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BF_2 Complex of Fluorinated Dipyrrolyldiketone: A New Class of Efficient Receptor for Acetate Anions

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The β-fluorinated derivative (**2b**) of the 1,3-dipyrrolyl-1,3-propanedione BF_2 complex has been prepared from 3,4-difluoropyrrole and malonyl chloride, followed by treatment with BF_3·OEt_2. Despite the simple, acyclic, and neutral structure, **2b** exhibits efficient 1:1 binding for anions in CH_2Cl_2 using the bridging CH and pyrrole NH as interaction sites. The binding constant (K_a) of **2b** for acetate ($CH_3CO_2^-$), associating more effectively than anions such as F^-, Cl^-, Br^-, $H_2PO_4^-$, and HSO_4^-, is estimated to be 9.6×10^5 M^{-1}, ~9 times larger than that of the β-H derivative **2a** (1.1×10^5 M^{-1}). The UV–vis and fluorescence spectral changes of **2b** elucidate the effective recognition of an amino acid, such as phenylalanine, in the anionic form; this is also supported by CD spectral changes with mirror images by L- and D-isomers. Furthermore, in the solid state, BF_2 complex **2b** provides Cl^--bridged supramolecular networks and, in sharp contrast, deprotonated "anionic" self-assembled structures by F^- binding.

Introduction

Recognition of inorganic and biotic anions such as acetate, phosphate, and halide, ubiquitous in biology, concerns essential aspects such as the activity of enzymes, transport of hormones, protein synthesis, and DNA regulation.[1] As an example, the antibiotic ristocetin has been known to efficiently and selectively bind amino acid carboxylates.[2] To date, considerable effort has been devoted to the development of artificial acetate ($CH_3CO_2^-$) and carboxylate receptors and carriers, and various binding motifs have been synthesized.[3] For example, thiourea-based naphthalimides make possible color changes by association with acetate in aqueous solution.[3c] Furthermore, amino acid binding has been achieved by synthetic receptors, such as guanidiniocarbonyl pyrroles and open-chain metal complexes.[4,5]

The acyclic and simple geometries of the oligopyrrole receptors are suitable for versatile anionic species using the conformation changes, and their binding behaviors would be modulated by the structure modifications.[6] Recently, we have reported a new class of anion receptors, BF_2 complexes of 1,3-dipyrrolyl-1,3-propanediones (e.g., **2a** and **2a′**),[7] which efficiently bind anions using two pyrrole NH units and a

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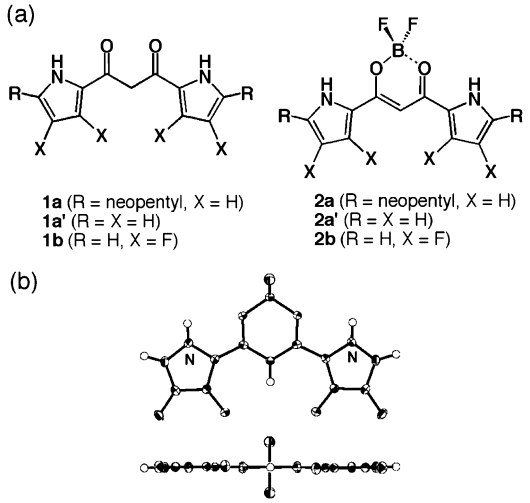

Figure 1. (a) Structures of dipyrrolyldiketones (**1a**, **1′**, and **1b**) and BF_2 complexes (**2a**, **2a′**, and **2b**) and an (b) an ORTEP drawing of **2b** by X-ray analysis (top and side view). Thermal ellipsoids are scaled to the 50% probability level.

bridging CH. A rather weak CH binding site plays an essential role in this system, elucidated by the derivatives with partially blocked interaction sites.[7b] Structural modification of these receptors would provide enhanced binding behaviors for anions including biotic negatively charged species. In this article, the selective acetate-binding property of the fluorinated derivative of the dipyrrolyldiketone BF_2 complex (**2b**), as shown in Figure 1a, is reported. The electron-withdrawing fluorine group not only makes NH more polarized to enhance the affinities for anions[6b] but also allows the receptor to associate with biotic anionic species such as amino acids in polar media.

