JOC The Journal of Organic Chemistry

Article

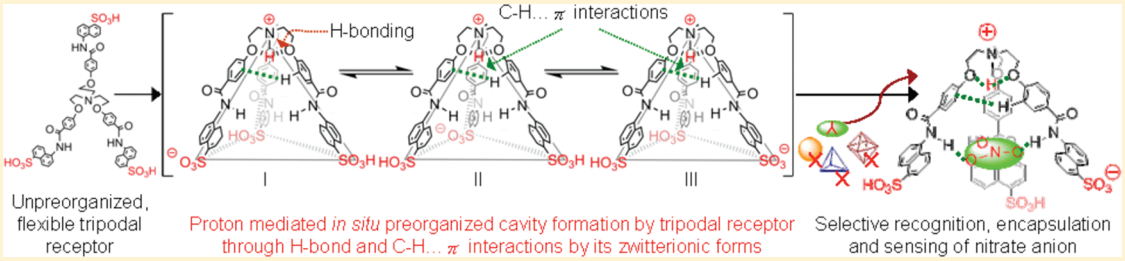
pubs.acs.org/joc

Recognition, Encapsulation, and Selective Fluorescence Sensing of Nitrate Anion by Neutral C_3-Symmetric Tripodal Podands Bearing Amide Functionality

Ashutosh S. Singh and Shih-Sheng Sun*

Institute of Chemistry, Academia Sinica, Taipei, 115, Taiwan, Republic of China

Supporting Information



ABSTRACT: A series of neutral C_3-symmetric acyclic artificial receptors incorporating amide functionality has been designed, synthesized, and fully characterized. Upon protonation, these conformationally flexible N-bridged tripodal podands **1**−**5** form in situ cone shape conformation through hydrogen bonding and C−H···π interactions. The protonation-induced interior preorganized cavity is capable of entrapping nitrate anions through the amide N−H bonds to form discrete nitrate complexes (**1a**−**5a**), which were fully characterized by NMR, HRESI mass spectra, and single crystal structures. By incorporating suitable fluorophores at each branch of the tripod receptor, the resulting fluorescent receptor **5** selectively recognized nitrate anions by fluorescent quenching in a DMSO solution and displayed one of the highest binding affinities for nitrate anions reported so far in polar media. Receptor **5** represents a unique example of a neutral receptor for the recognition of nitrate anions in polar solvent media by its zwitterionic form. The possible mechanism of proton-induced preorganization of these flexible, acyclic receptors in a convergent cone conformation followed by nitrate complexation has been proposed to rationalize the effective nitrate recognition.

INTRODUCTION

Selective recognition and sensing of anions by artificial receptors are of paramount significance in chemistry, biology, environmental science, and biomedical applications.[1] Developing effective probes for nitrate recognition and sensing is highly desirable because of its multiple sources of contamination from nuclear waste, industrial sewage, acid rain, fertilizers, and chemicals disposals. Because of the high hydration energy (ΔG_{hyd} = −300 kJ mol^{-1}), large ionic radii (196 pm),[1a] and weak basicity of nitrate anions that result in low affinity for hydrogen-bonding interactions, it is particularly challenging to design artificial receptors with appropriately matched complementary recognition motifs for weakly coordinating nitrate anions. To overcome the solvation effect, attempts have been made by using cage-typed receptors possessing a confined interior cavity for binding nitrate anions, and their selectivities are typically marginal in polar solvents such as DMSO.[2a,d,3] Thus, the design of receptors with straightforward synthetic procedures to achieve selective and effective recognition for nitrate anions is highly desirable.

Hydrogen-bonding interaction plays a crucial role in the anion recognition process.[4] The relative orientation[5] and the polarity[6] of hydrogen bonds as well as the numbers of available hydrogen bonds determine the strength of the resulting hydrogen-bonding interaction between a receptor and an anion. In general, an acyclic receptor without specific complementary structure favors to interact with basic anions via hydrogen-bonding interactions or, in some extreme cases, neat proton transfer process.[7] Inspired by biological processes of anion recognition and transporting via amide functionality,[8] many artificial receptors incorporating amide functional groups have been reported.[1c,2] Selective recognition of an anionic substrate in the biological process occurs in a specific hydrophobic recognition environment with complementary induced-fit conformation, and thus, free energy lost on the dehydration of anions upon binding is compensated by interaction of anions with available binding sites.[9] The lack of such unique binding nature in a typical artificial system renders selective recognition of weakly coordinating anions like nitrate anions a highly challenging task.

A variety of organic scaffolds and functional groups containing hydrogen-bond donors have been utilized for anion recognition, such as hydrazones,[10] amides,[2,11] sulfona-

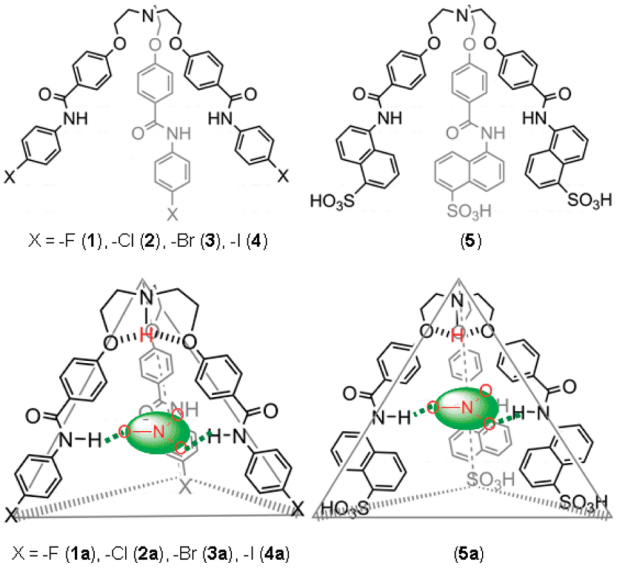
Received: December 6, 2011
Published: January 22, 2012

dx.doi.org/10.1021/jo202502f | J. Org. Chem. 2012, 77, 1880−1890

mides,[4,12] thioamides,[13] pyrroles,[14] imidazolium cations,[15] ureas,[16] thioureas,[17] and guanidinium and amidinium cations.[17a,18] For weakly coordinating nitrate anions with large hydration shells, however, even these hydrogen-bond donors alone are sometimes not sufficient for effective binding of nitrate anions, especially in a solution medium.[2c,19] Thus, a combination of electrostatic and hydrogen-bonding interactions imparted on the receptor moiety would be an appropriate choice for the selective recognition of weakly coordinating nitrate anions.

