Synthesis, Structural Characterization and Complexation Properties of the First "Crowned" Dipyrrolylquinoxalines

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The synthesis of four crown-substituted dipyrrolylquinoxalines **1**–**4** is reported. The key step in the synthesis is reaction of a 1,2-diaminobenzocrown with 1,2-bis(1*H*-pyrrol-2-yl)ethanedione (**20**). A single crystal X-ray diffraction analysis of the 18-crown-6-dipyrrolylquinoxaline **1** revealed that this molecule forms a tetramer centered around a single molecule of water, with no fewer than 10 hydrogen bonds holding the supramolecular structure together. In the case of the 15-crown-5-dipyrrolylquinoxaline **2**, however, X-ray diffraction analysis revealed that this species exists as a dimeric pair in the solid state, with the NH protons of one pyrrole lying within hydrogen-bonding distance of two oxygen atoms on an adjacent crown ether. A second single crystal structure of **2** was solved; it demonstrated that this system is able to coordinate a potassium cation, thereby forming an intermolecular sandwich complex, at least in the solid state. In [D_6]acetone solution receptor **2** and congeners **1**, **3** and **4** were also found to complex sodium and potassium cations within the crown diethyl ether binding sites, in a 1:1 manner as judged by ^{1}H NMR spectroscopic analyses. Although systems **1**–**4** appear to bind fluoride anion as well as cations, the inability to obtain quantitative binding affinities of **1**–**4** with fluoride anion rendered the evaluation of the systems for cooperative binding impossible.

Introduction

For over thirty years now, supramolecular chemists have worked to develop abiotic receptors capable of binding positively or negatively charged species with ever-improving selectivities.[1] As a result, there is now an abundant literature regarding the design, synthesis and study of such receptors. In spite of the progress this literature represents, significant challenges remain in the area. One of these involves the construction of so-called ditopic receptor species, that can complex cation and anion pairs concurrently within a single molecular system.[2] Incentives to prepare such systems include their capacity to coordinate zwitterionic amino acids[3] and peptides,[4] and their potential applicability as toxic material extractants[5] and through-membrane transport agents.[3d,6b,6g] To date, ditopic receptors reported in the literature have typically combined Lewis acid centers, positively charged groups, pyrroles, and amide or (thio)urea groups for anion recognition, with calixarene[6] and crown diethyl ether subunits[7] for cation complexation. In certain instances, allosteric effects have been observed,[6d–6f,6h–6j,7j–7l] and in a limited number of cases membrane transport has also been demonstrated.[3d,6b,6g]

Recently, dipyrrolylquinoxalines have emerged as a new class of neutral anion receptor, that demonstrate high selectivity towards fluoride anion.[8] In view of this and their recognized ease of construction, we felt that covalent conjugates, wherein a dipyrrolylquinoxaline moiety is linked to a cation selective crown diethyl ether would result in new ditopic receptors capable of effecting complementary anion and cation recognition. In this work we report the synthesis of four new "crowned" dipyrrolylquinoxalines namely, **1**–**4** as well as the control dimethoxy-dipyrrolylquinoxaline **21**. The solid-state structures of the free receptors **1**, **2**, and **21** and the potassium complex of **2** are also reported as are the results of ^{1}H NMR titration experiments. These latter findings support the conclusion that these systems are capable of complexing both alkali metal cations and fluoride anions in [D_6]acetone solution. However, these same studies also reveal no evidence of cooperative anion and cation binding.

Results and Discussion

Synthesis

The choice of 18-crown-6 and 15-crown-5 scaffold was obvious; simply put, the alkali metal cation complexation chemistry of these systems has been thoroughly investig-

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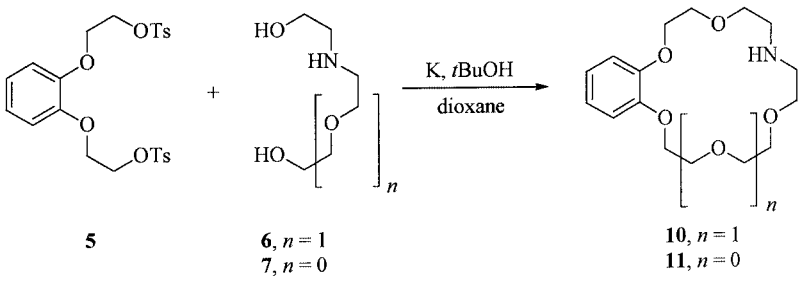


5 **6**, $n = 1$; **7**, $n = 0$ **10**, $n = 1$; **11**, $n = 0$

Scheme 1

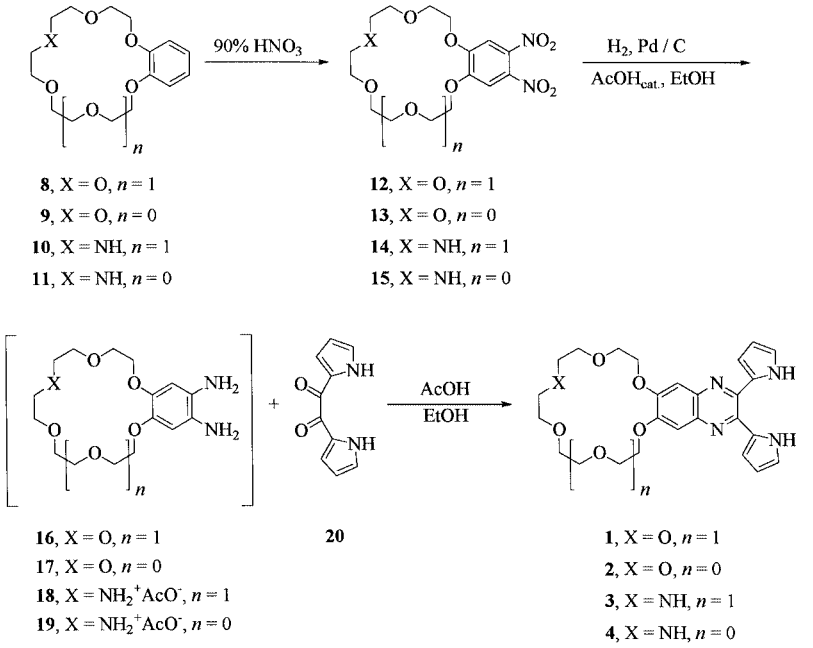
ated.[9] Inclusion of the nitrogen atom in receptors **3** and **4** was done to highlight the versatility of this synthetic approach with regard to potential future functionalizations. Such considerations then led to the identification of crown diethyl ethers **8**−**11** as key precursors. While **8** and **9** are commercially available, benzoaza crowns **10** and **11** had to be synthesized. They were obtained by adapting the procedure of Okahara and co-workers that was developed to prepare mono-azacrown diethyl ethers (Scheme 1).[10] Specifically, 1,2-bis[2-(*p*-tosyloxy)ethoxy]benzene (**5**)[11] was reacted with azadiol **6** or diethanolamine **7** in a *tert*-butyl alcohol/dioxane mixture in the presence of potassium *tert*-butoxide to give benzo-aza-18-crown-6 **10** (26%) and benzo-15-crown-5 **11** (16%), respectively.[12] To the best of our knowledge, this is the first time that the synthesis and full characterization of **10** has been described.