Results and Discussion

Synthesis and Solid State Structure. The fluorinated dipyrrolyldiketone derivative (**1b**) was synthesized from 3,4-difluoropyrrole[8] and malonyl chloride in CH_2Cl_2 in an 11% yield.[7,9] BF_2 complexation was performed by treatment with excess $BF_3{\cdot}OEt_2$ to give **2b** in a 64% yield. The exact conformation and self-assembly of **2b** were elucidated by X-ray single-crystal structure analysis. Three "heterocycles" are almost in flat geometry (Figure 1b), wherein the mean plane deviation, consisting of 16 atoms, is 0.014 Å. Similar to the β-H derivatives,[7] two pyrrole NH units point toward the oxygen site. NH intermolecularly interacts with βC−F (F···H−N = 3.290 and 3.327 Å), as well as B−F (F···H−N = 2.832 Å).

Anion Binding Properties in Solution. The anion binding properties of **2b** were examined by UV−vis absorption and fluorescence spectral changes in CH_2Cl_2. When $CH_3CO_2^-$ is added to the **2b** solution, the absorption maximum of **2b** at 421 nm, which is 36 nm blue-shifted compared to **2a** (457 nm), decreases and shifts to 426 nm with a new shoulder at ∼450 nm (Figure 2a). In contrast, the slightly decreased and red-shifted (3 nm) absorption is observed in **2a** (Figure 2b). The 1:1 binding stoichiometry is confirmed by a Job plot. In F^- binding, on the other hand, spectral changes similar to those for the $CH_3CO_2^-$ binding of **2b** are observed by the titration of small amount of anion, and further addition of F^- makes the band of **2b** at 456 nm increase, possibly because of the NH deprotonation.

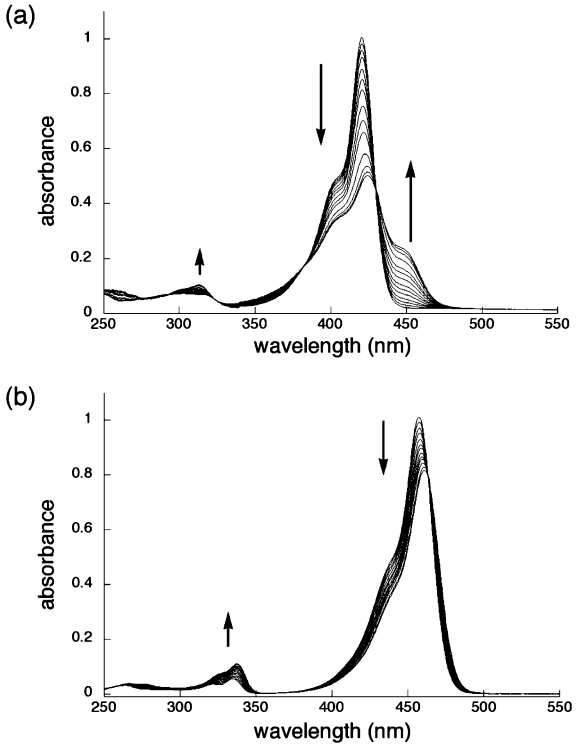

Figure 2. UV−vis absorption spectral changes of (a) **2b** (1.0×10^{-5} M) and (b) **2a** (1.6×10^{-5} M) upon the addition of $CH_3CO_2^-$ (0−3.1 and 0−4.9 equiv, respectively) as a tetrabutylammonium salt in CH_2Cl_2.

Table 1. Anion Binding Constants (K_a, M^{-1}) of **2a** and **2b** upon Addition of Anions as Tetrabutylammomium Salts in CH_2Cl_2

	2a	2b	$R_{2b/2a}$
F^-	81 000[a,b]	160 000	2.0
Cl^-	2000[a]	26000	13
Br^-	330[a]	1700	5.2
$CH_3CO_2^-$	110 000	960 000	8.7
$H_2PO_4^-$	13 000[a]	190 000	15
HSO_4^-	80[a]	1100	14

[a] Ref 7a. [b] Association constant for 1:1 binding was estimated by using the first stage of spectral changes. However, the K_a value is not exact because of the partial overlap with the second transition assignable to NH deprotonation, also inferred by X-ray diffraction analysis. The pK_a values of pyrrole and 3,4-difluoropyrrole are 16.5 and 11.8, respectively.[8]

