Fluorinated Calix[4]pyrrole and Dipyrrolylquinoxaline: Neutral Anion Receptors with Augmented Affinities and Enhanced Selectivities

Pavel Anzenbacher, Jr.,[†] Andrew C. Try,[†] Hidekazu Miyaji,[†] Karolina Jursíková,[†] Vincent M. Lynch,[†] Manuel Marquez,*[,‡] and Jonathan L. Sessler*[,†]

Contribution from the Department of Chemistry and Biochemistry and Institute for Cellular and Molecular Biology, University of Texas at Austin, Austin, Texas 78712-1167, Los Alamos National Laboratory, Chemical Science & Technology Division, Los Alamos, New Mexico 87545, and Kraft, R&D, The Nanotechnology Laboratory, 801 Waukegan Road, Glenview, Illinois 60025

Received June 12, 2000

Abstract: The use of the 3,4-difluoro-1*H*-pyrrole as a building block for the preparation of octamethyloctafluorocalix[4]pyrrole and 2,3-di(3′,4′-difluoropyrrol-2′yl)quinoxaline is described. These latter two entities act as neutral anion receptors and were found to bind anions such as fluoride, chloride, or dihydrogen phosphate with an enhanced affinity compared to their non-fluorinated congeners as judged from ^{1}H NMR, ^{19}F NMR, and fluorescence emission spectroscopic analyses. The increase in affinity was especially high in case of chloride and dihydrogen phosphate anion, with the 2,3-di(3′,4′-difluoropyrrol-2′-yl)quinoxaline system, in particular, displaying an affinity for $H_2PO_4^-$ that was improved by 3 orders of magnitude as compared to its non-fluorinated congener. This improvement in the affinity for the dihydrogen phosphate is accompanied by change of color from pale yellow to orange, thus allowing the use of such compounds as naked-eye sensors for phosphate anion. In the case of the octafluorocalix[4]pyrrole system X-ray diffraction analyses revealed the presence of four different macrocyclic conformations in the solid state, as well as close intermolecular contacts mediated by apparent CF- -HN hydrogen bonds.

Introduction

The search for receptors capable of effecting the selective complexation and sensing of negatively charged species continues to attract considerable attention within the scientific community.[1] Despite considerable effort, however, receptors capable of binding of simple inorganic anions such as fluoride, chloride, or phosphate with high affinity remain rare.[1,2] Unfortunately, attempts to increase the inherent affinity or improve specificity are generally accompanied by an increase in design complexity and attendant difficulties in receptor construction. Two classes of receptors that are easy to make are the calix[4]pyrroles and the dipyrrolylquinoxalines. Interestingly, calix[4]pyrroles were found to bind both neutral[3] and anionic[4] substrates, while dipyrrolylquinoxalines were found to act as colorimetric sensors for anions, namely for fluoride.[5a] In the case of the calix[4]pyrroles[4] we reported recently how the anion binding could be tuned via the synthetic placement of electron-withdrawing or -donating substituents at the β-pyrrolic positions.[4c] Likewise, the anion affinities of the dipyrrolylquinoxalines were found to be increased when nitro groups were present in the 6-position of the quinoxaline ring.[5a] In this work we report the synthesis of fluorinated analogues of calix[4]pyrrole **1** and dipyrrolylquinoxaline **3**, specifically receptors **2** and **4**, derived from 3,4-difluoro-1*H*-pyrrole (Figure 1).[6] These new systems not only exhibit anion binding affinities that are substantially increased relative to the unsubstituted "parents", they are also found to possess dramatically altered anion selectivities.

Experimental Section

All starting materials were purchased from Aldrich Chemical Co. and used without further purification unless otherwise stated. Pyrrole was distilled under argon prior to use. All solvents including the HPLC-grade solvents used in spectroscopic studies were purchased from EM Science. Methanol and dichloromethane used in the syntheses of receptors was distilled from calcium hydride under atmosphere of inert gas. All NMR solvents were purchased from Cambridge Isotope Laboratories, Inc. ^{1}H and ^{19}F NMR spectroscopic titrations were

[†] University of Texas at Austin.

