a pressurized hydrogenation apparatus. The chamber was charged with H_2 (30 psi) and shaken for 1 h and 45 min. The mixture was filtered through a silica gel/Celite plug and the solvent removed in vacuo. Compound **6** was isolated as a tan solid (0.640 g, 1.64 mmol, 98%, mp 178−182 °C, lit.[8] 180−184 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.73−3.82 (m, 8H), 3.89−3.98 (m, 8H), 4.65 (bs, 4H), 6.05 (dd, 2H, J = 8.4, 2.4 Hz), 6.23 (d, 2H, J = 2.3 Hz), 6.62 (d,

(23) For a discussion of the effects of water on hydrogen-bonding systems in chloroform, see: Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 678−680.

(24) It is possible that the solid-state structure is not maintained in solution. An attractive alternative is a host/guest complex that has the DMSO oxygen in contact with the receptor NH residues and both DMSO methyl groups involved in CH-π interactions with the aromatic rings lining the receptor cavity. This binding model is supported by the upfield complexation induced shift of 0.21 ppm for the DMSO methyl groups.

(25) For a recent example of a disordered host/guest system studied by NMR see ref 11 g.

(26) Zhang, X. X.; Bradshaw, J. S.; Izatt *Chem. Rev.* **1997**, *97*, 331−3361.

(27) Seel, C.; Vögtle, F. *Chem. Eur. J.* **2000**, *6*, 21−24.

(28) In the period since manuscript submission, we have successfully prepared a rotaxane using bicycle **1b** as the "wheel". Mass spectrometry experiments indicate that the rotaxane can bind metal cations but it is unable to bind anions. Shukla, R.; Deetz, M. J.; Smith, B. D. Unpublished results.

(29) Honda, H.; Ono, K.; Murakami, K. *Macromolecules* **1990**, *23*, 515−520.

2H, $J = 8.5$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.1, 143.4, 139.2, 115.6, 105.4, 100.8, 69.2, 69.2, 69.0, 67.6. MS (FAB$^+$) exact mass calcd for $C_{20}H_{26}N_2O_{10}$ [M + H]$^+$ 390.1791, found 390.1778.

***cis*-Di((4-nitrophenylcarboxamido)benzo)-18-crown-6, 4.** Di(aminobenzo)-18-crown-6, **3**, (0.50 g, 1.29 mmol) was dissolved in CH_2Cl_2 (50 mL) along with triethylamine (376 μL, 2.7 mmol, 2.1 equiv), and the solution stirred for 5 min at room temperature under an atmosphere of argon. 4-Nitrobenzoyl chloride (0.5 g, 2.7 mmol, 2.1 equiv, recently recrystallized from hexanes) was added as a solution in CH_2Cl_2 via dropping funnel over 10 min. A bright yellow precipitate formed immediately. The solution was stirred for 3 h, filtered, and rinsed with CH_2Cl_2, and **4** was isolated as a yellow-brown solid (0.82 g, 99%, mp > 260 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84 (m, 8H), 4.06 (m, 8H), 6.94 (d, 2H, $J = 9$ Hz), 7.32 (dd, 2H, $J = 9$, 2 Hz), 7.44 (d, 2H, $J = 2$ Hz), 8.16 (d, 4H, $J = 9$ Hz), 8.35 (d, 4H, $J = 9$ Hz), 10.41 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.4, 149.1, 147.6, 144.7, 140.7, 132.1, 129.1, 123.5, 112.5, 112.2, 68.9, 68.9, 67.8, 67.6. MS (FAB$^+$) exact mass calcd for $C_{34}H_{32}N_4O_{12}$ [M + H]$^+$ 689.2095, found 689.2123.

***cis*-Di((*N*-methyl-4-nitrophenylcarboxamido)benzo)-18-crown-6, 5.** Compound **4** (0.50 g, 0.73 mmol) was dissolved in warm, anhydrous DMF (100 mL). Sodium hydride (0.33 g, 8.3 mmol, ~12 equiv, 60% dispersion in mineral oil) was added to the solution all at once. The yellow-brown solution turned a deep red color. The solution was stirred at room temperature for 10 min under an atmosphere of argon. Methyl iodide (230 μL, 3.6 mmol, ~5 equiv) was added over 5 min. The solution was stirred for 30 min, and a color change from deep red to a pale brown color was observed. The solution was quenched with saturated NH_4Cl (aqueous) and poured into a separatory funnel containing water (100 mL) and EtOAc (100 mL). The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The mineral oil was removed by washing with hexanes. The residual brown oil was chromatographed (90:9:1 $CHCl_3$/MeOH/H_2O, $R_f = 0.33$), yielding **5** as a yellow syrup (0.54 g, 0.73 mmol, 99%, mp 86−90 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 6H), 3.94−3.88 (m, 12H), 4.07−4.04 (m, 4H), 6.54 (m, 4H), 6.63 (d, 2H, $J = 8$ Hz), 7.43 (d, 4H, $J = 8.6$ Hz), 8.03 (d, 4H, $J = 8.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 148.8, 147.8, 147.7, 142.3, 136.7, 129.2, 123.0, 119.6, 112.4, 69.5, 69.4, 69.4, 68.5, 68.4, 68.3, 68.2, 38.4. MS (FAB$^+$) exact mass calcd for $C_{36}H_{36}N_4O_{12}$ [M + H]$^+$ 717.2408, found 717.2453.