In our previous report, we have demonstrated the halide functionality-dependent properties on the formation of molecular receptors.[20] We have also shown the reversible binding of perchlorate anions by a structurally simple tripodal podand. However, the driving force for the formation of such a perchlorate-encapsulated dimer was mainly electrostatic interactions and solid-state packing effects, and thus no particular selectivity can be expected. In the present case, we have further elaborated the tripodal receptors by incorporating interior amide functionality with halide groups at the end of each tripodal arm. An elegant example reported by Moyer's group suggested that a C_3 symmetric arrangement of the amide functionality is required for the effective binding of nitrate anions.[21] Amide N−H bonds are well-known to interact with anions in both natural[8] and artificial systems,[1c,2,11b] whereas the halide group is expected to increase the amide N−H polarizability via an inductive effect. We herein report a series of highly flexible, acyclic molecular receptors **1**−**4** (see Scheme 1), which converge to form a cone shape conformation upon protonation that recognizes and reversibly binds nitrate anions by a combination of electrostatic and H-bonding interactions to form robust nitrate complexes **1a**−**4a**.

Scheme 1. Schematic Representation of Receptors (Top) and Topographical Representations of Their Nitrate Complexes (Bottom)[a]



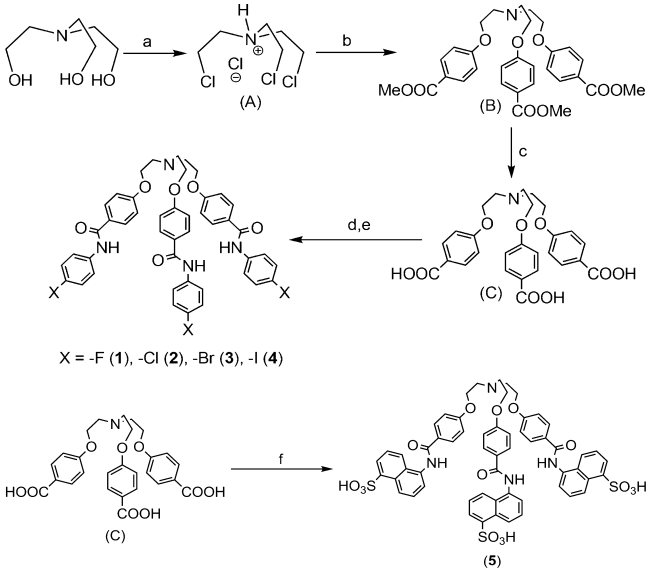
[a]The branches of each receptor in the nitrate complex lie on the apex of equilateral triangle.

In addition, incorporation of fluorescent dansyl groups to the tripodal framework effectively converts the tripodal receptor to a selective fluorescent nitrate anion probe (receptor **5**) in an aqueous DMSO solution. Here, the dansyl moiety serves two functions: (i) the ionization of sulfonic acid in the dansyl moiety helps receptor **5** transform to a cone shape conformation in polar solvents and (ii) the rotation of the dansyl moiety in receptor **5** around C−N bond would create a different steric environment to the in situ formed cavity by tripodal branches from those receptors **1**−**4**. These two special features of receptor **5** in its neutral form make it possible to recognize and encapsulate nitrate anions selectively in a highly polar aqueous DMSO solution. The crystal structures of nitrate complexes **2a**, **3a**, and **4a** further imply that apart from the flexibility of the receptors, the directionality of hydrogen bonds is equally significant for the selective recognition of weakly coordinating oxyanions such as the nitrate anion.

RESULTS AND DISCUSSION

Synthesis and Solid State Studies. Scheme 2 summaries the synthetic procedures for the tripodal receptors **1**−**5**. They were synthesized from previously reported tris(2-chloroethyl)-amine hydrochloride[22] (A) by simple SN_2 substitution with 4-hydroxymethylbenzoate in DMSO followed by basic hydrolysis to yield corresponding triacid (C). Conversion of the tracids (C) to their corresponding acyl chlorides followed by condensation reaction with 4-haloamines produced desired receptors **1**−**5** in 65−95% yields. The nitrate complexes (**1a**−**5a**) were prepared in 85−97% yields by dropwise addition of 10% nitric acid in aqueous methanol to the suspension of receptors in a mixture of methanol and chloroform at room temperature. When a suspension of receptors **1**−**5** in a mixture of MeOH and $CHCl_3$ was treated with dilute 10% nitric acid in aqueous MeOH, the solution mixture immediately became transparent and homogeneous. Precipitation of nitrate complexes **2a**−**5a** started to appear after stirring the solution mixture for 5−10 min. The rate of precipitation depends upon the ratio of $CHCl_3$ and MeOH in solution mixture, which was

Scheme 2. Synthetic Procedures for Receptors 1−5



(a) $SOCl_2$, $CHCl_3$, 92%. (b) *p*-OH-C_6H_4COOMe, KOH, DMSO, 78%. (c) 5 N NaOH, MeOH, dil HCl, 92%. (d) $SOCl_2$, DCM, DMF (cat.). (e) *p*-X-$C_6H_4NH_2$, DCM, Et_3N, 70%. (f) 5-aminonaphthalene-1-sulfonic acid, THF, Et_3N, 65%.