Nitration of benzocrowns **8**−**11** was then carried out and produced the dinitro intermediates **12**−**15** in moderate to high yields (44−88%). Reduction of the dinitro functionalities afforded the corresponding air-sensitive diamines (**16**−**19**), which were used directly in the final quinoxaline-producing step. This step involved reaction of 1,2-bis(1*H*-pyrrol-2-yl)ethanedione (**20**)[8a] with the appropriate diamine **16**−**19** in an approximately 1:1 mixture of EtOH and acetic acid, under reflux conditions. This produced the "crowned" dipyrrolylquinoxalines **1**−**4** in moderate to quantitative yields (49−100%) (Scheme 2). Gratifyingly, the all-oxygen analogues **1** and **2** were isolated in analytically pure form without the need for column chromatography. Crystals suitable for X-ray diffraction analysis were then obtained by recrystallization from acetone. Compounds **3** and **4** were purified by column chromatography (neutral alumina; 1.5% $MeOH/CH_2Cl_2$, eluent).

In a manner similar to that outline above, the control dimethoxydipyrrolylquinoxaline **21** was prepared by reaction of air-sensitive 1,2-dimethoxy-4,5-diaminobenzene[3d] with 1,2-bis(1*H*-pyrrol-2-yl)ethanedione (**20**) (Scheme 3). The synthesis of 2,3-bis(1*H*-pyrrol-2-yl)quinoxaline (**22**) is reported elsewhere.[8a]

Solid-State Structure of 1

Crystals of **1** suitable for X-ray structural analysis were grown by dissolving the receptor in boiling acetone, then the solution was cooled and left standing overnight. A top face view of the basic unit of the solid-state structure of 18-crown-6-dipyrrolylquinoxaline **1** shows a tetramer held



8, X = O, $n = 1$
9, X = O, $n = 0$
10, X = NH, $n = 1$
11, X = NH, $n = 0$

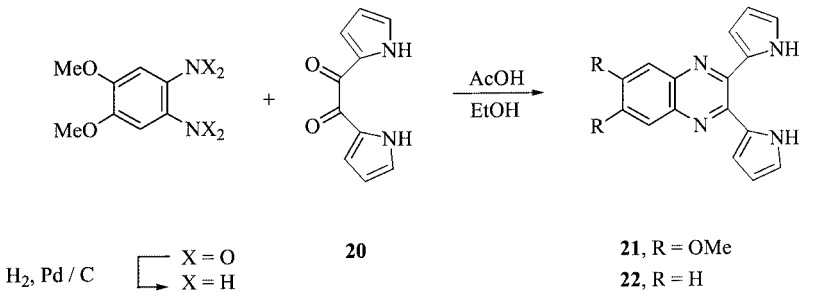
12, X = O, $n = 1$
13, X = O, $n = 0$
14, X = NH, $n = 1$
15, X = NH, $n = 0$

16, X = O, $n = 1$
17, X = O, $n = 0$
18, X = $NH_2^+AcO^-$, $n = 1$
19, X = $NH_2^+AcO^-$, $n = 0$

20

1, X = O, $n = 1$
2, X = O, $n = 0$
3, X = NH, $n = 1$
4, X = NH, $n = 0$

Scheme 2



Scheme 3

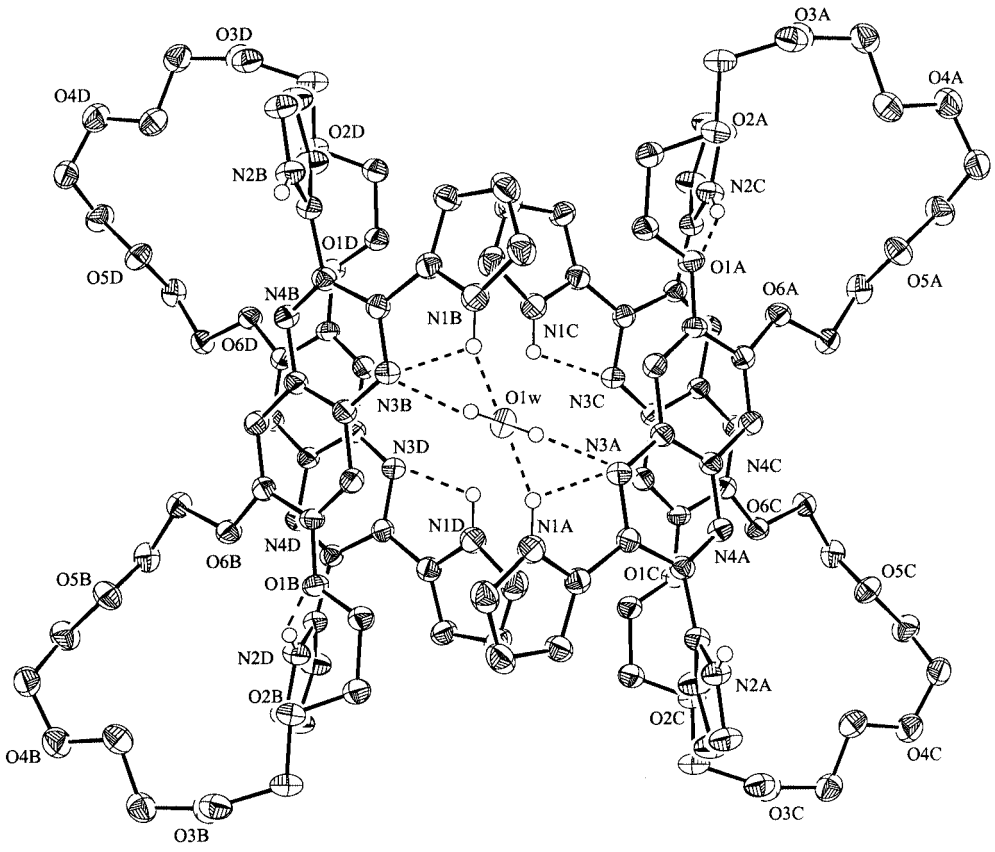


Figure 1. Ortep view of the supramolecular tetramer that exists as a repeating motif in crystals of **1**. Also shown is the heteroatom labeling scheme. Nonessential hydrogens have been omitted for clarity. Hydrogen bonding interactions are indicated by dashed lines. Thermal ellipsoids are scaled to the 50% probability level.

together by no fewer than ten hydrogen bonding interactions (Figure 1). In this arrangement, one pyrrole NH and one pyrazine nitrogen from each quinoxaline point inward into a water-filled pore. Additionally, the four crown diethyl ether moieties of each quinoxaline form the corners of a square.

When looking at the crystal lattice from the top face (Figure 2), the result of this conformation is the formation of five infinite sets of similarly oriented channels, four of which are formed by the "corner" crown diethyl ethers, and one in the center framed by a network of inward-pointing pyrrole and pyrazine nitrogens. The side view (Figure 3) shows that the tetramer is comprised of two sets of two intermolecular interactions relative to the plane of each quinoxaline unit, one of which is perpendicularly directed, and the other of which is directed in a parallel fashion from this plane. To exemplify, the set of nearly perpendicular quinoxalines are oriented at a 103° angle to one another; this arrangement is facilitated by hydrogen bonding interactions between the inward-facing pyrazine nitrogen on each quinoxaline and a bound water molecule. The set of nearly parallel interactions involves one of the molecules from the first set and a molecule directly above or below it at a distance ranging from 4.16 Å to 5.70 Å across the face of the two planes formed by the quinoxaline units.