The association constant (K_a) of **2b** for F^-, smaller for the binding cavity,[7b] is only 2-fold larger than that of **2a** (Table 1). On the other hand, for other anions such as $CH_3CO_2^-$, and Cl^-, Br^-, $H_2PO_4^-$, and HSO_4^-, the β-F derivative **2b** exhibited enhanced binding constants, estimated by 1:1 curve fitting according to the previous procedures.[7] Among the examined anions, the interaction with $CH_3CO_2^-$ is much higher ($K_a = 1.1 \times 10^5$ and $9.6 \times$

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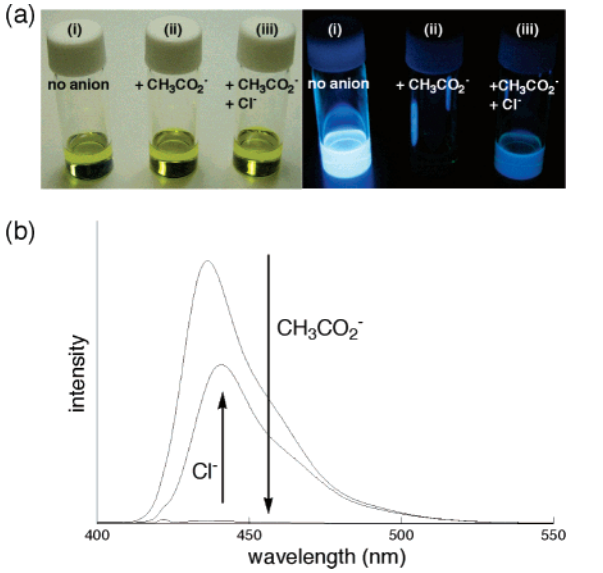

Figure 3. (a) Color (left) and fluorescent emission (right, $\lambda_{ex} = 365$ nm) changes of **2b** (1×10^{-3} M) in CH_2Cl_2: (i) no anion, (ii) $CH_3CO_2^-$ (2 equiv), and (iii) the mixture of $CH_3CO_2^-$ (2 equiv) and Cl^- (2000 equiv) in each photograph. (b) The recovery of emission ($\lambda_{ex} = 420$ nm) upon the addition of Cl^- (3 equiv) into the CH_2Cl_2 solution of **2b** (1.5×10^{-6} M) quenched by $CH_3CO_2^-$ (3000 equiv).

10^5 M^{-1} for **2a** and **2b**, respectively) than that for the other anions, possibly because of the adequate size and multiple binding sites of $CH_3CO_2^-$. Moreover, the fluorescence emission of **2b** at 436 nm is completely quenched upon the addition of $CH_3CO_2^-$, as well as the addition of F^- and $H_2PO_4^-$ in CH_2Cl_2, possibly because of the intramolecular electron transfer. On the other hand, Cl^-, Br^-, and HSO_4^- do not suppress the fluorescence and recover the emission by competition with "quenching" anions (Figure 3). In contrast, the β-H derivative **2a** does not show any significant fluorescence quenching upon addition of $CH_3CO_2^-$ and $H_2PO_4^-$.

The bridging CH···X^- interaction[10−12] has been suggested by ^{1}H NMR chemical shifts in CD_2Cl_2. Upon addition of $CH_3CO_2^-$ at −50 °C, both the NH and CH peaks (9.02 and 6.65 ppm) disappear, and new signals appear in the downfield region (12.09 and 8.23 ppm, respectively, Figure 4a). Similar downfield shifts by $CH_3CO_2^-$ are also observed in **2a** (Figure 4b). Cl^- also shifts the signals of **2b** to 11.82 (NH) and 8.31 ppm (CH) at −50 °C. The discrete resonances of two species, the anion complex and the free receptor, provide the suggestion that the equilibrium between these situations is slow to be detected on the NMR time scale. Upon F^- titration, on the other hand, the CH signal is shifted to 6.81 from 6.71 ppm at room temperature, and the NH signal is broadened and fades out even at low temperature.