dx.doi.org/10.1021/jo202502f | J. Org. Chem. 2012, 77, 1880−1890

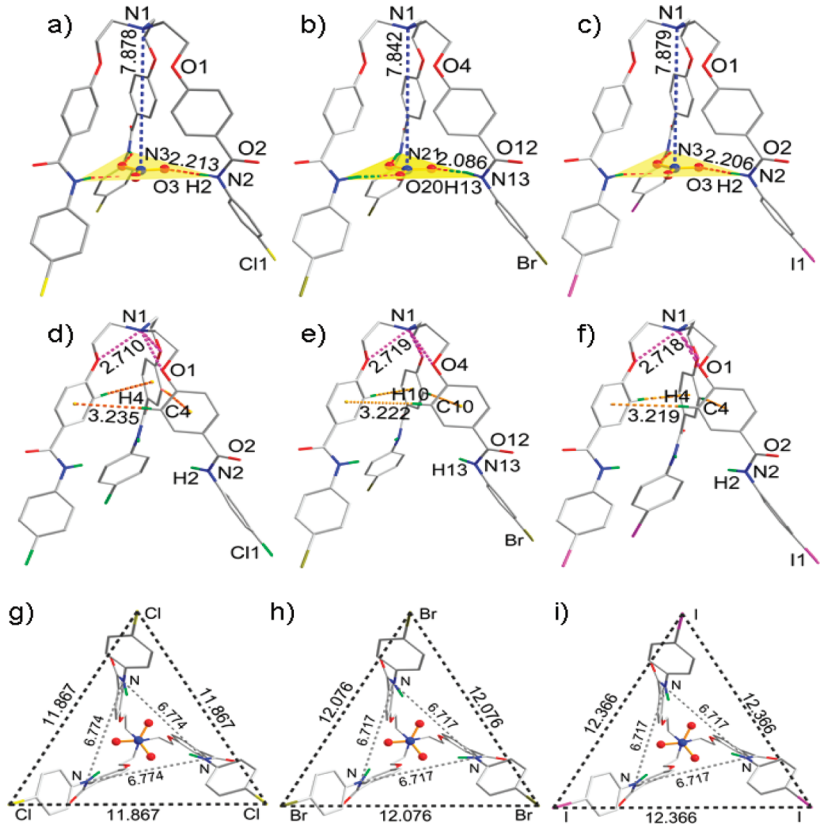


Figure 1. Crystal structures of nitrate complexes **2a** (left), **3a** (middle), and **4a** (right). (a–c) Formation of a discrete unit and (d–f) cavity formed by cooperative hydrogen-bonding interactions between the protonated centrally bridged N-atom and O-atom of aliphatic arm and C–H···π interactions among the C-terminal aromatic rings. The nitrate anions were removed for clarity, and (g–i) branches of the tripod lie at the apex of equilateral triangle. All hydrogen atoms have been deleted for clarity except for those interacting with the nitrate anions and showing C–H···π interactions.

speeded up by increasing the ratio of MeOH in solution. The nitrate complex **1a** was obtained after slow evaporation of the solution mixture over a period of one week. Alternatively, the nitrate complexes can also be prepared from other solvent mixtures such as MeOH/CH_2Cl_2, MeOH/CCl_4, EtOH/$CHCl_3$, and ^{t}BuOH/$CHCl_3$. The identity of receptors and their corresponding nitrate complexes have been fully characterized by NMR and high-resolution electrospray mass spectrometry (HRESIMS). Nitrate complexes **2a**–**4a** were further characterized by single crystal structures. The single crystals of **2a**, **3a**, and **4a** with suitable sizes for X-ray diffraction studies were grown by slow diffusion of chloroform to a methanolic solution of complex **2a** and **3a** and slow evaporation of a THF solution of complex **4a**, respectively. The formation of nitrate salts in current cases that can be crystallized and examined by X-ray diffraction represents an interesting concept for the anion recognition.

The crystallographic data and parameters for structure refinements of crystals **2a**, **3a**, and **4a** are collected in Table S1 and selective bond distances and bond angles are summarized in Table S2 (see the Supporting Information). The homogeneous nature of crystals for these nitrate complexes was confirmed by powder X-ray diffraction studies. Figure 1 illustrates the crystal structures and important structural characteristics. The single crystal X-ray diffraction studies show 1:1 identity of all nitrate complexes. The crystal structures of three nitrate complexes are isostructural with the same space group ($P\bar{3}$) and very similar cell parameters. All three structures **2a**, **3a**, and **4a** are C_3-symmetric, and the halide atoms of these complexes lie at the apex of isosceles (Figure 1g–i). The bridge N-atoms of the nitrate complexes are protonated, and the O-atoms of each aliphatic branch are equal distances from centrally bridged N-atoms, indicative of hydrogen-bonding interactions between the proton attached to central N-atom and O-atoms of each aliphatic branch. The closest distance between the centrally bridged N-atom and O-atoms of each aliphatic branch is 2.710 Å for **2a**, 2.719 Å for **3a**, and 2.718 Å for **4a**, respectively (Figure 1d–f).

One *ortho* hydrogen atom of the *C*-terminal aromatic ring of each branches are connected to *C*-terminal aromatic ring of neighboring arm through C–H···π interactions (Figure 1d–f) in a tilted edge-to-face form.[23] The amide N–H bonds of each branch protrude inside toward center *in plane* with the nitrate anion (Figure 1a–c). The interatomic distances between the receptor and nitrate anions of three nitrate complexes are summarized in Table S1 (see the Supporting Information). The nitrate anion is bound inside the cavity by strong H-bonds between O-atoms of the nitrate anion and three amide N–H protons ($d_{N-H\cdots O}$ 2.21 Å, $\theta_{N-H\cdots O}$ 156.88° for **2a**, $d_{N-H\cdots O}$ 2.09 Å, $\theta_{N-H\cdots O}$ 169.35° for **3a**, and $d_{N-H\cdots O}$ 2.21 Å, $\theta_{N-H\cdots O}$ 154.10° for **4a**, respectively). The data are in agreement with the reported examples.[24] The crystal structure of nitrate anion encapsulated complex through amide functional group by organic compound is rare.[3d,24] An interesting example of nitrate anion recognition in both solid and solution state by amide-based ditopic receptor has been reported by Smith's group,