The supramolecular motif highlighted in Figure 2 and 3 is reinforced by numerous hydrogen bonds, all of which occur in a regular pattern. For instance, when looking at the

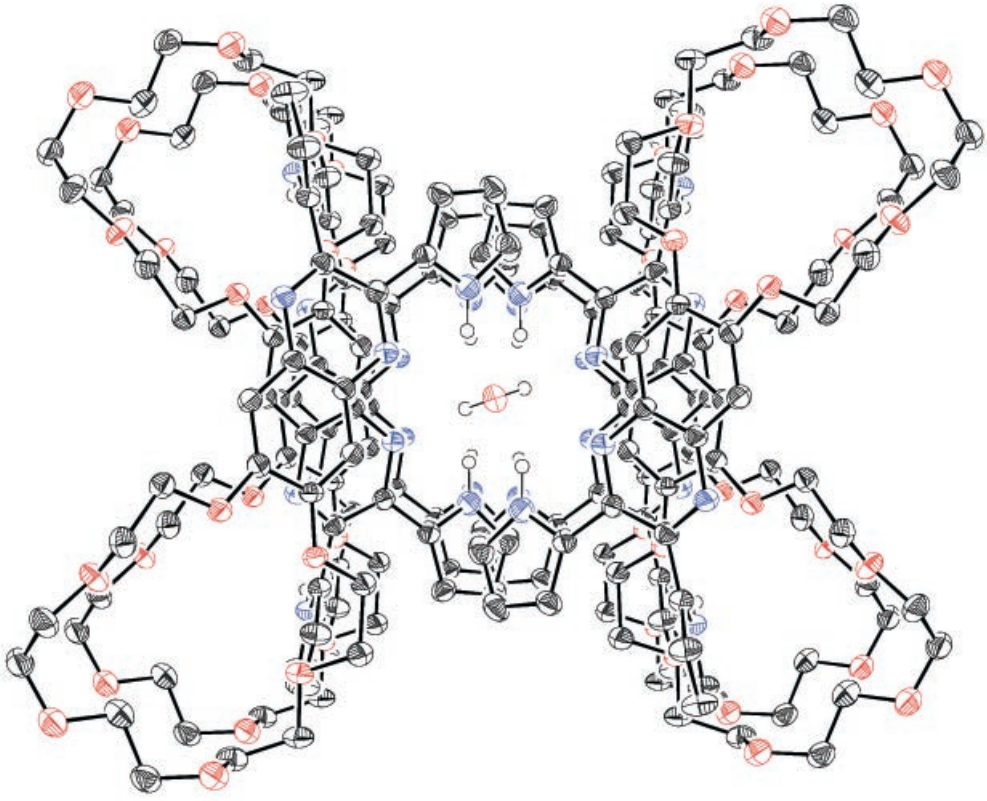


Figure 2. Ortep view of the top face of the crystal lattice of **1**. Encapsulated water molecules are repeated twice within each unit cell. Nonessential hydrogens have been omitted for clarity. Thermal ellipsoids are scaled to the 50% probability level.

top face of the tetramer unit (Figure 1), it can be seen that there are two molecules on opposite corners of the "square" that have their quinoxaline unit overlaying the quinoxaline unit on the molecule adjacent to it. Only the inward facing pyrrole NH atoms (N1A and N1B) of the two overlaying molecules participate in hydrogen bonding to the encapsulated water molecule (NH···Ow of 2.13 Å). Likewise, it is also only the overlaying, inward facing pyrazine nitrogens (N3A and N3B) that participate in hydrogen bonding to this same molecule of water (N···H−Ow of 2.08 Å). Intramolecular hydrogen bonding interactions are present between the inward-pointing pyrazine nitrogen atoms of all four quinoxalines in the tetramer and the inward pointing pyrrole NH atoms, specifically N3A to N1A, N3B to N1B, N3C to N1C, and N3D to N1D; N···HN of 2.49 Å. Curiously, the only direct interactions between the two "layers" seen in this view are hydrogen bonds between one of the methoxy-like oxygens in the phenolic position of the overlaying quinoxaline and the NH of the outward-facing pyrrole of the corresponding underlying unit (O1A to N2C and O1B to N2D; NH···O of 2.20 Å). This extraordinary ensemble is thus stabilized by ten hydrogen bonds: two NH···Ow, two N···H−Ow, four N···HN, and two NH···O interactions.

Solid-State Structure of 2 and its KCF_3SO_3 Complex [2·K^+]

Crystallization of **2**, also from acetone, yielded the structure shown in Figure 4. This side view shows that **2** exists as a hydrogen-bound dimer in the solid state, stabilized by two sets of identical intermolecular bifurcated hydrogen bonds from N2···O4′ (2.90 Å) and N2···O5′ (3.36 Å). In this antiparallel arrangement, the quinoxaline groups appear to be stacking, with atom-to-atom distances ranging from 4.15 to 4.28 Å. However, this distance is greater, by a considerable margin, than the approximately 3.3 to 3.6 Å separations typically seen for stacked systems.[13] The fused aromatic rings are not completely planar, but are twisted slightly in opposite directions. This would appear to be the result of an intramolecular hydrogen bonding involving the second out-of-plane pyrrole NH proton (N1) and the pyrazine nitrogen atom N3 (N1···N3 = 2.77 Å).

Crystals of the potassium complex of **2** suitable for X-ray structural analysis were grown by vapor diffusion of diethyl ether into an acetonitrile solution containing the ligand and potassium trifluoromethanesulfonate. The side view of the complex is shown in Figure 5. As anticipated, the receptor forms a 2:1, ligand:K^+ intermolecular complex with the benzo-15-crown-5 unit from each dipyrrolylquinoxaline sandwiching the potassium cation. The K···O distances range from 2.795(2) to 2.995(2) Å. The formation of such a sandwich complex is not uncommon, and the distances are well within the normal limits for such contacts.[14] As a result of these interactions, the two sets of bifurcated hydrogen bonds between N2···O4′ and N2···O5′ seen in Figure 4 for the free receptor are no longer present. Presumably as a consequence, molecules of the "crowned"

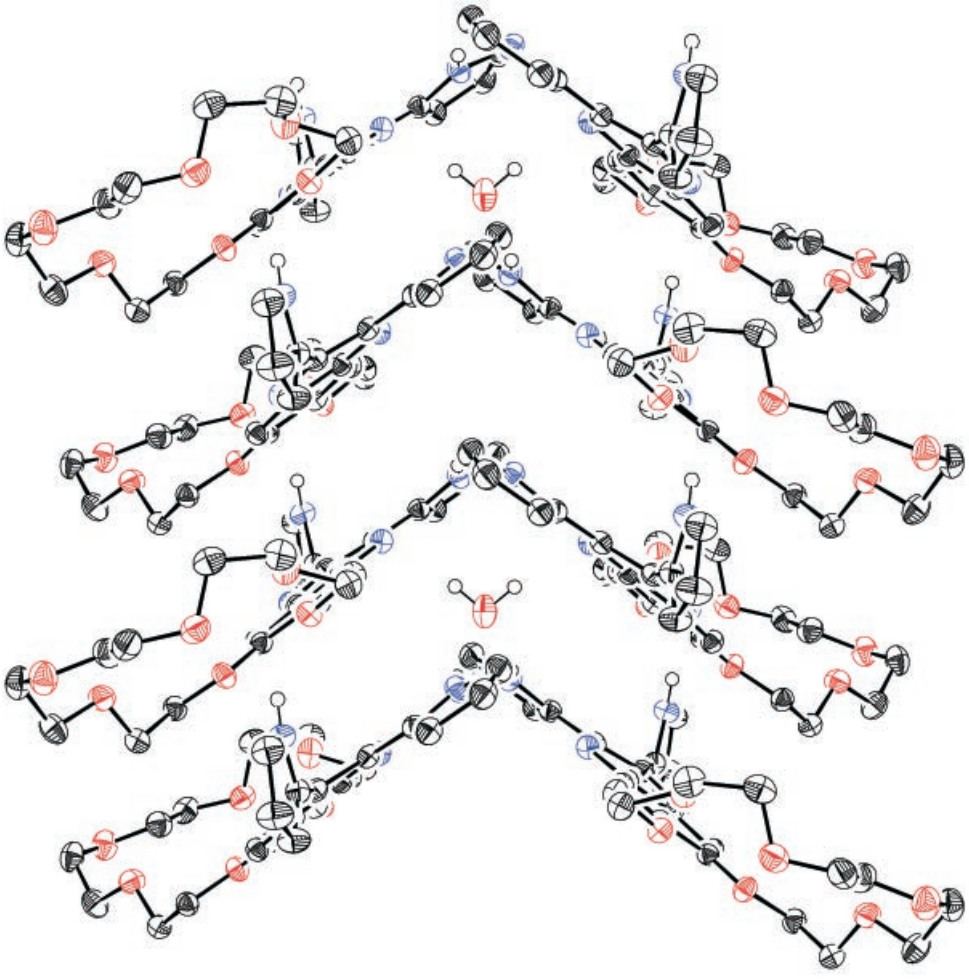


Figure 3. Ortep view of the side face of the unit cell of **1**. Nonessential hydrogens have been omitted for clarity. Thermal ellipsoids are scaled to the 50% probability level.