[‡] Los Alamos National Laboratory.

(1) (a) Desverne J.-P., Czarnik A. W., Eds. *Chemosensors of Ion and Molecular Recognition*; NATO Advanced Study Institute Series C; Kluwer: Dordrecht, 1997; Vol. 492. (b) de Silva A. P.; Guanarante, H. Q. N.; Gunnlaugson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515−1566. (c) Beer P. D. *Chem. Commun.* **1996**, 689−696. (d) Atwood, J. K.; Holman, K. T.; Steed, J. W. *Chem. Commun.* **1996**, 1401−1407. (e) Dickens, R. S.; Gunnlaugson, T.; Parker, D.; Peacock, R. D. *Chem. Commun*. **1998**, 1643−1644. (f) Fabbrizzi, L.; Faravelli, I.; Francese, G.; Licchelli, M., Perotti, A.; Tagletti, A. *Chem. Commun*. **1998**, 971−972. (g) Lavigne, J. J.; Anslyn, E. V. *Angew. Chem., Int. Ed*. **1999**, *38*, 3666−3669. (h) Kubo, Y.; Tsukahara, M.; Ishihara, S.; Tokita, S. *Chem. Commun.* **2000**, 653−654. (i) Hayashita, T.; Onodera, T.; Kato, R.; Nishizawa, S.; Teramae, N. *Chem. Commun.* **2000**, 755−756.

(2) (a) Cooper, C. R.; Spencer, N.; James, T. D. *Chem. Commun.* **1998**, 1365−1366. (b) Beer, P. D.; Szemes, F.; Balzani, V.; Salà, C. M.; Drew, M. G. B.; Dent, S. W.; Maestri, M. *J. Am. Chem. Soc.* **1997**, *119*, 11864−11875, (c) Huston, M.; Akkaya, E.; Czarnik, A. W. *J. Am. Chem. Soc.* **1989**, *111*, 8735−8737.

(3) Allen, W. E.; Gale, P. A.; Brown, C. T.; Lynch, V. M.; Sessler, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 12471−12472.

(4) (a) Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140−5141. (b) Gale, P. A.; Sessler, J. L.; Král, V. *Chem. Commun.* **1998**, 1−8. (c) Gale, P. A.; Sessler, J. L.; Allen, W. E.; Tvermoes, N. A.; Lynch, V. *Chem. Commun.* **1997**, 665−666.

(5) (a) Black, C. B.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 10438−10439, (b) Oddo, B. *Gazz. Chim. Ital.* **1911**, *41*, 248, (c) Behr, D.; Brandänge S.; Lindström, B. *Acta Chem. Scand.* **1973**, *27*, 2411−2414.

(6) Woller, E. K.; Smirnov V. V.; DiMagno, S. G. *J. Org. Chem.* **1998**, *63*, 3, 5706−5707.

10.1021/ja002112w CCC: $19.00
Published on Web 10/07/2000

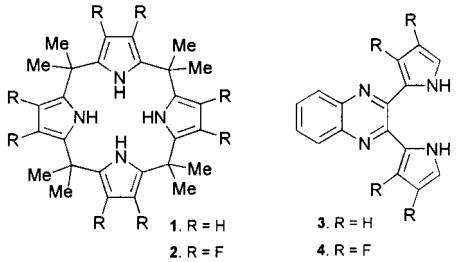

Figure 1. Structure of the *meso*-octamethylcalix[4]pyrrole (**1**, R = H) and dipyrrolylquinoxaline (**3**, R = H) and their octafluoro- (**2**, R = F) and tetrafluoro- (**4**, R = F) congeners.

recorded on Varian 300 MHz spectrometer. NMR spectra used in the characterization of products were recorded on Varian Unity 300 MHz and Varian 500 MHz spectrometers. Excitation and emission spectra were recorded using a Fluorolog 3 (Jobin Yvon-Spex) fluorimeter. Elemental analyses were performed by Canadian Microanalytical Service, Ltd, Delta, British Columbia, Canada. TLC analyses were carried out using Whatman K6F silica gel 60 Å, 250 μm plates. Column chromatography was performed on Whatman silica gel 60 Å (230−400 mesh). All NMR spectra were referenced to solvent; the ^{19}F NMR spectra were referenced to fluorotrichloromethane (internal standard). Calixpyrrole **1**[7] and dipyrrolylquinoxaline **3**[5] were prepared according to literature procedures.