dx.doi.org/10.1021/jo202502f | J. Org. Chem. 2012, 77, 1880–1890

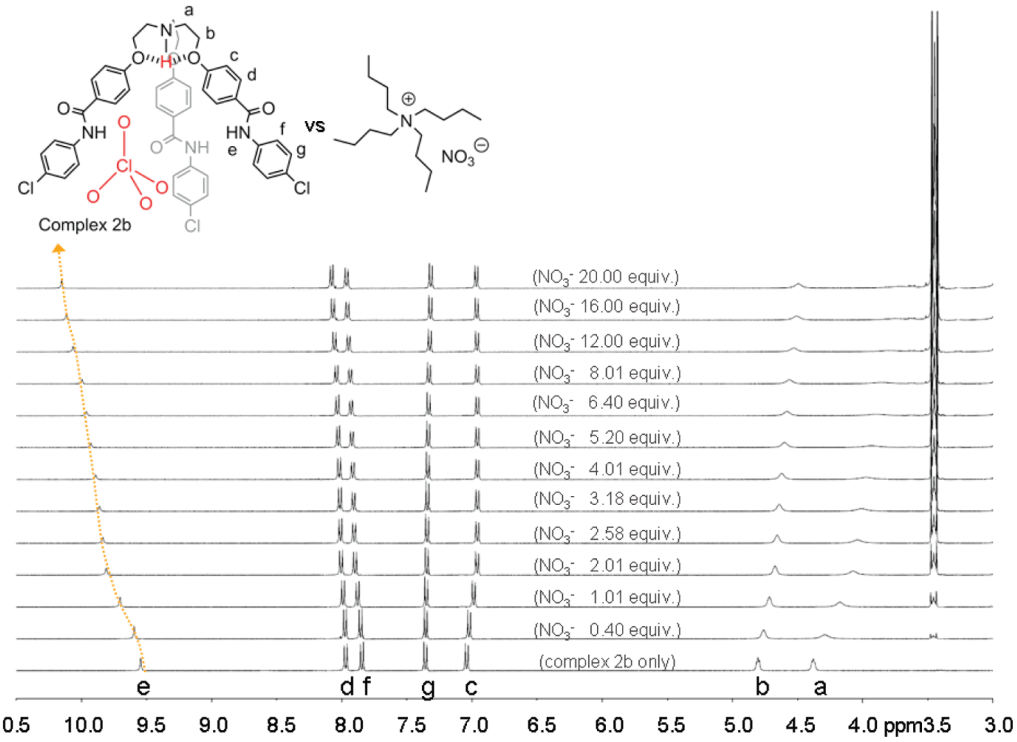


Figure 2. Partial ^{1}H NMR (400 MHz, 20 °C) titration spectra of receptor **2b** (1.5×10^{-3} M) with tetrabutylammonium nitrate in an acetone-d_6 solution.

where the interatomic distances between the receptor and anion depend upon the counterion employed.[24] The encapsulated nitrate anion is not symmetrically located inside the cavity by the reported ditopic receptor. To the best of our knowledge, the current report represents the first example in which a nitrate anion is symmetrically encapsulated by amide groups bearing acyclic tripodal receptors with one of the highest binding affinities in a polar aqueous solvent by a neutral receptor (receptor **5**, vide infra).

The distances between the N-atom of nitrate anions and the bridged N-atom of receptors in a discrete unit are both 7.88 Å for **2a** and **4a**, whereas it is 7.84 Å for **3a** (Figure 1a–c). The closest distances between the centrally bridged N-atom of the podand and the center of nitrate anion in crystal packing are 3.59 Å for **2a** and **4a** and 3.52 Å for **3a**. In the crystal structures of all three complexes **2a**, **3a**, and **4a**, there are infinite channels along the *c*-axis, which are filled by solvent molecules ($CHCl_3$ in **2a** and **3a** and THF in **4a**). The remarkable differences observed in the three crystal structures were that the edge of isosceles increase from 11.87 Å of nitrate complex **2a** to 12.37 Å of nitrate complex **4a** (Figure 1g–i) with decreasing electronegativity of the halide group. However, the distance between the amide N-atom of neighboring branch of nitrate complex **2a** is 0.05 Å larger than that of nitrate complexes **3a** and **4a** (Figure 1g–i).

Nitrate Binding in Solution and Gaseous NO_2 Fixation Studies. ^{1}H NMR spectra recorded in DMSO-d_6 for nitrate complexes **1a–4a**, prepared from $CHCl_3$/MeOH mixture solution, showed downfield shifted peaks for the aliphatic C–H protons compared to those in the corresponding neutral receptors, which suggests that the centrally bridged N-atom in all nitrate complexes is protonated. Addition of tetrabutylammonium nitrate ($TBANO_3$) to a solution of neutral receptors **1–4** in DMSO-d_6 resulted in no apparent shift of the amide N–H signals in all four receptors. This observation indicates that (i) the protonation of the centrally bridged N-atom is mandatory to reorganize the otherwise floppy neutral receptors to a convergent conformation via intramolecular hydrogen bonding interaction between the protonated N–H and aliphatic O-atoms (vide infra) and (ii) very weak binding of nitrate anions in DMSO-d_6 may not be observed through ^{1}H NMR titration experiment.