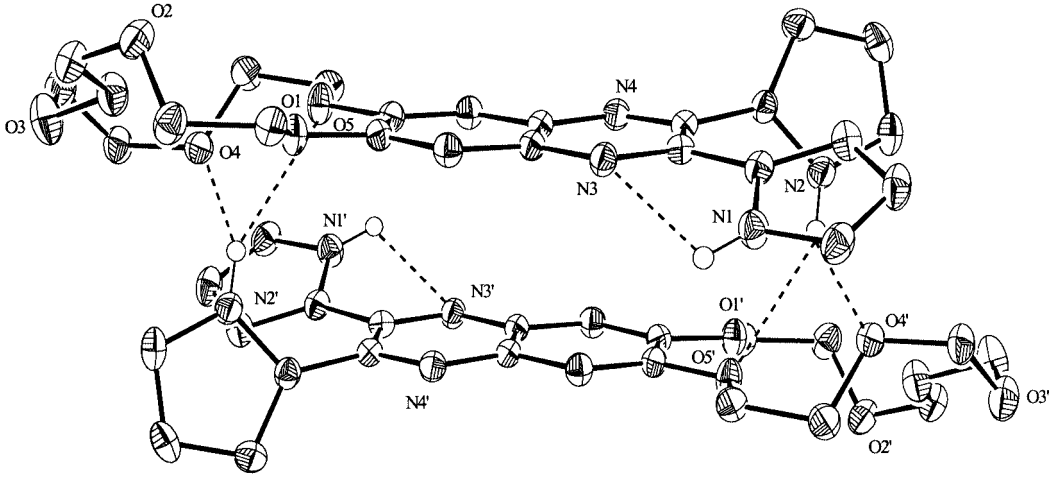


Figure 4. Ortep view of the hydrogen bonded dimer seen in crystals of **2**. Also shown is the heteroatom labeling scheme. Non-essential hydrogens have been omitted for clarity. Hydrogen bonding interactions are indicated as dashed lines. Thermal ellipsoids are scaled to the 50% probability level.

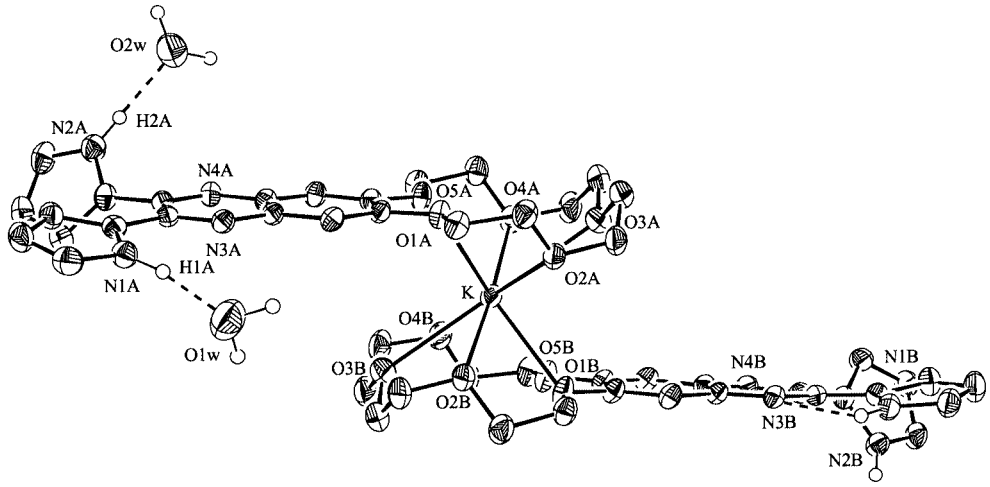


Figure 5. Ortep view of (18-crown-6-quinoxaline)$_2$·K·CF_3SO_3·$2H_2O$·CH_3CN showing the heteroatom labeling scheme. Nonessential hydrogens, the $CF_3SO_3^-$ counter anion, and a CH_3CN solvent molecule have been omitted for clarity. Hydrogen bonding interactions are indicated as dashed lines. Thermal ellipsoids are scaled to the 50% probability level.

quinoxaline are offset from one another, giving what is presumably the lowest energy, least sterically hindered structure.

In the above structure, examination of the pyrrole groups reveals that each is tilted out of the plane defined by the ten atom quinoxaline rings. Interestingly, two water molecules are present, but are hydrogen-bound to only one of the quinoxaline groups present in the K^+-bridged dimer via pyrrole NH···O interactions, with distances of 1.980 Å (H1A···O1w) and 1.984 Å (H2A···O2w). Also present is an intramolecular hydrogen bond of 2.70 Å length between N1B and N3B. This interaction is presumed to play an important role in defining the dihedral angle between the quinoxaline core and this particular pyrrole. The counter trifluoromethanesulfonate anion and a molecule of acetonitrile are present in the crystal lattice but only as spectator species.

Solid-State Structure of 21

Crystallization of **21**, from acetone, yielded the structure shown in Figure 6. This side view shows that **21** exists, like the 15-crown-5 derivative, as an antiparallel hydrogen-bound dimer, also stabilized by two sets of identical intermolecular hydrogen bonds from N4···O1′ (3.06 Å) and N4···O2′ (3.29 Å). Interestingly, the two quinoxaline groups are offset from one another and hence "slipped" relative to what is seen for the 15-crown-5 analog (**2**) (Figure 4). The two fused benzene rings present in **21** appear to stack but the atom-to-atom distances of approximately 4 Å, although shorter than those observed for **2**, are greater than those expected for systems linked by strong π-π stacking interactions. In the unit cell, each dimer is further hydrogen-bound to an adjacent dimer, via a set of two pyrazine-N···pyrrole-NH interactions of 2.247 Å.