Octamethyloctafluorocalix[4]pyrrole, 2. Calix[4]pyrrole **2** was prepared from the 3,4-difluoro-1*H*-pyrrole[6] using a modification of the standard literature methods:[7] 3,4-difluoropyrrole (206 mg, 2.0 mmol), acetone (146 μL, 2.0 mmol), and methanesulfonic acid (130 μL, 2.0 mmol) were dissolved in methanol (25 mL) and stirred at room temperature. After 5 days, the reaction mixture was worked up in the usual manner,[7] and the crude product was purified by flash chromatography (silica gel; dichloromethane-hexane 4:1, eluent). The calix[4]pyrrole product **2** was isolated in 55−60% yield. Slower eluting bands, containing predominantly calix[*n*]pyrrole materials with $n = 5$ and 8 (as inferred from mass spectrometric analysis) were also observed. For **2**: mp > 280 °C; ^{1}H NMR (dichloromethane-d_2, δ ppm) 1.51−1.64 (m, 24H, CH_3), 6.26 (bs, approximately 2H, NH monomeric form), 6.74−6.80 (b, approximately 2H, NH aggregate). ^{13}C NMR (dichloromethane-d_2, δ ppm, ^{19}F decoupled) 26.52−27.26 (multiple CH_3 signals), 35.38−39.20 (multiple meso-carbons), 114.95−115.29 (multiple pyrrole signals), 134.58−136.95 (multiple pyrrole signals). ^{19}F NMR (dichloromethane-d_2, Hz) −176.46 (monomeric form), −176.92, −176.93, −177.03, −177.07 (signals of the aggregate)

MS/CI$^+$ (*m*/*z*) 573 [M + H]. For $C_{28}H_{28}F_8N_4$·MeOH, calcd: C 57.61, H 5.33, N 9.27; found: C 58.01, H 5.1, N 8.98.

The di(3,4-pyrrolyl)quinoxaline **4** was prepared in two steps using a modification of the standard literature methods.[5]

1,2-Di(3′,4′-difluoropyrrol-2′-yl)ethanedione. Oxalyl chloride (800 μL, 8.64 mmol) and dichloromethane (15 mL) were placed together under an argon atmosphere and stirred. After the mixture cooled to −78 °C in an acetone/CO_2 bath, dry pyridine (1.28 mL, 15.8 mmol) was added, resulting in the formation of a yellow precipitate. To this cooled suspension was added a solution of 3,4-difluoropyrrole (1.49 g, 14.4 mmol) in dichloromethane (3 mL) via syringe. The reaction was allowed to stir for 3 h at −60 °C and then warmed to 0 °C over a 4 h period. The solution was then diluted with dichloromethane (20 mL) and washed with hydrochloric acid (3 M, 2 × 50 mL). The organic phase was separated and washed subsequently with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The acidic aqueous phase from the initial extraction was extracted with ethyl acetate (50 mL). The organic phase was separated off and washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. This afforded a green precipitate which was purified by column chromatography on silica gel (dichloromethane/ethyl acetate, 95:5 to 9:1 (v/v) as eluent) to afford 1,2-di(3′,4′-difluoropyrrol-2′-yl)ethanedione (405 mg, 21%, unoptimized) as a yellow powder: mp 260−263 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43−7.46 (2H, m), 12.36 (2H, br s, NH); ^{13}C NMR (125 MHz, DMSO d_6, ^{19}F decoupled) δ 110.7 (m), 113.3 (d, $J = 192$ Hz), 136.8 (dd, $J_1 = 9.1$, $J_2 = 1.5$ Hz), 141.0 (t, $J = 8.2$ Hz), 178.8; ^{19}F NMR (470 MHz, DMSO-d_6) δ −164.1, −177.9; HRMS (CI$^+$) *m*/*z* (M + 1) calcd for $C_{10}H_5F_4N_2O_2$: 261.0287, found: 261.0288. UV−vis (CH_2Cl_2) λ_{max} [nm] (ϵ) 260 (25 600), 300 (26 400), 412 (17 100); Anal. Calcd for $C_{10}H_4F_4N_2O_2$: C, 73.85; H, 4.62; N, 21.54. Found C, 73.66; H,4.60; N, 21.57.