DFT calculations at the B3LYP/6-31G(d,p) level also afforded possible anion binding modes of **2b**, wherein two NH units and one CH associate with each anion (Figure 5).[13] The estimated C−H···X (X = F, Cl, O) distances for each anion are 2.853 (F^-), 3.465 (Cl^-), 3.027 ($CH_3CO_2^-$), and 3.030 Å ($H_2PO_4^-$), respectively. In the $CH_3CO_2^-$ and $H_2PO_4^-$ complexes, the optimized structures, inferred by ^{1}H NMR, in Figure 5 are 2.41 and 4.27 kcal/mol more unstable than those with two N−H···O interactions. In solution, however, two binding modes are exchanged by rapid equilibrium because of the symmetrical resonances, as well as the downfield shifts of bridging CH.

Amino Acid Binding. Selective $CH_3CO_2^-$ binding of the receptors **2a** and **2b** has prompted us to investigate the association behaviors for amino acids.[14] The affinity with such species by fluorinated **2b** was examined by the tetrabutylammonium salt of anionic amino acids.[15] The binding constant of **2b** for L-phenylalanine carboxylate, used because of its good solubility in organic solvents as an anionic form, was estimated to be 2×10^6 M^{-1}, enhanced by 14 times compared to that of **2a** (1.4×10^5 M^{-1}), by absorption spectral changes in CH_2Cl_2. Amino acid binding was further confirmed by fluorescence quenching and circular dichroism (CD) signals, in which the L- and D-phenylalanines exhibited mirror images (Figure 6). The K_a values are comparable to those for $CH_3CO_2^-$. The DFT calculations for **2a′** and **2b** show two types of binding mode for anionic glycine, as a simple amino acid adequate for theoretical study, like $CH_3CO_2^-$.

Furthermore, in DMSO, the binding constants of **2a** and **2b** for L-phenylalanine carboxylate are 1.9×10^4 and 3.9×10^6 M^{-1}, respectively, which indicate that the augmentation

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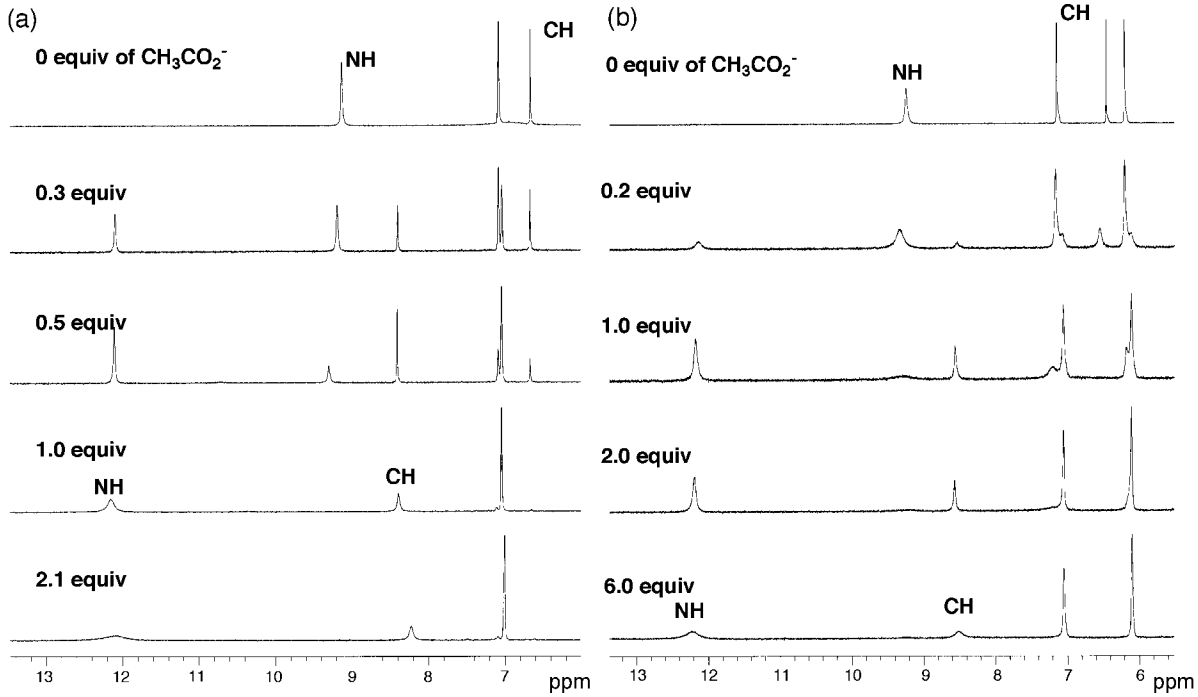

Figure 4. ^{1}H NMR spectral changes of (a) **2b** (2.3×10^{-3} M) and (b) **2a** (3.0×10^{-3} M) in CD_2Cl_2 at −50 °C upon addition of $CH_3CO_2^-$ (0−2.1 and 0−6.0 equiv, respectively) as a tetrabutylammonium salt.