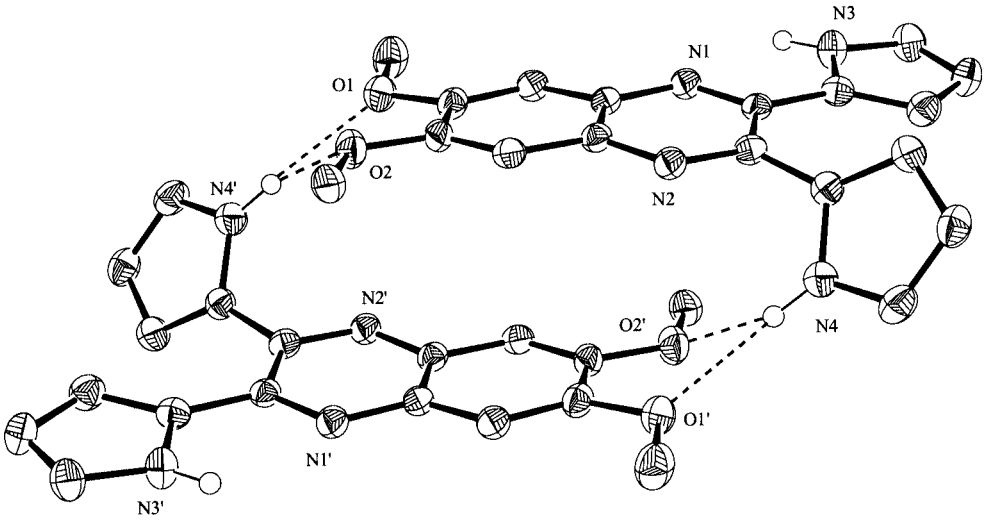


Figure 6. Ortep view of **21** showing the heteroatom labeling scheme. Nonessential hydrogens have been omitted for clarity. Hydrogen bonding interactions are indicated as dashed lines. Thermal ellipsoids are scaled to the 50% probability level.

Cation and Anion Binding Studies

Solution state ^{1}H NMR spectroscopic titrations of the four crown-substituted dipyrrolylquinoxalines **1**−**4** were undertaken. [D_6]acetone was chosen as the solvent due to its ability to solubilize all of the species being studied, as well as to minimize potential ion pairing. Initially, the binding of the alkali metal cation (as the trifluoromethanesulfonate salt) to each receptor was performed in order to obtain a "baseline" of sorts against which evidence of cooperativity in mixed studies could be judged. These results, which show a number of patterns, are summarized in Table 1.

Table 1. Binding constants (K_a) measured in M^{-1} for compounds **1**−**4**

Compound[a]	**1**	**2**	**3**	**4**
Na^+ [b]	57500[c]	1200[d]	11400[c]	200[d]
K^+ [b]	86900[c]	[e]	13100[c]	[e]

[a] Titrations were performed in [D_6]acetone. All errors are ≤ 20% in goodness of fit. [b] Used as trifluoromethansulfonate salts. [c] Determination of 1:1 binding stoichiometry by mole ratio method. [d] Unable to determine stoichiometry. [e] Not measured due to the apparent formation of 2:1 complexes.[14]

The cation binding behavior of receptors **1**−**4**, studied in [D_6]acetone, follows two distinct patterns for both Na^+ and K^+. First, the 18-crown-6 **1** (K_a = 57500 ± 7820 M^{-1}) and the aza-18-crown-6 **3** (K_a = 11400 ± 1140 M^{-1}) showed higher binding for Na^+ than their smaller 15-crown-5 counterparts **2** and **4** (K_a = 1230 ± 22 M^{-1} and 195 ± 6 M^{-1}, respectively), a finding that is consistent with the crown diethyl ether binding literature.[9] A similar comparison could not be made for K^+ since clean 1:1 binding was not observed in the case of **2** and **4**. This is fully consistent with the extensive literature precedence that details the formation of 2:1 complexes of K^+ with the benzo-15-crown-5 unit.[14] It is also in agreement with our own observation that **2** forms a 2:1 K^+ complex in the solid state (Figure 5).

Additionally, the all-oxygen receptors **1** and **2** exhibited stronger binding for Na^+ cation than the corresponding aza-analogs **3** and **4**, respectively. Likewise, **1** demonstrated enhanced binding for K^+ cation compared to its aza-analog **3**. This occurrence can be explained by classic crown diethyl ether coordination chemistry; the softer nitrogen donors in the aza analogs **3** and **4** do not bind alkali metals as strongly as their harder oxygen counterparts.[15]

Mole ratio plots were also used to confirm classical crown−diethyl ether type 1:1 binding stoichiometries for the 18-crown-6 **1** with both Na^+ and K^+, as well as for the aza-18-crown-6 **3** with Na^+ and K^+. The binding of the 15-crown-5 **2** and the aza-15-crown-5 **4** with Na^+ was too weak to be determined by the mole ratio method; however, there is ample precedence to suggest a 1:1 binding mode.[9,15]

Next, our attention turned to the investigation of fluoride anion binding by the crowned dipyrrolylquinoxalines. Initial studies were conducted using *tert*-butylammonium fluoride trihydrate leading to inconclusive results. This could potentially be explained by the inherent instability of tetra-*n*-alkylammonium fluorides,[16] coupled with the recent observations of Schmidtchen[17] that quaternary ammonium cations are less innocent as spectator species than previously thought. As a result we considered an alternative source of fluoride anion, the potassium cryptand[2,2,2] fluoride salt (see Exp. Sect. for preparation) for ^{1}H NMR and UV/Vis spectroscopic titrations. Unfortunately, the inability of the cryptand[2,2,2] to solubilize KF in the presence of 18-crown-6 **1** in acetone, dimethyl sulfoxide, and methanol precluded quantitative analysis of fluoride anion binding or evaluation of systems **1**−**4** as ditopic receptors.

During the course of these investigations it was thought that the propensity of "crowned" dipyrrolylquinoxalines to engage in cooperative anion and cation recognition could be increased by reducing the large distance between the cation and anion binding sites. In a number of known ditopic receptors, the simultaneous binding of the cation and anion takes place over a shorter distance. The benefits of this approach are particularly well exemplified by the diazacrown-based receptor prepared by Smith and co-workers[7n] that binds alkali halides within contact ion pairing distance. Such systems take advantage of the driving force for the formation of the ion contact pair while concurrently hydrogen bonding each ion to the corresponding portion of the receptor. It is of particular interest to note that Nishizawa et al.[7k] successfully demonstrated the ditopic binding properties of a thiourea-functionalized benzo-15-crown-5, similar to our current design, but which has an inherently shorter distance between the cation and anion binding sites. The present results suggest that the generation of bona fide ditopic anion−cation receptors wherein such conditions are met remains a substantial challenge.

Conclusions

The four new "crowned" dipyrrolylquinoxalines reported here have been shown to bind alkali-metal cations effectively, with binding constants in good agreement with those for analogous pure crown diethyl ether systems. Although compounds **1**−**4** act as effective receptors for alkali metal cations, their affinity for fluoride anion and subsequent ability to behave as ditopic receptors in [D_6]acetone was unable to be evaluated. We are currently pursuing the possibilities of reducing the separation distance between the cation and anion binding sites.

Separate from their properties as receptors, the solid state structure of **1** deserves comment. Unlike 15-crown-5-dipyrrolylquinoxaline **2** and dimethoxydipyrrolylquinoxaline **21** which both form intermolecular dimers in the solid state, the "crowned" system **1** is found to form a tetramer in the solid state that is characterized by five infinite channels. The key feature of this unique structure is the finding that one pyrrole NH and one pyrazine nitrogen from each quinoxaline point inward into a water-filled pore. The elegance of

this structure coupled with the current interest in nanotube technology, particularly artificial ion channels, leads us to suggest that supramolecular assemblies of this type could have a role to play as mimics of the biologically significant aquaporin water channels,[18] or anion-conducting channels, of which there is currently only one example in the literature.[19]

Experimental Section

General: Proton and ^{13}C NMR spectra were obtained on a Bruker AC250 spectrometer. All high-resolution (HR) chemical ionization (CI) mass spectra were performed on a VG ZAB-2E instrument. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA, and are reported as percentages. All reactions were conducted under dry Ar unless otherwise stated. All solvents were of reagent grade quality and purchased commercially. All starting materials, except for 1,2-dimethoxy-4,5-dinitrobenzene (from Lancaster) were purchased from Aldrich Chemical Co. and used without further purification. The trifluoromethanesulfonate sodium and potassium salts, cryptand[2,2,2] and KF (99.99%) were obtained from Aldrich. All NMR spectroscopic solvents were purchased from Cambridge Isotope Laboratories. Merck type 60 (230−400 mesh) silica gel and Brockmann I activated neutral alumina (150 mesh) were used for column chromatography. Thin-layer chromatography (TLC) analyses were performed on silica gel 60 F_{254} (200 μm thickness) or aluminum oxide 60 F_{254} (200 μm thickness) as appropriate, with 5% MeOH in CH_2Cl_2 as the eluent. 1,2-Bis[2-(*p*-tosyloxy)ethoxy]benzene (**5**),[11] 1,2-bis(1*H*-pyrrol-2-yl)ethanedione (**20**),[8a] and 2,3-bis(1*H*-pyrrol-2-yl)quinoxaline (**22**)[8a] were prepared as previously reported.