2,3-Di(3′,4′-difluoropyrrol-2′-yl)quinoxaline (4). 1,2-Di(3′,4′-difluoropyrrol-2′-yl)ethanedione (112 mg, 0.43 mmol) and *ortho*-phenylenediamine (125 mg, 1.15 mmol) were dissolved in glacial acetic acid (20 mL). The resultant mixture was then heated at reflux under an atmosphere of argon in the dark overnight. The reaction mixture was evaporated to dryness under vacuum. The residue obtained in this way was purified using silica gel column chromatography (dichloromethane eluent). This afforded 2,3-di(3′,4′-difluoropyrrol-2′-yl)quinoxaline as a yellow-green powder (133 mg, 93%): mp 188−192 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.94−6.98 (2H, m, pyrrole H), 7.80−7.84 (2H, m, quinoxaline H), 8.01−8.05 (2H, m, quinoxaline H), 11.47 (2H, broad s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 104.0 (d, $J = 22$ Hz), 111.1 (d, $J = 16$ Hz), 128.3, 130.3, 136.3 (dd, $J_1 = 244$, $J_2 = 11$ Hz), 137.6 (dd, $J_1 = 235$, $J_2 = 11$ Hz), 139.7, 142.4; ^{19}F NMR (470 MHz, DMSO-d_6) δ −172.6 (dt, $J_1 = 12.2$, $J_2 = 3.3$ Hz), −180.5 (dt, $J_1 = 12.6$, $J_2 = 3.3$ Hz); HRMS (CI$^+$) *m*/*z* (M + 1) calcd for $C_{16}H_9F_4N_4$: 333.0763, found: 333.0754; UV−vis (CH_3CN) λ_{max} [nm] (ϵ) 220 (22 700), 253 (28 700), 295 (24 200), 397 (13 350); Anal. Calcd for $C_{16}H_8F_4N_4$: C, 57.84; H, 2.43; N, 16.86. Found C, 57.71; H, 2.50; N, 16.81.

^{1}H and ^{19}F NMR Titrations. The receptor **2**, as a 0.014 M acetonitrile-d_3 (0.5% v/v D_2O) solution, was titrated by addition of concentrated acetonitrile-d_3 (0.5% v/v D_2O) solutions of the anions in question (in the form of their tetrabutylammonium salts). To account for dilution effects, these anion solutions also contained receptor **2** at its initial concentration. The data were fit to a 1:1 binding profile according to the method of Wilcox[8a] using changes in both the NH and β-F pyrrolic resonances in the ^{1}H and ^{19}F NMR spectra, respectively, that were assigned to the portion of the total receptor concentration that was considered to be monomeric. Specifically, the change in the position of the peaks initially at 7.24 ppm (^{1}H NMR) and −177.03 ppm (^{19}F NMR) were followed. Integration of the two pyrrolic NH resonances (corresponding to calix[4]pyrroles that are "free" and bound to the next receptor molecule) made it possible to estimate the relative concentration of the monomeric fraction in the acetonitrile-d_3 (0.5% v/v D_2O) solutions being subject to analysis. This estimated monomeric receptor concentration was used to calculate the affinity constants. The affinity constants obtained in this way (see Results and Discussion section) were found to be independent of concentration over an initial receptor range of 4−14 mM. Estimated errors were <20%.