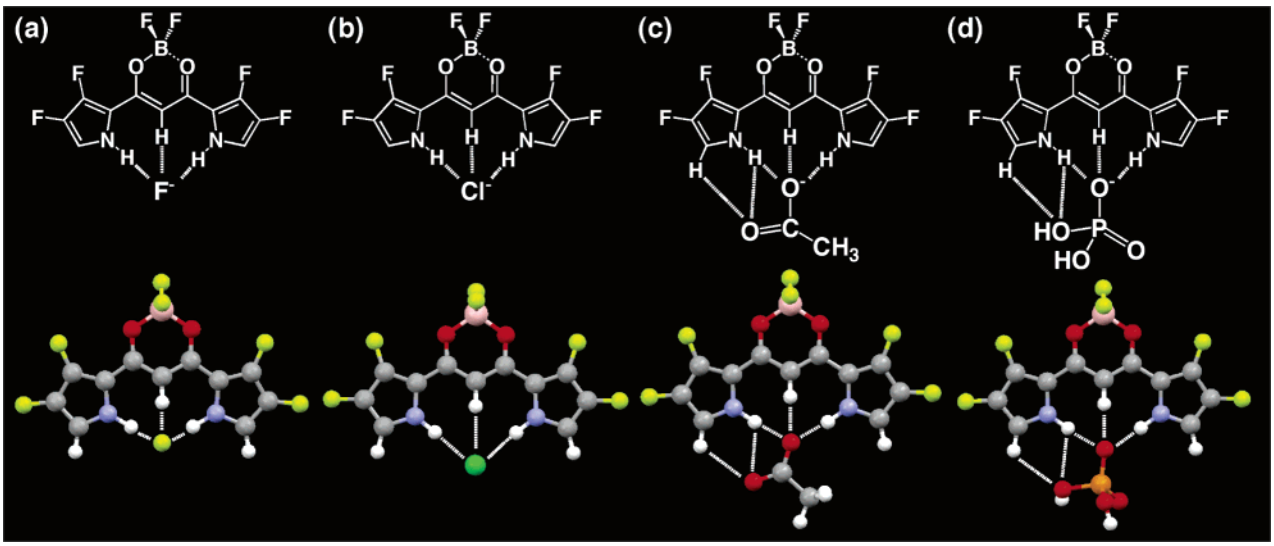

Figure 5. Possible binding structures of **2b** optimized by DFT calculations for (a) F^-, (b) Cl^-, (c) $CH_3CO_2^-$, and (d) $H_2PO_4^-$.

of **2b**, compared to that of **2a**, is much larger (∼200 times) in polar solvent than in nonpolar CH_2Cl_2 (Table 2).[16] The larger K_a of **2b** in DMSO may be related to the conformational changes of the receptor. Similarly, the binding constants of **2a** and **2b** for $CH_3CO_2^-$ were estimated to be 4.1×10^4 and 2.9×10^6 M^{-1}, respectively, in DMSO, in which fluorescence of **2b** was quenched by amino acid and $CH_3CO_2^-$. Acyclic receptors, especially the β-F derivative, are suitable for binding such rather large biotic anions.

1-D Supramolecular Networks. In contrast with the 1:1 binding mode of receptor **2b** in solution, the interaction with anions in the solid state would provide versatile fine-tuned nanostructures. So far, for example, self-assembled infinite rods have been fabricated using biscarboxylates.[17] In the anion binding system **2b**, actually, the formation of 1-D networks bridged by spherical Cl^-, probably appropriate for supramolecular assembly, was revealed by X-ray analysis (Figure 7a). Although the inverted pyrrole and bridging CH associate with the anion in the Cl^- complex of the unsubstituted BF_2 complex **2a′** (R = X = H in Figure 1),[7a] **2b**, instead, uses only the NH interaction site to fabricate the

(16) In a preliminary experiment using fluorescence, a small amount of water in DMSO has not interfered the amino acid binding.