3-Aza-6-oxaoctane-1,8-diol (6): This compound was prepared in agreement with the procedure used to synthesize 6-aza-3,9-dioxaundecane-1,11-diol.[20] 2-Chloroethanol (38.29 g, 0.48 mol) in toluene (120 mL) was added to a mixture of 2-(2-aminoethoxy)-ethanol (200.0 g, 1.90 mol) and Na_2CO_3 (55.44 g, 0.52 mol) heated at reflux in toluene (1.2 L). The resulting mixture was stirred at reflux for a further 2 days using a condenser equipped with a Dean−Stark adaptor. The reaction mixture was allowed to cool, filtered and concentrated in vacuo. The remaining residue was purified by fractional distillation to give **6** as a pale yellow oil (28.68 g, 40%). The physical properties of this material agree with those previously reported.[10]

Benzoaza-18-crown-6 (10): 3-Aza-5-oxaoctane-1,8-diol (**6**) (18.41 g, 0.123 mol) and potassium metal (5.79 g, 0.118 mol) were dissolved in *tert*-butyl alcohol (160 mL), with stirring at 40 °C. 1,2-Bis[2-(*p*-tosyloxy)ethoxy]benzene (**5**) (25.00 g, 0.049 mol) dissolved in dioxane (140 mL) was added dropwise over 90 min. After the addition was complete, heating and stirring was continued for a further 2 h. The reaction mixture was then allowed to cool, upon which point it was passed through a sintered funnel. The resulting precipitate was washed with CH_2Cl_2 and the combined filtrates were concentrated in vacuo. The residue obtained in this way was redissolved in water (30 mL), washed with hexanes (40 mL), and then extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 extracts were concentrated to ca. 50 mL, and extracted with 1 M HCl (50 mL). The aqueous layer was adjusted to pH 10−11 using Na_2CO_3, and extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts were concentrated in vacuo. Purification by column chromatography (neutral alumina, 2.5% MeOH/CH_2Cl_2 eluent) gave a pale orange oil which solidified on standing. Recrystallization from hexanes afforded **10** as a white crystalline solid (3.96 g, 26%). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.21 (br. s, 1 H, NH), 2.77−2.83 (m, 4 H, CH_2N), 3.60−3.74 (m, 8 H, CH_2O), 3.80−3.84 (m, 2 H, CH_2O), 3.88−3.92 (m, 2 H, CH_2O), 4.12−4.19 (m, 4 H, $PhOCH_2$), 6.88 (*pseudo*-s, 4 H, Ph-H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 49.3, 68.6, 68.8, 69.4, 69.8, 70.3, 70.7, 113.9, 114.6, 121.3, 121.4, 149.0, 149.06 ppm. HRMS (CI^+): calcd. for $C_{16}H_{26}N_1O_5$ $[M + H]^+$ 312.1811; found *m*/*z*: 312.1812. $C_{16}H_{25}N_1O_5$: calcd. C 61.72, H 8.09, N 4.50; found C 61.73, H 8.13, N 4.44.

Benzoaza-15-crown-5 (11): This compound was prepared in agreement with the procedure used for **10** but starting from diethanolamine (**7**) (10.38 g, 0.10 mol) and potassium metal (4.63 g, 0.12 mol) in *tert*-butyl alcohol (160 mL), and **5** (25.00 g, 0.05 mol) in dioxane (140 mL). Purification by column chromatography (neutral alumina, 1.5% MeOH/CH_2Cl_2 eluent) gave the product as a white solid. Recrystallization from *n*-heptane afforded **11** as a white crystalline solid (2.12 g, 16%). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.60 (br. s, 1 H, NH), 2.80−2.84 (m, 4 H, CH_2N), 3.71−3.75 (m, 4 H, CH_2O), 3.85−3.88 (m, 4 H, CH_2O), 4.09−4.12 (m, 4 H, CH_2O), 6.80−6.89 (m, 4 H, Ph-H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 49.1, 67.6, 68.9, 70.2, 112.4, 120.8, 148.7 ppm. HRMS (CI^+): calcd. for $C_{14}H_{21}NO_4$ $[M + H]^+$ 268.1549; found *m*/*z*: 268.1558. $C_{14}H_{21}N_1O_4$: calcd. C 62.90, H 7.92, N 5.24; found C 63.12, H 7.89, N 5.03.

General Procedure. Synthesis of Dinitro-3*n*-benzo-*n*-crowns 12−14: To a stirred solution of the appropriate benzo-3*n*-crown-*n* (**8**−**11**) (4.6−20.8 mmol) in glacial acetic acid (7−30 mL) cooled to less than 15 °C, was added conc. nitric acid (70%, 5−20 mL) dropwise over 15 min. After the addition the solution was stirred at ambient temperature for 15 min. The reaction mixture was allowed to warm to room temp. and stirred overnight. The solution was again cooled to less than 15 °C and fuming nitric acid (90%, 11−50 mL) was added dropwise over a period of 30 min. The orange solution was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo.

Dinitrobenzo-18-crown-6 (12): 12 was synthesized from benzo-18-crown-6 (**8**) (6.5 g, 20.8 mmol). Product **12** was obtained as a yellow solid after recrystallization from acetone (7.34 g, 88%). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.64 (*pseudo*-s, 4 H, CH_2O), 3.66−3.70 (m, 4 H, CH_2O), 3.73−3.76 (m, 4 H, CH_2O), 3.93−3.96 (m, 4 H, CH_2O), 4.26−4.30 (m, 4 H, $PhOCH_2$), 7.34 (*pseudo*-s, 2 H, Ph-H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 68.8, 69.8, 70.4, 70.7, 71.0, 108.3, 133.3, 151.6 ppm. HRMS (CI^+): calcd. for $C_{16}H_{23}N_2O_{10}$ $[M + H]^+$: 403.1353; found *m*/*z*: 403.1345. $C_{16}H_{22}N_2O_{10}$: calcd. C 47.76, H 5.51, N 6.96; found C 47.80, H 5.53, N 6.98.

Dinitrobenzo-15-crown-5 (13): 13 was synthesized from benzo-15-crown-5 (**9**) (2.50 g, 9.3 mmol). Product **13** was obtained as a yellow solid after recrystallization from acetone (2.78 g, 84%). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.70−3.77 (m, 8 H, CH_2O), 3.91−3.95 (m, 4 H, CH_2O), 4.23−4.26 (m, 4 H, $PhOCH_2$), 7.31 (s, 2 H, Ph-H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 68.7, 69.7, 70.1, 71.1, 108.5, 136.8, 151.9 ppm. HRMS (CI^+): calcd. for $C_{14}H_{19}N_2O_9$ $[M + H]^+$ 359.1091; found *m*/*z*: 359.1082. $C_{14}H_{18}N_2O_9$: calcd. C 46.93, H 5.06, N 7.82; found C 47.02, H 5.04, N 7.88.