To meet both requirements, anion binding in solution was conducted by addition of $TBANO_3$ to an acetone-d_6 solution of protonated perchlorate complexes **1b–4b**. The protonated perchlorate complexes were chosen for solution binding studies because of the large ionic radii and the lipophilic nature of perchlorate anion, which cannot be effectively encapsulated inside the tripodal cavity of the protonated receptors and interfere with the subsequent binding events. These perchlorate complexes also show better solubility in common deuterated solvents than their parent receptors. The pK_a values of receptors **1b–4b** are expected to be similar to triethylammonium ion with a value near 9 in a DMSO solution.[25]

A representative ^{1}H NMR titration spectra of protonated receptor **2b** upon addition of nitrate anions is illustrated in Figure 2, and the binding constants of different anions with protonated receptors **1b–4b** calculated from a 1:1 binding stoichiometry according to the crystal structures are summarized in Table 1 (see Figures S26–S40 in the Supporting Information for all titration spectra). Although the peaks of protonated centrally bridged amines were not observable, the amide N–H signals of protonated receptors were consistently downfield shifted upon addition of different anions indicative of the presence of hydrogen-bonding interactions between the anion and amide N–Hs. Two peaks corresponding to the aromatic H_d and H_f also downfield shifted, which is ascribed to the effect of through space electrostatic interaction (see Figure

dx.doi.org/10.1021/jo202502f | J. Org. Chem. 2012, 77, 1880–1890

Table 1. Binding Constants (K_a, M^{-1}) Determined by ^1H NMR Titrations of Perchlorate Complexes 1b−4b (1.48×10^{-3} M) with Different Anions as Their Tetrabutylammonium Salts in an Acetone-d_6 Solution

	1b	2b	3b[a]	4b
NO_3^-	940 ± 80	1120 ± 50		1000 ± 90
Br^-	250 ± 50	870 ± 60		500 ± 40[b]
Cl^-	710 ± 100	1840 ± 150		720 ± 90
HSO_4^-	870 ± 70	1580 ± 20		840 ± 110
$H_2PO_4^-$	*c*	*c*		*c*

[a]Complex **3b** is sparingly soluble in acetone-d_6, and immediate precipitation appeared after addition of anions. [b]The amide N−H peak disappeared after addition of 1 equiv of bromide anion and hence the binding constant determined by the changes of aromatic C−H proton of N-terminal aromatic ring (proton "f"). [c]Deprotonation of centrally bridged N-atom occurred after addition of 3 equiv of $H_2PO_4^-$ anion.

2 for the proton labels).[16b] The observed data suggests that the binding affinity for anions does not fully correlate with the electronegativity of the halide atoms attached on the receptors. In general, complex **2b** shows higher binding affinities to anions compared to complexes **1b** and **4b**. Complex **2b** displays the highest binding affinity to chloride anions, whereas complexes **1b** and **4b** are slightly selective for nitrate anions over chloride and hydrogen sulfate anions. Upon titration of protonated receptors **1b−4b** with $H_2PO_4^-$, no shift was observed for amide N−H peak until the addition of 3 equiv of $H_2PO_4^-$ anion. However, the peak for protons attached to C-atom adjacent to bridged N-atom shifted upfield and splitted to a triplet and remains almost unchanged after further addition of $H_2PO_4^-$ anions (see Figures S30, S35, and S40 in the Supporting Information). This observation suggests that centrally bridged N-atom was deprotonated after addition of 1 equiv of $H_2PO_4^-$ anion, and hence no encapsulation of $H_2PO_4^-$ anion is possible by protonated receptors **1b−4b**.

For comparative studies, the binding behavior of isostructural trigonal planar anions such as acetate anions has also been studied. Concentration-dependent ^1H NMR spectra of the corresponding acetate complex **4c** (see Figure S41 in the Supporting Information) showed a similar pattern to that of free receptor **4**. The inability of acetate binding is ascribed to the weak acidity of AcOH to protonate the bridged N-atom, and hence the formation of a preorganized interior cavity did not effectively take place in this case. Upon titration of perchlorate complexes **1b−4b** with tetrabutylammonium acetate, peaks corresponding to aliphatic C−H proton remarkably shifted upfield after addition of 1 equiv of acetate anions. The significant upfield shift of peaks corresponding to aliphatic C−H protons suggests that the centrally bridged protonated N-atom got deprotonated from complexes **1b−4b** in the presence of basic acetate anion, and hence, encapsulation of acetate anions can not be expected.

Recently, a mechanism for nitric oxide in contact with water to form nitric acid was reported by Gerber's group.[25] We envisioned that the high affinity of receptors **1−4** to bind nitrate anion in acidic medium renders the trapping of nitrogen dioxide gas after water contact by these receptors highly feasible. Therefore, the fixation of gaseous nitrogen oxide to nitrate was explored with these receptors. Nitrogen dioxide was prepared by treating copper turnings with concentrated nitric acid, and the resulting reddish brown gas was bubbled through a suspension of receptor **2** in $CHCl_3$/MeOH (1/1 in *v*/*v*) mixture solution for 3−5 min. The precipitate thus obtained was simply filtered and dried in air. The identity of this isolated solid was fully matched with the nitrate complex **2a** on the basis of a variety of characterization methods including ^1H NMR, ^{13}C NMR, and HRESI mass spectra. HRESI mass spectra has been successfully utilized for detection of supramolecular species in solution.[26]

Despite the fact that no particular selectivity was observed for nitrate anions by protonated receptors **1b**, **2b**, and **4b** in solution, the anion-binding studies by receptor **5** showed very intriguing results. For receptor **5**, anion binding studies were performed in DMSO-d_6, as the $-SO_3H$ group of the dansyl moiety is expected to dissociate in a polar solvent like DMSO to form a convergent cone shape conformation by its zwitterionic form (see Figure 3), and hence anion-binding

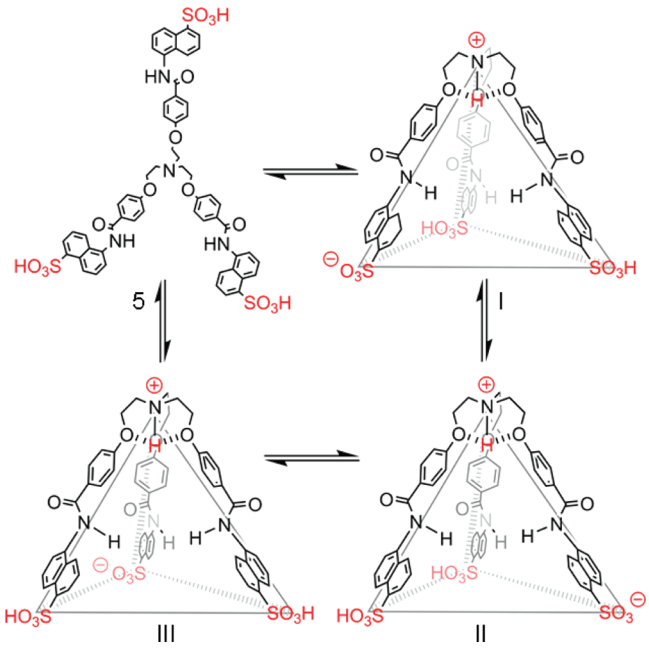


Figure 3. Formation of in situ preorganized interior cavity by zwitterionic form (I, II, and III) of tripodal receptor **5** for encapsulation of nitrate anion.