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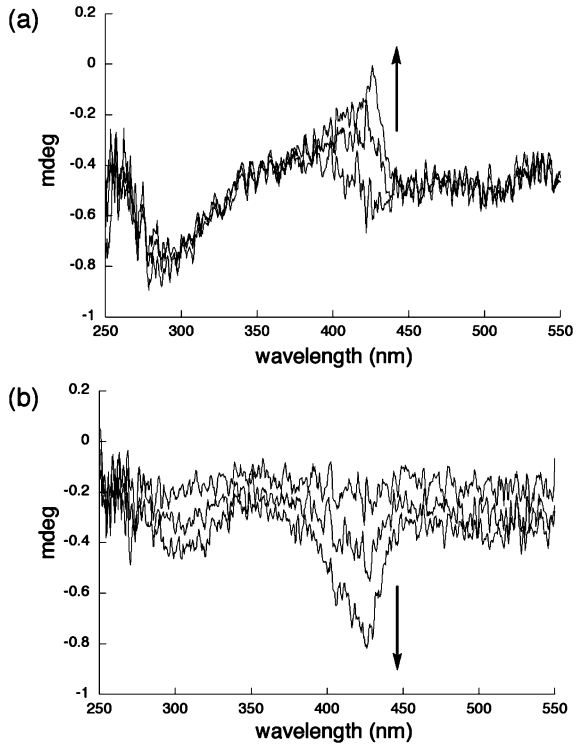

Figure 6. CD spectral changes of **2b** (1.0×10^{-5} M) with anionic (a) L- and (b) D-phenylalanine (0, 0.6, and 2.6 equiv) as tetrabutylammonium salts in CH_2Cl_2.

Table 2. Anion Binding Constants (K_a, M^{-1}) of **2a** and **2b** upon Addition of L-Phenylalanine as a Tetrabutylammomium Salt in CH_2Cl_2 and DMSO

	2a	**2b**	$R_{2b/2a}$
in CH_2Cl_2	140 000	2 000 000	14
in DMSO	19 000	3 900 000	210

supramolecular structure, possibly because of the more polarized NH than β-H derivatives. The atom distances between N−H···Cl^- are within hydrogen bonding, 3.085−3.087 Å. The neighboring anions are found to have a Cl···Cl length of 9.670 Å and a Cl−Cl−Cl angle of 130.053°.

In sharp contrast, the crystallization of a 1:1 mixture of **2b** with Bu_4NF gave self-assembly of the anionic form of **2b** by deprotonation of one of the pyrrole NH units, also observed in the solution study, in which the atom distances of N−H···N are 2.803 and 2.949 Å (Figure 7b). Similar deprotonations of the pyrrolic NH by fluoride and the formation of ion pair complex have been previously reported.[18] Surprisingly, single crystals obtained from CH_2Cl_2 and CH_2ClCH_2Cl, possible "chloride" sources, gave chloride-bridged supramolecular networks which are the same as those in the structure in Figure 7a by anion exchange.

Summary

Despite the simple, acyclic, and neutral structure, β-fluorinated derivative **2b**, a more efficient anion receptor than

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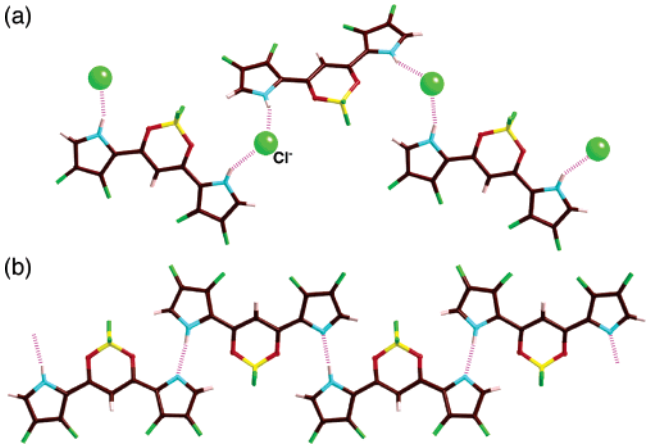

Figure 7. (a) Chloride-bridged network and (b) self-assembly of the anionic form of **2b** elucidated by X-day diffraction analysis. In both cases, the Bu_4N cations are omitted for clarity. Atom color code: brown, pink, blue, yellow, green, and yellow-green refer to carbon, hydrogen, nitrogen, boron, fluorine, and chlorine, respectively.