Dinitrobenzoaza-18-crown-6 (14): 14 was synthesized from benzoaza-18-crown-6 (**10**) (3.6 g, 11.6 mmol). However, the workup was modified in the following manner: The orange solution was poured into water (150 mL), and washed with CH_2Cl_2 (3 ×

150 mL). The aqueous layer was adjusted to pH 10−11 using Na_2CO_3 and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford **14** as a yellow solid (3.61 g, 78%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.33 (br. s, 1 H, NH), 2.76−2.82 (m, 4 H, CH_2N), 3.59−3.72 (m, 8 H, CH_2O), 3.84−3.92 (m, 4 H, CH_2O), 4.24−4.29 (m, 4 H, $PhOCH_2$), 7.30 (s, 1 H, Ph-H), 7.31 (s, 1 H, Ph-H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 49.4, 68.3, 68.7, 69.3, 69.6, 70.1, 70.6, 70.7, 107.8, 108.1, 136.5, 151.5, 151.6 ppm. HRMS (CI^+): calcd. for $C_{16}H_{24}N_3O_9$ $[M + H]^+$ 402.1513; found *m*/*z*: 402.1510. $C_{16}H_{23}N_3O_9$: calcd. C 47.88, H 5.78, N 10.47; found C 47.94, H 5.87, N 10.37.

Dinitrobenzoaza-15-crown-5 (15): 15 was synthesized from benzoaza-15-crown-5 (**11**) (1.24 g, 4.6 mmol). Workup in the manner described for **14**, afforded **15** as a yellow solid (1.15 g, 44%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.50 (br. s, 1 H, NH), 2.79−2.83 (m, 4 H, CH_2N), 3.73−3.76 (m, 4 H, CH_2O), 3.88−3.92 (m, 4 H, CH_2O), 4.20−4.23 (m, 4 H, $PhOCH_2$), 7.27 (s, 2 H, Ph-H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 49.2, 68.1, 68.8, 70.5, 107.5, 136.7, 151.6 ppm. HRMS (CI^+): calcd. for $C_{14}H_{19}N_3O_8$ $[M + H]^+$ 358.1250; found *m*/*z*: 358.1252. $C_{14}H_{19}N_3O_8$: calcd. C 47.06, H 5.36, N 11.76; found C 47.02, H 5.35, N 11.73.

General Procedure. Synthesis of 3*n*-Crown-*n*-dipyrrolylquinoxalines 1−4 and 6,7-Dimethoxy-2,3-bis(1*H*-pyrrol-2-yl)quinoxaline (21): The appropriate dinitro-3*n*-benzo-*n*-crown (**12−15**) (2.35−7.0 mmol) or 1,2-dimethoxy-4,5-dinitrobenzene (3.58 g, 15.70 mmol), and 10% Pd/C (170−500 mg) were suspended in ethanol (33−135 mL) and glacial acetic acid (2−7 mL) and shaken in a Parr hydrogenation apparatus at 50 psi H_2 pressure and ambient temperature for 44 h. The resultant diamine was assumed to form in quantitative yield and was used immediately in the subsequent reaction. The reaction mixture was filtered through a pad of Celite into the next reaction vessel and washed with ethanol (50 mL). 1,2-Bis(1*H*-pyrrol-2-yl)ethanedione (**20**) (1.1−7.24 mmol) dissolved in glacial acetic acid (80−180 mL) was added to the solution and the resultant mixture was heated at reflux for 24 h. The reaction mixture was allowed to cool, and then concentrated in vacuo. The remaining residue was redissolved in a mixture of CH_2Cl_2 (75 mL) and water (75 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed sequentially with saturated $NaHCO_3$ solution (100 mL), water (100 mL), and brine (100 mL), before being dried ($MgSO_4$) and concentrated in vacuo.

18-Crown-6-dipyrrolylquinoxaline (1): The intermediate diamine **16** was synthesized from **12** (2.82 g, 7.0 mmol) according to the general procedure given above. This was then treated with **20** (0.60 g, 3.2 mmol). Product **1** was obtained in pure form as a fine brown powder (1.58 g, 100%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.68−3.84 (m, 16 H, CH_2O), 4.10−4.13 (m, 4 H, $PhOCH_2$), 6.26 (m, 2 H, pyr-H), 6.55 (m, 2 H, pyr-H), 6.96 (s, 2 H, Ph-H), 6.99 (m, 2 H, pyr-H), 9.64 (br. s, 2 H, pyr-NH) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 68.8, 69.0, 70.4, 70.9, 71.1, 106.9, 109.8, 111.2, 120.2, 120.2, 129.3, 136.7, 141.9, 151.5 ppm. HRMS (CI^+): calcd. for $C_{26}H_{31}N_4O_6$ $[M + H]^+$ 495.2244; found *m*/*z*: 495.2235. $C_{26}H_{30}N_4O_6 \cdot H_2O$: calcd. C 60.93, H 6.29, N 10.93; found C 60.97, H 6.16, N 10.51. UV/Vis: λ_{max} (CH_3CN, ε/M^{-1} cm^{-1}) = 271 (28900), 407 (23300) nm.

Crystallization of 1: Receptor **1** was dissolved in boiling acetone and then allowed to cool to room temp. Yellow-green crystals of **1**, suitable for X-ray diffraction analysis, were obtained by letting the solution stand overnight.

15-Crown-5-dipyrrolylquinoxaline (2): The intermediate diamine **17** was synthesized from **13** (2.50 g, 6.98 mmol) according to the general procedure given above. This was then treated with **20** (0.60 g, 3.2 mmol). Product **2** was obtained, pure, as a fine brown powder (1.44 g, 100%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.78−3.85 (m, 12 H, CH_2O), 4.06−4.09 (m, 4 H, $PhOCH_2$), 6.26 (m, 2 H, pyr-H), 6.54 (m, 2 H, pyr-H), 6.93 (s, 2 H, Ph-H), 6.98 (m, 2 H, pyr-H), 9.62 (br. s, 2 H, pyr-NH) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 68.2, 69.1, 70.3, 71.3, 106.9, 109.8, 111.2, 120.9, 129.3, 136.8, 141.9, 151.5 ppm. HRMS (CI^+): calcd. for $C_{24}H_{27}N_4O_5$ $[M + H]^+$: 451.1981; found *m*/*z*: 451.1964. $C_{24}H_{26}N_4O_5$: calcd. C 63.99, H 5.82, N 12.44; found C 63.73, H 5.72, N 12.22. UV/Vis: λ_{max} (CH_3CN, ε/M^{-1} cm^{-1}) = 269 (27,800), 402 (17,700) nm.

Crystallization of 2 and its KCF_3SO_3 Complex: Receptor **2** was dissolved in boiling acetone and then allowed to cool to room temp. Pale yellow crystals of **2**, suitable for X-ray diffraction analysis, were obtained by letting stand overnight. The complex was obtained by dissolving **2** and excess KCF_3SO_3 in MeCN at ambient temperature, and allowing vapor diffusion of Et_2O in a screw-capped vial. In this manner, amber crystals, suitable for X-ray diffraction analysis, were obtained after several days.