Fluorescence Titration Studies. Fluorescence quenching experiments were carried out in the following manner: Solutions of sensor **4** in dichloromethane were titrated with increasing quantities of concentrated solutions of the anion in question (in the form of their tetrabutylammonium salts). To account for dilution effects, these concentrated anions solutions also contained sensor **4** at its initial concentration. The concentration of sensor **4** in all experiments was 2.0 μM. The emission scan parameters used were as follows: excitation at $\lambda = 410$ nm, excitation and emission slits = 2 nm, spectrum increment = 1 nm, integration time = 1s. The binding isotherms (i.e., the dependence of F/F_o upon anion concentration) were linearized using Scott plot analyses as described by Connors[9] and detailed in a previous publication.[5a] The titration experiments were performed in triplicate. In all cases the resulting binding constants, corresponding to 1:1 receptor−substrate stoichiometries as judged from Job plots, did not

(7) (a) Rothemund, P.; Gage, C. L. *J. Am. Chem. Soc.* **1955**, *77*, 3340−3342.

(8) (a) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: Weinheim, 1991. (b) Anzenbacher, P., Jr.; Jursíková, K.; Lynch, V. M.; Gale, P. A.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 11020−11021.

(9) Connors, A. K. *Binding Constants: the Measurement of Molecular Complex Stability*; Wiley: New York, 1987.

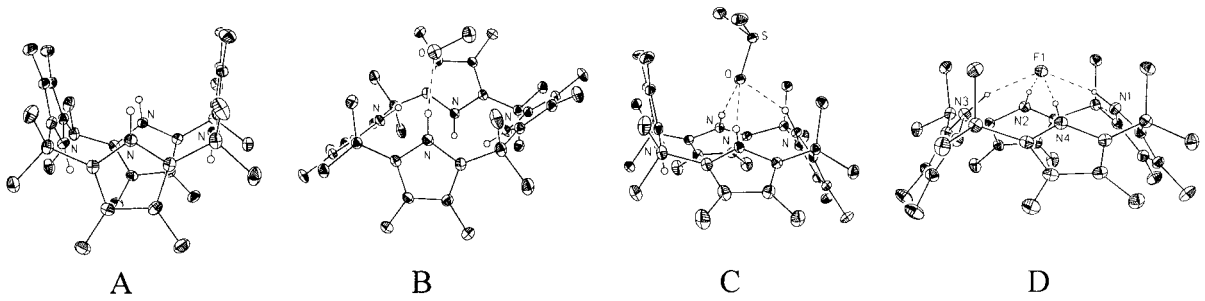

Figure 2. View of the 1,3-alternate (A) and 1,2-alternate (B), partial cone (B) and the cone (D) conformation of the calix[4]pyrrole **2**.

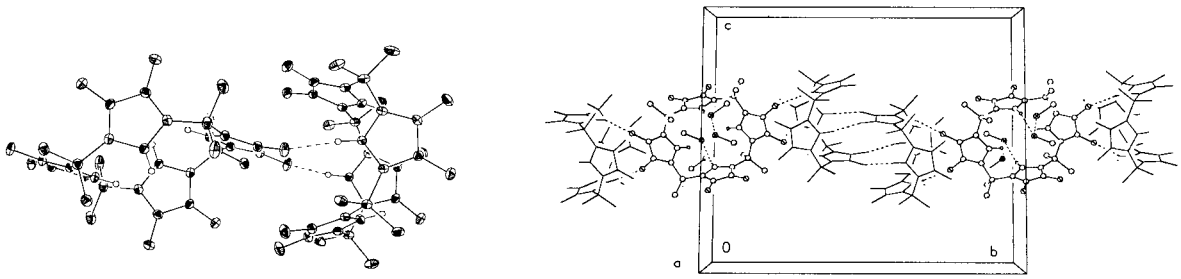

Figure 3. Schematic representation of the X-ray structure of aggregated form of **2** showing hydrogen bonding (dashed lines) between two molecules of **2**, and unit cell packing diagram. The aggregated form of **2** consists of a 1:1 mixture of the 1,3-alternate (see Figure 2A above), and the 1,2-alternate conformations (see Figure 2B above).

differ from one another by more than 15%. Control experiments carried out using unsubstituted quinoxaline did not show significant decreases in fluorescence intensity when exposed to F^-, Cl^-, or $H_2PO_4^-$ anions.