2a, can recognize natural amino acids in polar solvent. Planar but acyclic geometry should be appropriate for the interaction with versatile negatively charged moieties such as oxoanions. Therefore, further modification in the acyclic receptor will realize the binding and transportation of such biotic anionic species, including proteins and nucleotides, in water.

Experimental Section

General Procedures. Starting materials were purchased from Wako Chemical Co., Nacalai Chemical Co., and Aldrich Chemical Co. and used without further purification unless otherwise stated. UV−vis spectra were recorded on a Hitachi U-3500 spectrometer. The NMR spectra used in the characterization of products were recorded on JEOL AL-400 400 MHz and JEOL ECA-600HR 600 MHz spectrometers. All NMR spectra were referenced to solvent. Electrospray-ionization time-of-flight mass spectrometries (ESI-TOF-MS) were recorded on a BRUKER microTOF spectrometer using the negative ion mode. TLC analyses were carried out on aluminum sheets coated with silica gel 60 (Merck 5554). Column chromatography was performed on Sumitomo alumina KCG-1525, Wakogel C-200, C-300, and Merck silica gel 60 and 60H.

1,3-Bis(3′,4′-difluoropyrrol-2′-yl)-1,3-propanedione (1b). In analogy to a literature procedure,[7a,9b] a CH_2Cl_2 solution (10 mL) of 3,4-difluoropyrrole[8] (313 mg, 3.0 mmol) was treated with malonyl chloride (214 mg, 1.5 mmol) at room temperature and stirred for 6 h at the same temperature. After the consumption of the starting pyrrole was confirmed with TLC analysis, the mixture was washed with saturated Na_2CO_3 (aq) and water, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was then purified with flash silica gel column chromatography (eluent, 3% MeOH/CH_2Cl_2) and recrystallized from CH_2Cl_2/hexane to yield **1b** (44.0 mg, 11%) as a pale yellow solid. $R_f = 0.36$ (5% MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C; diketone **1b** is obtained as a mixture of keto and enol tautomers in the ratio of 1:0.83): δ (keto form) 8.53 (s, br, 2H, NH), 6.79 (m, 2H, pyrrole-H), 4.24 (s, 2H, CH_2); (enol form) 8.40 (s, br, 2H, NH), 6.72 (m, 2H, pyrrole-H), 6.43(s, 1H, CH_2). ESI-MS (%): *m*/*z* calcd for $C_{11}H_6F_4N_2O_2$ (M^+) 274.04; found 273.0 (100, M^- − 1).

BF_2 complex of 1b (2b). To an ether solution (12 mL) of diketone **1b** (10.0 mg, 3.7×10^{-2} mmol), BF_3·OEt_2 (0.14 mL, 1.1 mmol) was added and stirred for 1 h at room temperature. After

Table 3. Summary of Crystallographic Data for **2b**, **2b**·Bu_4NCl, and **2b**$^-$·Bu_4N^+

	2b	**2b**·Bu_4NCl	**2b**$^-$·Bu_4N^+
formula	$C_{11}H_5BF_6N_2O_2$	$C_{27}H_{39}BF_6N_3O_2Cl$	$C_{27}H_{40}BF_6N_3O_2$
fw	321.98	599.89	563.43
cryst size (mm)	0.60 × 0.30 × 0.20	0.45 × 0.30 × 0.07	0.45 × 0.15 × 0.10
cryst syst	orthorhombic	monoclinic	triclinic
space group	*Pbcn* (No. 60)	$P2_1/c$ (No. 14)	$P\bar{1}$ (No. 2)
a (Å)	9.554(2)	8.2698(18)	13.5058(15)
b (Å)	12.210(3)	20.811(5)	15.8124(17)
c (Å)	9.679(2)	18.059(4)	15.9566(17)
α (deg)	90	90	105.741(2)
β (deg)	90	98.926(4)	107.046(2)
γ (deg)	90	90	108.798(2)
V (Å^3)	1129.1(5)	3070.4(12)	2821.1(5)
ρ_{calcd} (g cm^{-3})	1.894	1.298	1.327
Z	4	4	4
T (K)	90(2)	90(2)	90(2)
reflns	6298	18 083	45 994
unique reflns	1321	6774	12 690
variables	101	365	711
λ(Mo Kα) (Å)	0.71073	0.71073	0.71073
R_1 [$I > 2\sigma(I)$]	0.0352	0.0749	0.0423
R_2 [$I > 2\sigma(I)$]	0.0897	0.1629	0.0952
GOF	1.034	1.318	1.040