studies can be carried out in its neutral form without external proton source. The peaks for protonated centrally bridged amine, amide N−H, and $-SO_3H$ group of receptor **5** were all not observable (see Figures S17 and S19 in the Supporting Information) in the ^1H NMR spectrum recorded in a DMSO-d_6 solution, possibly because of a rapid proton exchange with the residual water in deuterated DMSO. A very minor shift observed for peaks in titration experiment of neutral receptor **5** with chloride and bromide anions indicates very weak interactions between receptor **5** and these two anions. On the other hand, the peaks of aromatic protons in dansyl moiety gradually upfield-shifted with increasing concentration of nitrate anion as illustrated in the ^1H NMR titration spectra of neutral receptor **5** in a DMSO-d_6 solution (see Figure 4). A similar titration pattern was observed with hydrogen sulfate anions. These observations suggest hydrogen bond formation between the incoming anions and the amide N−H protons of neutral receptor **5**. Nonlinear regression analysis of the binding isotherms based on the upfield shift of proton *f* with a 1:1 binding stoichiometry yielded binding constants of 550 ± 40

dx.doi.org/10.1021/jo202502f | J. Org. Chem. 2012, 77, 1880−1890

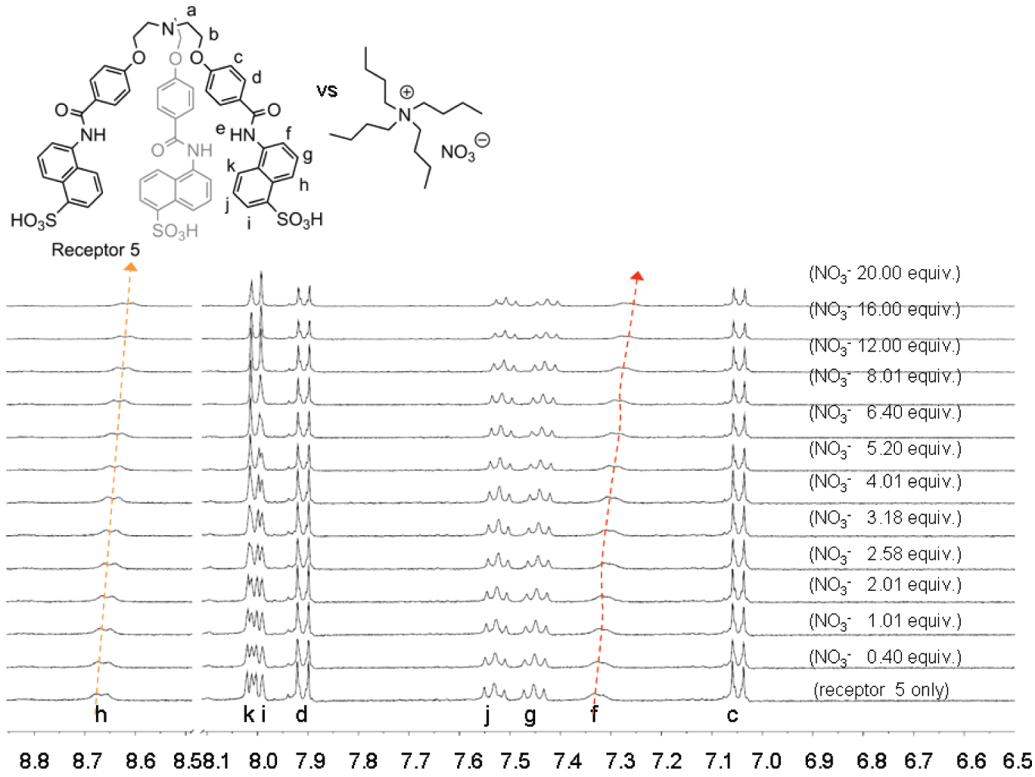


Figure 4. Partial ^{1}H NMR spectra of receptor **5** (1.48×10^{-3} M) upon addition of nitrate anion in a DMSO-d_6 solution.

M^{-1} and 240 ± 30 M^{-1} for NO_3^- and HSO_4^- anions, respectively.[27] Receptor **5** shows more than 2-fold higher affinity for NO_3^- anion than HSO_4^- anion in a DMSO-d_6 solution. Control experiments were also carried out in the presence of excess innocent tetrabutylammonium perchlorate to verify that the changes of chemical shifts observed during the ^{1}H NMR titration experiments for nitrate recognition were not simply due to the variation of solution ionic strength caused by the addition of salts. The binding affinities for nitrate anion were calculated to be 510 ± 30 M^{-1} and 850 ± 60 M^{-1} in the presence of 10 and 100 equiv of tetrabutylammonium perchlorate, respectively (see Figures S42, S43, and S53 in the Supporting Information). These results suggest that the changes of the chemical shifts upon addition of nitrate anions were actually due to the binding event between receptor **5** and the incoming nitrate anion. Moreover, the increasing ionic strength of solution in the presence of 100 equiv of tetrabutylammonium perchlorate results in an enhanced ionization of the sulfonic acid in receptor **5** that further shifts the equilibrium to a conical conformation shown in Figure 3 by facilitating protonation of the central bridged nitrogen atom. To the best of our knowledge, this is one of the highest binding constants reported so far in polar solvents for nitrate anion by a neutral acyclic receptor.