Aza-18-crown-6-dipyrrolylquinoxaline (3): The intermediate diamine **18** was synthesized from **14** (2.01 g, 5.0 mmol) according to the general procedure given above. This was then treated with **20** (0.43 g, 2.3 mmol) to yield the crude product as the acetate salt. Therefore, the workup was modified in the following manner: The reaction mixture was redissolved in a mixture of CH_2Cl_2 (100 mL) and a 20% w/v aqueous Na_2CO_3 solution (100 mL). The aqueous solution was further extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed sequentially with saturated $NaHCO_3$ solution (100 mL), water (100 mL), and brine (100 mL), before being dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (neutral alumina, 1.5% MeOH/CH_2Cl_2 eluent) afforded **3** as a fine brown powder (0.697 g, 62%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.84−2.87 (m, 4 H, CH_2N), 3.64−3.81 (m, 12 H, CH_2O), 4.10−4.14 (m, 4 H, $PhOCH_2$), 6.25 (m, 2 H, pyr-H), 6.55 (m, 2 H, pyr-H), 6.94 (s, 1 H, Ph-H), 6.97 (s, 1 H, Ph-H), 6.99 (2 H, pyr-H), 9.64 (br. s, 2 H, pyr-NH) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 49.2, 49.3, 68.3, 68.4, 68.6, 69.0, 70.0, 70.1, 71.2, 70.7, 106.7, 106.8, 109.8, 111.2, 120.1, 129.3, 136.7, 142.0, 151.3 ppm. HRMS (CI^+) calcd. for $C_{26}H_{32}N_5O_5$ $[M + H]^+$: 494.2403; found *m*/*z*: 494.2408. UV/Vis: λ_{max} (CH_3CN, ε/M^{-1} cm^{-1}) = 270 (25700), 405 (20900) nm.

Aza-15-crown-5-dipyrrolylquinoxaline (4): The intermediate diamine **19** was synthesized from **15** (0.84 g, 2.35 mmol) according to the general procedure given above. This was then treated with **20** (0.20 g, 1.1 mmol) to yield the crude product as the acetate salt. Workup was effected in the manner described for **3**. Purification by column chromatography (neutral alumina, 1.5% MeOH/CH_2Cl_2, eluent) then afforded **4** as a fine red-brown powder (0.234 g, 49%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.98−3.01 (m, 4 H, CH_2N), 3.84−3.88 (m, 4 H, CH_2O), 3.97−4.01 (m, 4 H, CH_2O), 4.22−4.26 (m, 4 H, $PhOCH_2$), 6.27 (m, 2 H, pyr-H), 6.72 (m, 2 H, pyr-H), 6.97 (m, 2 H, pyr-H), 7.13 (s, 2 H, Ph-H), 9.49 (br. s, 2 H, pyr-NH) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 49.0, 67.5, 68.7, 69.3, 106.6, 109.8, 111.3, 120.1, 129.3, 136.8, 141.8, 151.5 ppm. HRMS (CI^+) calcd. for $C_{24}H_{28}N_5O_4$ $[M + H]^+$ 450.2141; found *m*/*z*: 450.2142. UV/Vis: λ_{max} (CH_3CN, ε/M^{-1} cm^{-1}) = 270 (24800), 404 (13300) nm.

Table 2. X-ray Crystallographic and experimental data for receptors **1**, **2**, **21** and **2·K⁺**.

Receptor	**1**	**2**	**21**	**2·K⁺**
Formula	$C_{53.5}H_{65}N_8O_{13.5}$	$C_{24}H_{26}N_4O_5$	$C_{18}H_{16}N_4O_2$	$C_{51}H_{59}F_3KN_9O_{15}S$
Formula mass (g mol^{-1})	1036.14	450.49	320.35	1166.23
Space group	Pccn	*P*21/*n*	*C*2/*c*	*P*21/*c*
a (Å)	17.5406(2)	9.7020(1)	23.9261(7)	10.0780(1)
b (Å)	32.6958(4)	15.1942(2)	7.6176(2)	21.1467(2)
c (Å)	9.3167(1)	14.7039(2)	17.0385(5)	25.4861(3)
α (deg)	90	90	90	90
β (deg)	90	101.686(1)	101.385	92.829(1)
γ (deg)	90	90	90	90
Z	4	4	8	4
V (Å^3)	5343.17(11)	2122.63(5)	3044.32(15)	5424.89(10)
$\rho_{calcd.}$ (Mg m^{-3})	1.288	1.410	1.398	1.428
T (K)	153(2)	153(2)	153(2)	153(2)
λ (Å)	0.71073	0.71073	0.71073	0.71073
μ (mm^{-1})	0.094	0.100	0.095	0.223
$R_w(F^2)$	0.142	0.1024	0.0979	0.168
$R(F)$ [$I > 2\sigma(I)$]	0.0532	0.0440	0.0492	0.0648
Goodness-of-fit on F^2	1.357	1.02	1.030s	1.247

6,7-Dimethoxy-2,3-bis(1*H*-pyrrol-2-yl)quinoxaline (21): The requisite intermediate, 1,2-diamino-4,5-dimethoxybenzene was synthesized from 1,2-dimethoxy-4,5-dinitrobenzene (3.58 g, 15.70 mmol). This was then treated with **20** (1.36 g, 7.24 mmol) in agreement with the standard procedures described above. This gave product **21** as a yellow powder (2.05 g, 89%) after purification by column chromatography (silica, 2% MeOH/CH_2Cl_2, eluent). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.04 (s, 6 H, OCH_3), 6.28 (m, 2 H, pyr-H), 6.77 (m, 2 H, pyr-H), 6.97 (m, 2 H, pyr-H), 7.24 (s, 2 H, Ph-H), 9.48 (br. s, 2 H, pyr-NH) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 56.2, 106.1, 109.9, 111.5, 120.2, 129.3, 136.8, 141.7, 152.2 ppm. HRMS (CI^+) calcd. for $C_{18}H_{17}N_4O_2$ [M + H]$^+$ 321.1352; found *m*/*z*: 321.1352. $C_{18}H_{16}N_4O_2$·0.25 H_2O: calcd. C 66.55, H 5.12, N 17.25; found C 66.55, H 5.08, N 17.11.

Crystallization of 21: Receptor **21** was dissolved in boiling acetone and then allowed to cool to room temp. Yellow crystals of **21**, suitable for X-ray diffraction analysis, were obtained by letting stand overnight.

^{1}H NMR and UV/Vis Titration Studies

^{1}H NMR titration studies were carried out with either a Varian 300-MHz or Bruker 250-MHz NMR spectrometer. All samples were prepared in [D_6]acetone, dried over activated 4-Å molecular sieves. The trifluoromethanesulfonate salts (sodium and potassium), Kryptofix® 222 and KF were dried under vacuum at 40 °C for 12 h prior to use. The preparation of the potassium cryptand[2,2,2] fluoride salt was attempted by stirring a 1:1 mixture of the Kryptofix® 222 and KF in a known concentration of crowned dipyrrolylquinoxaline host for 12 hours. The cationic guest in question was dissolved in a solution of the receptor at the initial concentration of the receptor to account for dilution effects. The guest was added in aliquots to provide increasing concentrations of the guest in the initial receptor solution until saturation of the signal was observed. For the cation binding studies, the shift of the benzyl hydrogen on the quinoxaline unit was followed. The data were fit to a 1:1 binding profile using the Wilcox equation.[21] Job plots and mole ratio plots were used to determine binding stoichiometry when possible.[22] Fits of the titration profiles for **1**−**4** and **21** from ^{1}H NMR titration experiments, and stoichiometric determinations can be found in the Supporting Information.

X-ray Crystallographic Study

Single crystal X-ray diffraction data were collected for free receptors **1**, **2**, **21** and the potassium complex of **2** ([**2·K⁺**]). For each structure the data were collected on a Nonius−Kappa CCD diffractometer at 153(2) K by using a graphite monochromator with Mo-K_α radiation (λ = 0.71073 Å). Crystal and refinement data are listed in Table 2. CCDC-183336 to -183339 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) + 44-1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

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