***cis*-Di((*N*-methyl-4-aminophenylcarboxamido)benzo)-18-crown-6, 6.** Compound **5** (0.31 g, 0.43 mmol) was dissolved in concentrated HCl (10 mL). Iron powder (~0.3 g) was added to the solution and the flask swirled. The flask was placed in a oil bath at 80 °C with occasional swirling until the bubbling subsided and the liquid became transparent. The residual iron was removed by extraction with a magnetic stir bar. The mixture was poured into a separatory funnel with ice and concentrated NaOH (aqueous) was added until a gray precipitate persisted. The aqueous layer was extracted six times with EtOAc. The combined organic layers were dried over $MgSO_4$, and removal of the solvent yielded **6** as a white solid (0.23 g, 0.35 mmol, 81%, dec 117 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 6H), 3.71 (m, 4H), 3.77 (m, 4H), 3.91 (m, 4H), 3.98 (m, 4H), 5.32 (bs, 4H), 6.31 (d, 4H, $J = 8.6$ Hz), 6.54 (dd, 2H, $J = 8.5$, 2.3 Hz), 6.72 (d, 2H, $J = 2.4$ Hz), 6.77 (d, 2H, $J = 8.6$ Hz), 6.96 (d, 4H, $J = 8.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 148.4, 146.7, 139.2, 130.8, 124.6, 119.2, 113.4, 112.4, 111.9, 69.5, 69.4, 68.3, 68.2, 38.8. MS (FAB$^+$) mass calcd for $C_{36}H_{41}N_4O_8$ [M + H]$^+$ 657, found 657.

Macrobicycle 1a. To a solution of compound **6** (0.097 g, 0.15 mmol), and triethylamine (45μL, 0.33 mmol) dissolved in anhydrous CH_2Cl_2 (150 mL), was added a solution of isophthaloyl dichloride (0.031 g, 0.15 mmol) dissolved in anhydrous CH_2Cl_2 (75 mL) via dropping funnel over 3 h at room temperature. The mixture was heated overnight under an atmosphere of argon. The solvent was removed leaving a white solid. Chromatography on silica (190:9:1 → 90:9:1 $CHCl_3$/MeOH/H_2O) yielded **1** as a white solid (0.064 g, 0.081 mmol, 55%, mp >260 °C). R_f (90:9:1 $CHCl_3$/MeOH/H_2O) = 0.17. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.00 (s, 2H), 8.57 (s, 1H), 8.05 (d, 2H, $J = 7.7$ Hz), 7.65 (t, 1H, $J = 7.8$ Hz), 7.57 (d, 4H, $J = 8.6$ Hz), 7.29 (d, 4H, $J = 8.5$ Hz), 7.06 (s, 2H), 6.64 (d, 2H, $J = 8.5$ Hz), 6.40 (d, 2H, $J = 8.2$ Hz), 4.10 (bs, 4H), 3.85 (bs, 8H), 3.72 (bs, 4H), 3.30 (s, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.7, 164.2, 147.8, 146.5, 139.0, 137.5, 134.0, 132.2, 131.4, 128.5, 125.7, 120.7, 120.1, 119.1, 111.9, 111.0, 68.8, 67.6, 67.1, 37.5 ppm. MS (FAB$^+$) exact mass calcd for $C_{44}H_{43}N_4O_{10}$ [M + H]$^+$ 787.2979, found 787.2947.