The degree of ionization for the $-SO_3H$ group is expected to be even higher in more polar solvent media. ^{1}H NMR titration experiments were performed in DMSO-d_6 solutions of receptor **5** with NO_3^- anion in the presence of various amounts of water. The binding constants obtained for 1:1 stoichiometry are summarized in Table 2. The binding affinities of receptor **5** with nitrate anion are comparable in pure DMSO-d_6 and DMSO-d_6 solution with 5% water. However, a 50% enhancement in binding constant was observed in the presence of 10% water in a DMSO-d_6 solution for receptor **5** with nitrate anion.

Table 2. Effect of Solvent Polarity on the Binding Constants (K_a, M^{-1}) Determined by ^{1}H NMR Titration of Receptor 5 (1.48×10^{-3} M) with Nitrate Anion in DMSO-d_6 Solutions in the Presence of Various Amounts of H_2O

solvent	K_a (M^{-1})[a]
DMSO-d_6 only	550 ± 40
DMSO-d_6 + 5% H_2O	590 ± 40
DMSO-d_6 + 10% H_2O	870 ± 60
DMSO-d_6 + 20% H_2O	430 ± 40

[a]Binding constants determined with proton *f* of the dansyl moiety in receptor **5**.

Such enhancement in binding affinity may be attributed to a higher degree of proton ionization in a more polar solvent medium that results in more protonated receptor **5** with convergent conformation to bind nitrate anion in solution (see Figure 4). It is not surprising to see that the binding affinity decreased upon further increasing the water content in solution where the excess water would compete with protonated receptor **5** for the hydrophilic nitrate anion.

A ^{1}H NMR titration experiment of receptor **5** with basic $H_2PO_4^-$ anion was also conducted in a DMSO-d_6 solution. After addition of 2 equiv of $H_2PO_4^-$ anion, the color of the solution turned from purple to creamy yellow. The aromatic proton *h* of dansyl moiety upfield shifted until the addition of 3 equiv of $H_2PO_4^-$ anion, and thereafter no shift in peak position was observed (see Figure S47 in the Supporting Information). Moreover, aromatic proton *f* adjacent to the amide N–H group also upfield shifted until the addition of 3 equiv of $H_2PO_4^-$ anion and thereafter remained silent. This observation shows that the basic $H_2PO_4^-$ anion interacted with the sulfonic protons in a Bronsted acid–base fashion. The net effect upon

dx.doi.org/10.1021/jo202502f | J. Org. Chem. 2012, 77, 1880–1890

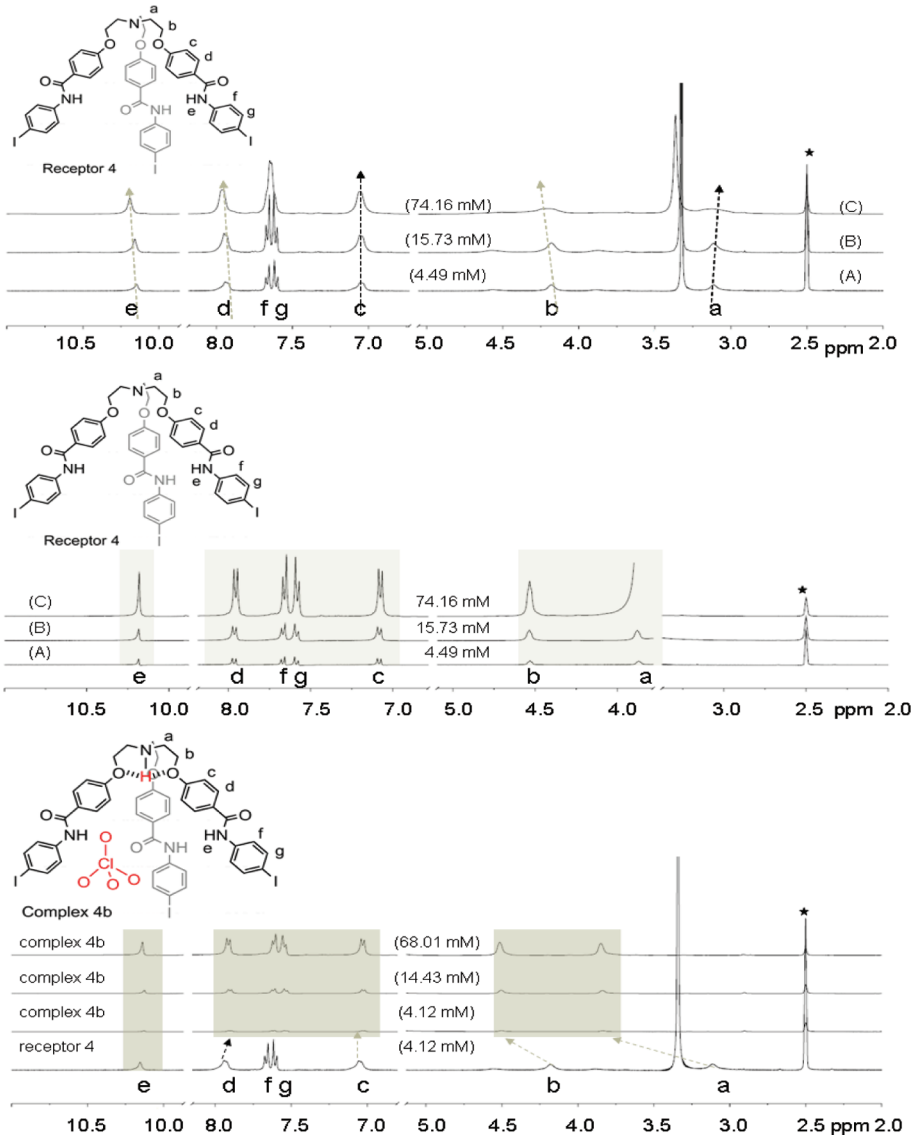


Figure 5. Concentration-dependent ^{1}H NMR spectra (400 MHz, DMSO-d_6, 20 °C) of receptor **4** (top), receptor **4** in the presence of perchloric acid (middle), and perchlorate complex **4b** (bottom).

titration of receptor with $H_2PO_4^-$ resulted in deprotonation of sulfonic acid without $H_2PO_4^-$ anion encapsulation.