Results and Discussion

The synthesis of octafluorocalixpyrrole **2**, involving the condensation between 3,4-difluoropyrrole and acetone, was performed according to previously published procedures.[7] However, the low reactivity of the starting 3,4-difluoropyrrole requires longer reaction time ($\geq$5 days) as compared to the synthesis of **1**.[7] Nonetheless, good yields (55−60%) of **2** are obtained. Smaller quantities of calix[n]pyrrole products with inter alia $n = 5$ and 8 also appear to be formed as inferred from mass spectrometric analysis of the crude reaction mixture; the isolation and characterization of these latter products is currently in progress.

The introduction of the fluorine substituents in the β-pyrrolic positions of **2** led to a dramatic increase in the overall binding abilities of the receptor **2** compared to those of the non-fluorinated congener **1**. This is reflected by the increased affinity of **2** toward both neutral substrates and anions. In fact, we used this unprecedented affinity for neutral substrates to study the conformational behavior of the calixpyrrole **2**. The degree to which the hydrogen-bonding acceptors attract protons has a strong impact on the calix[4]pyrrole conformation. Weak hydrogen bond acceptors such as neutral substrates (alcohols, *N*,*N*-dimethyl formamide, etc.) generally support the 1,3-alternate or 1,2-alternate conformation,[3,4b] while stronger hydrogen bond acceptors enforce the conversion of the 1,3- and 1,2-alternate to the cone-like conformation, with all four pyrrole NHs hydrogen bonded to the acceptor. Good examples of these strong hydrogen bond acceptors are anions such as fluoride or chloride. The excellent hydrogen-bonding donor ability of receptor **2** suggested that the less stable conformations might be stabilized by the presence of weaker hydrogen bond acceptors. Hence we decided to crystallize receptor **2** from several different media, varying the ability of the medium to participate as the hydrogen bond acceptor. Predicative ^{1}H NMR spectral studies carried out in acetonitrile-d_3 (0.5% v/v D_2O) were used to select the appropriate hydrogen bond acceptors. On the basis of these analyses, we decided to use methanol as a weak acceptor, DMSO-d_6 as a medium strength acceptor, and fluoride anion as a very strong hydrogen bond acceptor. This use of different substrates has permitted all four basic conformations of the same calix[4]pyrrole macrocycle **2** to be identified unambiguously by X-ray crystallographic means. In the presence of methanol, the solid-state studies revealed that aggregated form of **2** (Figure 3) consists of a 1:1 mixture of the 1,3-alternate (Figure 2A), and the 1,2-alternate conformations (Figure 2B). Conversely, the presence of DMSO or fluoride anions led to the formation of the partial cone (Figure 2C) and the cone conformation (Figure 2D), respectively.

The ^{1}H NMR, ^{19}F NMR, and X-ray studies of **2** (cf. Figure 3) revealed rather complex behavior of **2** in both solution and the solid state. Calix[4]pyrrole **2** was found to form aggregates of hydrogen-bonding interactions involving two pyrrole NH donor sites on a single calixpyrrole ring and the fluorine substituents of a second molecule (Figure 3). This aggregation behavior of **2** was also reflected in the appearance of two different pyrrolic NH resonances in the ^{1}H NMR spectrum. For example in deuterated acetonitrile containing 0.5% v/v D_2O, the major upfield resonance (65−70%) at 7.24 ppm was attributed to the monomer, whereas the smaller downfield shifted resonance at 7.37 ppm was assigned to the NH protons involved in the aggregate-forming hydrogen-bonding interactions. Similarly, two resonances −177.03 and −177.52 (δ, ppm), corresponding to the "free" and bound (engaged in the hydrogen bonding) β-pyrrolic fluorine substituents, were likewise observed in the ^{19}F NMR spectrum of **2** in acetonitrile-d_3 (0.5% v/v D_2O).[10]

Quantitative assessments of the anion binding affinities of **2**

(10) Not surprisingly, the percentage of the monomeric fraction was seen to vary as a function of solvent and concentration. For instance, whereas 14 mM solutions of **2** in deuterated acetonitrile containing 0.5% v/v D_2O are ~65−70% monomeric in composition, this percentage increases to ~80 ± 5% at 4 mM. By contrast, in dichloromethane-d_2, very little monomer was seen at any concentration. In DMSO no signals ascribable to aggregate and very little to monomer were seen. In this case, the spectral features were best interpreted in terms of a DMSO complex.