***tert*-Butyl Macrobicycle 1b.** To a solution of compound **6** (0.063 g, 0.096 mmol), and triethylamine (29 μL, 0.21 mmol) dissolved in anhydrous CH_2Cl_2 (50 mL) was added a solution of 5-*tert*-butylisophthaloyl dichloride (0.025 g, 0.096 mmol) dissolved in anhydrous CH_2Cl_2 (50 mL) via dropping funnel over 2 h at room temperature. The mixture was heated overnight under an atmosphere of argon. The solvent was removed leaving a white solid. Chromatography on silica (90:9:1 $CHCl_3$/MeOH/H_2O, $R_f = 0.17$) yielded **1b** as a glass (0.060 g, 0.071 mmol, 75%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.94 (s, 2H), 8.40 (s, 1H), 8.06 (s, 2H), 7.56 (d, 4H, $J = 8.5$ Hz), 7.28 (d, 4H, $J = 8.7$ Hz), 7.06 (d, 2H, $J = 2.1$ Hz), 6.64 (d, 2H, $J = 8.6$ Hz), 6.41 (d, 2H, $J = 8.5$ Hz, 2.1 Hz), 4.09 (bs, 4H), 3.85 (bs, 8H), 3.71 (bs, 4H), 3.29 (s, 6H), 1.34 (s, 9H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.6, 164.3, 151.9, 147.8, 146.5, 138.9, 138.8, 137.4, 133.9, 132.1, 128.5, 127.9, 123.1, 120.1, 119.0, 118.9, 111.9, 111.1, 68.8, 67.6, 67.1, 37.4, 34.6, 30.8 ppm. MS (FAB$^+$) exact mass calcd for $C_{44}H_{42}N_5O_{12}$ [M + H]$^+$ 832.2830, found 832.2828.

Triethyleneglycol Di(3-nitrobenzoyl) Ester, 8. 3-Nitrobenzoyl chloride (0.21 g, 1.1 mmol) and triethylamine (0.34 mL, 2.5 mmol) were dissolved in CH_2Cl_2 (10 mL). Triethylene glycol (0.07 mL, 0.5 mmol) was added via dropping funnel as a solution in CH_2Cl_2 (5 mL) over 5 min. The mixture was heated to reflux under an atmosphere of argon for 30 min, cooled, washed twice with 0.5 M HCl (aqueous), then saturated $NaCO_3$ (aqueous), and finally with water. The organic phase was dried over $MgSO_4$. Removal of the solvent gave a yellow oil which was chromatographed on silica (1:1 EtOAc/hexanes, $R_f = 0.23$) yielding **8** as a clear oil (0.11 g, 0.25 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 2H), 8.40 (d, 2H, $J = 8.0$ Hz), 8.38 (d, 2H, $J = 8.0$ Hz), 7.65 (t, 2H, $J = 7.5$ Hz), 4.53 (t, 2H, $J = 4.0$ Hz), 3.87 (t, 2H, $J = 4.2$ Hz), 3.72 (s, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 148.1, 135.2, 131.7, 129.5, 127.3, 124.4, 70.6, 68.9, 64.7 ppm. MS (FAB$^+$) mass calcd for $C_{20}H_{20}N_2O_{10}$ [M + H]$^+$ 449, found 449.

Triethyleneglycol Di(3-aminobenzoyl) Ester, 9. Compound **8** (0.44 g, 1 mmol) was dissolved in THF (15 mL). Pd−C (0.1 g) was added, and the flask was charged with H_2 (~1 atm) after 3.25h the reaction was filtered through a Celite/silica gel plug and the solvent removed in vacuo leaving **9**, (0.39 g, 1 mmol) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (ddd, 2H, $J = 1.0$, 1.5, 8.0 Hz), 7.34 (dd, 2H, $J = 1.9$, 2.2 Hz), 7.18 (t, 2H, $J = 7.6$ Hz), 6.83 (ddd, 2H, $J = 1.0$, 2.5, 8.0 Hz), 4.41−4.44 (m, 4H), 3.90 (bs, 4H), 3.79−3.82 (m, 4H), 3.70 (s, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 146.5, 131.0, 129.2, 119.7, 119.4, 115.8, 70.7, 69.2, 64.0 ppm. MS (FAB$^+$) mass calcd for $C_{20}H_{24}N_2O_6$ [M + H]$^+$ 389, found 389.

Control Macrocycle 10. A three-necked flask was equipped with two dropping funnels and charged with THF (40 mL). The addition funnels were charged with solutions of compound **9** (0.12 g, 0.32 mmol) and Et_3N (0.1 mL, 0.7 mmol) in THF (50 mL) and 5-*tert*-butylisophthaloyl dichloride (0.08 g, 0.32 mmol) in THF (50 mL), with the contents emptied concurrently over a period of 1 h. The mixture was stirred overnight under an atmosphere of argon. The solution was filtered to remove some Et_3N·HCl and the solvent removed in vacuo. Chromatography on silica (1:1 EtOAc/hexanes → 100% EtOAc) yielded **10** (0.1 g, 0.19 mmol, 59%, mp >260 °C) as a white solid. R_f (1:1 EtOAc/hexanes) = 0.16. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (bs, 2H), 8.93 (d, 2H, $J = 7.5$ Hz), 7.95 (t, 2H, $J = 8.0$ Hz), 7.85 (bs, 2H), 7.81 (d, 2H, $J = 7.9$ Hz), 7.69 (bs, 1H), 7.62 (bs, 2H), 4.52 (m, 4H), 3.98 (bs, 4H), 3.87 (s, 4H), 1.01 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 166.2, 151.8, 138.5, 133.8, 130.7, 130.5, 127.9, 125.7, 123.1, 121.6, 119.7, 70.9, 70.4, 65.3, 34.4, 30.5 ppm. MS (FAB$^+$) exact mass calcd for $C_{32}H_{34}N_2O_8$ [M + H]$^+$ 575.2393, found 575.2417.