removal of the solvent, flash silica gel column chromatography and crystallization from CH_2Cl_2/hexane afforded **2b** (7.5 mg, 64%) as a yellow solid. R_f = 0.50 (10% MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ 8.78 (br, 1 H, NH), 6.96 (s, 2 H, pyrrole-H), 6.69 (s, 1 H, CH). UV−vis (CH_2Cl_2, λ_{max} (ϵ, ×10^5 M^{-1} cm^{-1}): 421.0 (1.0). ESI-MS (%): *m*/*z* calcd for $C_{11}H_5BF_6N_2O_2$ (M^+) 322.03; found 321.0 (100, M^- − 1). This compound was further characterized by X-ray diffraction analysis.

Single-Crystal Diffraction Analysis. Data were collected on a Bruker SMART CCDC for **2b**, **2b**·Bu_4NCl, and **2b**$^-$·Bu_4N^+ and refined by full-matrix least-squares procedures with anisotropic thermal parameters for the non-hydrogen atoms. The hydrogen atoms were calculated in ideal positions. The solutions of the structures were performed by using the Crystal Structure crystallographic software package (Molecular Structure Corporation). Crystals of **2b** were obtained by vapor diffusion of hexane into a CH_2Cl_2 solution of **2b**. Crystals of the Cl^- complex of **2b** were obtained by vapor diffusion of hexane into a CH_2Cl_2 solution of the mixture of **2b** and 1 equiv of Bu_4NCl. Crystals of anionic **2b** were obtained by vapor diffusion of hexane into a THF solution of the mixture of **2b** and 1 equiv of Bu_4NF. The crystallographic details are summarized in Table 3.

Ab Initio Calculation. DFT calculations of **2a′** and **2b** and its F^-, Cl^-, $CH_3CO_2^-$, and $H_2PO_4^-$ binding complexes, as well as the amino acid complexes, were carried out using Gaussian 03 program[13] and an HP Compaq dc5100 SFF computer. The structures were optimized, and the total electronic energies were calculated at the B3LYP level using a 6-31G** basis set.

Titration Methods. The binding behaviors of **2b**, as well as those of **2a**, were investigated by ^{1}H NMR, UV−vis absorption, fluorescence, and CD spectral changes by anion binding. Anions such as F^-, Cl^-, $CH_3CO_2^-$, and $H_2PO_4^-$ as tetrabutylammonium salts, CH_2Cl_2 (for an analytical use, Nacalai), and anhydrous DMSO (Aldrich) were used without further purification. According to the previous procedures,[14] anionic amino acids were prepared from tetrabutylammonium hydroxide and slightly excess amino acids in methanol/water (1:1) followed by the removal of solvents. UV−vis absorption and fluorescence spectral changes, recorded on a Hitachi U-3500 and F-4500 spectrometers, respectively, were performed by the addition of anionic species in the corresponding solvent into the host solution. ^{1}H NMR spectral changes were recorded on a JEOL ECA-600HR 600 MHz spectrometer. CD spectra were recorded on a JASCO J-720W spectropolarimeter.

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Supporting Information Available: Synthetic procedures, ^{1}H NMR, UV−vis absorption, fluorescence, CD spectral changes by anion binding, and CIF files for the X-ray structural analyses of **2b**, **2b**·TBACl, and **2b**$^-$·TBA^+. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data (CCDC 290270−290272) for **2b**, **2b**·Bu_4NCl, and **2b**$^-$·Bu_4N^+ can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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