Table 1. Affinity Constants[8] for **1**[8b] and **2** (mol^{-1}) for Anionic Substrates[a] and DMSO-d_6 as a Neutral Substrate Recorded in Acetonitrile-d_3 (0.5% v/v D_2O) at 22 °C

	1	**2**[b]	$R_{2/1}$
F^-	>10000	17100	≥1.71
Cl^-	5000	10 700	2.14
$H_2PO_4^-$	1300	9100	7.0
DMSO-d_6	<5[c]	20	>4.0

[a] Anions used in this assay were in the form of their tetrabutylammonium salts. [b] Fits were performed for the monomeric fraction of **2** using both pyrrole NH and pyrrole F resonances in the ^1H NMR and ^{19}F NMR spectra, respectively. For **2** the calculated affinity constants were found to be independent of concentration over the concentration range of 4 mM ≤ [**2**] ≤ 14 mM. All errors were ≤20%. For detailed description of titration experiments, see Experimental Section and literature reference.[8] [c] The interaction of **1** with DMSO-d_6 is too weak to allow for a more accurate estimation of the associated affinity constant.

were made by following the changes induced in the ^1H NMR and ^{19}F NMR spectra of the monomeric fraction of receptor **2** upon the addition of increasing concentrations of the anionic substrates in question, namely F^-, Cl^-, $H_2PO_4^-$, and DMSO-d_6 (Table 1). These experiments confirmed our expectation that **2** displays not only increased affinity for anions, specifically chloride and dihydrogen phosphate for which accurate K_a values for 1:1 complex formation could be obtained but also increased selectivities for certain anions as compared to **1**.[11] This increased selectivity is summarized in terms of the ratio of the binding constants, $R_{2/1}$. Separate from the issue of binding to the monomeric form, but complicating the analyses somewhat, was the finding that the addition of phosphate and fluoride to wet acetonitrile solutions of **2** led to deaggregation. This qualitative result is consistent with the proposed dramatic increase in affinity for phosphate that occurs when the β-pyrrolic protons of **1** are "replaced" by fluorine atoms to produce **2**.

Encouraged by the almost order of magnitude increase in the affinity for phosphate recorded with receptor **2**, we decided to apply the same approach to a second pyrrole-based anion receptor. Here, our choice was 2,3-dipyrrol-2′-ylquinoxaline, an easy-to-make species recently discovered to act as an effective colorimetric sensor for fluoride anion, but not chloride and dihydrogen phosphate.[5a] 2,3-Di(3′,4′-difluoropyrrol-2′-yl)quinoxaline **4** was prepared in 20% overall yield in two steps from difluoropyrrole according to methods described in the literature.[5]

With receptor **4** in hand, its anion sensing ability relative to the 2,3-dipyrrole-2′-ylquinoxaline **3** was studied by making a visual inspection of the color changes induced for dichloromethane, acetonitrile or DMSO solutions of **3** and **4** in the presence of anions (Figure 4). Whereas, compound **3** undergoes significant yellow-to-orange color change in the presence of fluoride anion, it does not undergo any color change in the presence of other anions tested, specifically Cl^-, Br^-, or $H_2PO_4^-$ (Figure 4, left panel). By contrast, compound **4** undergoes a sharp yellow-to-orange color change in the presence of both fluoride and dihydrogenphosphate anions. It does not, however, undergo any change of color in the presence of chloride anion (Figure 4, right panel).