Extraction Studies. Solutions of receptors in appropriate deuterated solvents were prepared (~1 mM) in 5 mm NMR tubes. An initial ^{1}H NMR spectrum was acquired for each tube. Insoluble guests were added in excess as powders, and the NMR tubes were shaken for 5 min and then incubated for 15 h at room temperature. The NMR spectra were acquired and the change in receptor chemical shifts extracted from the

following formula: $\Delta\delta = \delta_{final} - \delta_{initial}$. In the case of KCl extraction, the % of receptor that was bound to KCl was determined from the NH $\Delta\delta$ values.[13]

^{1}H NMR Titrations. Salt-Binding. Receptor **1a** was titrated with tetrabutylammonium halide in the presence and absence of alkali tetraphenylborate. In each case, a 10 mM solution of **1a** in DMSO-d_6/CD_3CN (3:1) was prepared in a 5 mm NMR tube (solution volume 750 μL). Where applicable the solution also contained 1 mol equiv of alkali tetraphenylborate. Small aliquots of tetrabutylammonium halide stock solution (0.75 M) were added, and a spectrum was acquired after each addition. Care was taken to avoid water absorption from the atmosphere. The concentrations and equivalents were adjusted to give the optimum change in Weber p values (0.2−0.8).[15] The total volume of added guest solution was 100 μL or 10 mol equiv. Titration isotherms for all receptor protons that exhibited significant complexation-induced shifts (usually the signals corresponding to H3, H4, and H5; see Figure 1) were fitted to a 1:1 binding model using an iterative curve-fitting method that has been previously described.[5c] For each system the extracted association constants for the different isotherms were always within 15% of the average value.

Neutral Molecule-Binding. Receptor **1b** (10mM) was titrated with neutral guest in $CDCl_3$ (750 μL). Aliquots of guest stock solution (0.75 M) were added, and a spectrum was acquired after each addition. The total volume of added guest was 200 μL or 20 mol equiv. Titration isotherms for all receptor protons that exhibited significant complexation-induced shifts (generally the signals corresponding to H3, H4, and H5; see Figure 1) were fitted to a 1:1 binding model using an iterative curve-fitting method that has been previously described.[5c]

X-ray Structure of 1a·NaCl. Single crystals were obtained from a solution of **1a**, tetrabutylammonium chloride, and sodium tetraphenylborate in chloroform/methanol/water solvent. Crystallographic summary: [**1a**·NaCl·2.62$CHCl_3$·2.14H_2O·0.31C_6H_{14}], $M_r = 1223.29$, monoclinic, $P2_1/n$, $Z = 4$ in a cell of dimensions $a = 14.075(2)$ Å, $b = 17.906(7)$ Å, $c = 23.885(3)$ Å, $\beta = 106.455(17)°$, $V = 5773(3)$ Å^3, $\rho_{calc} = 1.407$ mg M^{-3}, $F(000) = 2523$. The structure was refined on F^2 to a $R_w = 0.2408$, with a conventional $R = 0.0925$ (5166 reflections with $I > 2\sigma(I)$), and a goodness of fit = 1.06 for 724 refined parameters. Hydrogen atoms were restrained using riding models or by bond length restraints.

X-ray Structure of 1a·DMSO. Single crystals were obtained from slow cooling of **1a** in DMSO. Crystallographic summary: monoclinic, [**1a**·1.5DMSO·2H_2O], $M_r = 940.04$, $C2/c$, $Z = 8$ in a cell of dimensions $a = 38.531(3)$ Å, $b = 14.1236(10)$ Å, $c = 17.5199(17)$ Å, $\beta = 102.880(3)°$, $V = 9294.4(13)$ Å^3, $\rho_{calc} = 1.344$ mg M^{-3}, $F(000) = 3976$. The structure was refined on F^2 to a $R_w = 0.2165$, with a conventional $R = 0.0856$ (5419 reflections with $I > 2\sigma(I)$), and a goodness of fit = 0.989 for 631 refined parameters. All non-amide hydrogens were restrained using riding models, while the amide hydrogens restrained by bond length.

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Supporting Information Available: NMR spectra of receptors (PDF). X-ray crystal data in CIF format, This material is available free of charge via the Internet at http://www.pubs.acs.org.

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