More quantitative analyses of the anion-binding ability of **4** were made by observing the extent to which the fluorescence intensity of **3** and **4** was quenched in the presence of anions.[5a]

(11) Unfortunately, the presence of these two different receptor forms in solution precluded the use of Job plots to analyze binding stoichiometries. The presence of "spectator" aggregate species that do not participate materially in anion recognition would give rise to receptor/substrate ratios that were anomalously high, at least by such a proportional mole fraction-based method.

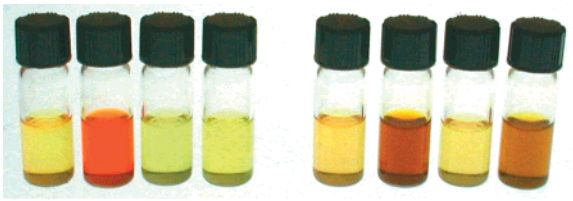

Figure 4. Color changes induced by the addition of anions (in the form of their tetrabutylammonium salts). From left to right: **3**; **3** + F^-; **3** + Cl^-; **3** + $H_2PO_4^-$; **4**; **4** + F^-; **4** + Cl^-; **4** + $H_2PO_4^-$. The concentrations of sensors **3** and **4** were 1 mM in dichloromethane and the concentrations of the anions were roughly 10 mM in all cases.

Table 2. Affinity Constants[9] for Compounds **3**[5a] and **4** (mol^{-1}) for Anionic Substrates[a] in Dichloromethane at 22 °C

	3	**4**	$R_{4/3}$
F^-	18200	61600	3.4
Cl^-	50	180	3.6
$H_2PO_4^-$	60	17300	288.3

[a] Anions used in this assay were in the form of their tetrabutylammonium salts. Fits were performed using single reciprocal plots[9] with stoichiometries (1:1) being obtained from Job plots. All errors were <12%. For a detailed description of titration experiments, see the Experimental Section and ref 5a.

The resulting values are listed in Table 2.

While, as expected,[5a] fluoride anion gave rise to the largest response, an inspection of Table 2 reveals that introduction of fluorine atoms on to the β-pyrrolic positions of 2,3-dipyrrole-2′-ylquinoxaline moiety leads to a remarkable increase in the selectivity for $H_2PO_4^-$ relative to Cl^-. The 3 orders of magnitude increase in affinity for phosphate, something not seen previously in dipyrrolylquinoxaline systems,[5a] may be potentially advantageous in biological phosphate-sensing applications where a high concentration of interfering Cl^- (but not F^-) pertains.

Conclusions

The introduction of the electron-withdrawing fluorine substituents to the β-pyrrolic positions of the calix[4]pyrrole and 2,3-dipyrrol-2′-ylquinoxaline results in dramatic increases in the affinity these receptors display toward anionic substrates in solution. It also appears to increase the propensity of the first of these systems to interact with neutral substrates in the solid state. These latter interactions, as well as those involving anions, allowed all four of the possible conformations of a calix[4]-pyrrole macrocycle to be characterized by X-ray crystallographic analysis, a feat that to the best knowledge is unequaled in the hetero-calix[4]arene literature as a whole.

The present results also illustrate how the anion binding properties of receptors may be very effectively tuned by the introduction of fluorine substituents. This is not only potentially useful, it is also scientifically noteworthy, since the introduction of other halogens, such as bromine, did not lead to a substantial change in substrate selectivity in the case of the calixpyrroles.[4b,c] In the case of the dipyrrolylquinoxalines, the introduction of fluorine substituents opens up the possibility of producing more efficient and selective optical sensors capable of sensing of not only fluoride anion but also biologically more relevant species, such as dihydrogen phosphate, via a so-called "naked eye" approach.

Acknowledgment. This work was supported by NSF and NIH (Grants CHE9725399 and GM58907, respectively, to J.L.S.) as well as the Texas Advanced Research Program.

Supporting Information Available: Full experimental data for the solid-state studies on compound **2**, fits of the titration profiles for **2** from ^{1}H NMR,^{19}F NMR titration experiments, Scott plot analyses for the fluorescence titrations using **4**, and Job plots for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA002112W