Proposed Mechanism for Nitrate Anion Encapsulation. Solution binding studies suggest that the receptor would be protonated first upon addition of dilute HNO_3, thereby increasing its solubility in a protic solvent such as MeOH. After protonation of the centrally bridged N-atom, all three branches of the podand converge to a conical shape by cooperative N−H···O hydrogen bonding and C−H···π interactions to form an interior cavity. The amide N−Hs in the protonated receptor would be preorganized in a trigonal planar fashion and able to extract anions from solution by a synergistic electrostatic interaction and increasing hydrogen-bonding interactions between the anion and amide N−Hs. In the crystal structures of **2a**, **3a**, and **4a**, the distances between the centrally bridged N-atom and O-atom of aliphatic chain are 2.710 Å for **2a**, 2.719 Å for **3a**, and 2.718 Å for **4a**, respectively, which suggest the possible hydrogen-bonding interactions between the bridged N−H and O-atom of the aliphatic chain (Figure 1d−f). Close inspection of crystal structures of **2a**, **3a**, and **4a** shows that the *ortho* H-atoms with respect to the alkoxy chain of the C-terminal aromatic ring are in close contact with the centroid of the C-terminal aromatic ring of the neighboring branch via intermolecular tilted edge-to-face C−H···π interactions ($d_{C-H\cdots d}$ 3.235 Å and $\theta_{C-H\cdots\pi}$ 177.0° for **2a**, $d_{C-H\ldots d}$ 3.222 Å and $\theta_{C-H\cdots\pi}$ 176.3° for **3a**, and $d_{C-H\cdots d}$ 3.219 Å and $\theta_{C-H\cdots\pi}$ 175.9° for **4a**, respectively (see Figure 1), where *d* is centroid of C-terminal aromatic ring).[24]

Concentration-dependent ^{1}H NMR spectra were recorded for receptor **4**, its corresponding perchlorate complex **4b**, and receptor **4** in the presence of perchloric acid in order to further prove that the in situ formation of an interior cavity via N−H···O hydrogen bonds and C−H···π interactions is due to the protonation effect of the centrally bridged N-atom. The ^{1}H NMR spectrum of receptor **4** showed a notable shift of all peaks with increasing concentration of receptor **4** from 4.49 to 74.2 mM (Figure 5, top), whereas the concentration-dependent ^{1}H NMR spectra of complex **4b** (Figure 5, bottom) and receptor **4** in the presence of perchloric acid (Figure 5, middle) showed no shift of peaks either in aromatic or aliphatic regions. The upfield and downfield shifts of peaks corresponding to protons H_a and H_b, respectively, of aliphatic branches in receptor **4** as well as

dx.doi.org/10.1021/jo202502f | J. Org. Chem. 2012, 77, 1880−1890

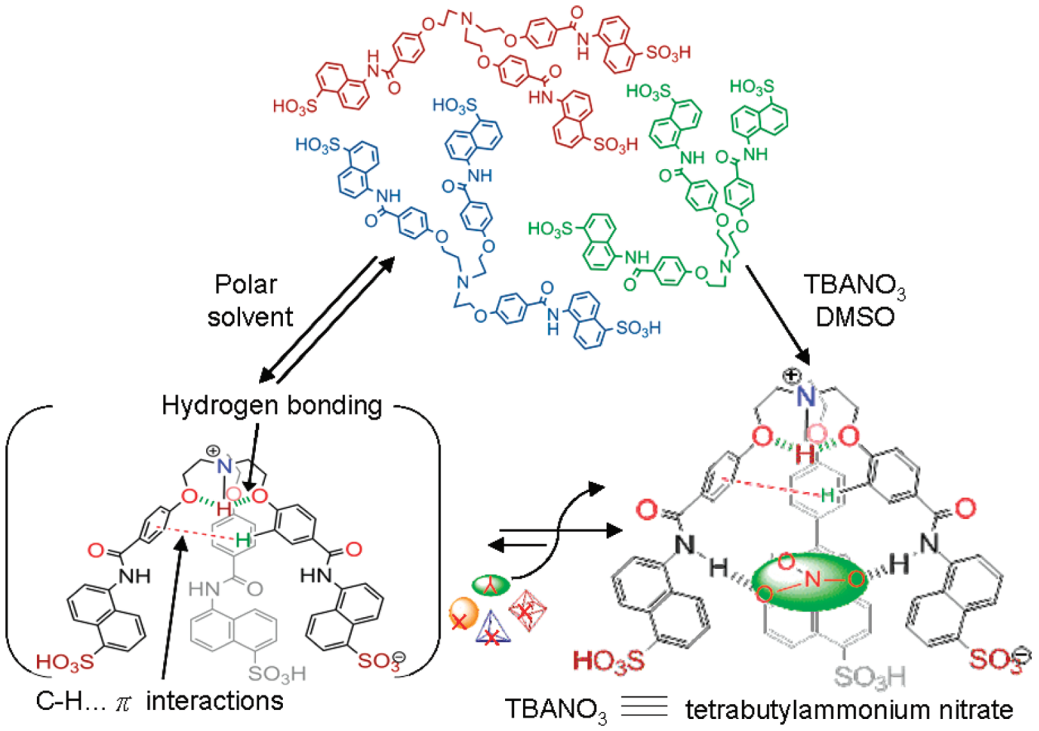


Figure 6. A schematic diagram showing proton-mediated in situ formation of the preorganized cavity via N−H···O hydrogen bonding and C−H···π interactions, which is able to extract trigonal planar nitrate anion selectively in polar media.

the lack of changes for the same protons in its corresponding perchlorate complex **4b** signify that receptor **4** exits in a different conformation from its protonated form (its corresponding perchlorate complex **4b** or receptor **4** in the presence of perchloric acid). This result also implies that the conformational flexibility of tripodal moiety get reduced upon protonation of centrally bridged N-atom to form the interior cavity. These results further support the observation made in crystal structures that although tripodal podands **1**−**4** are conformationally flexible with a large degree of freedom, encapsulation of the nitrate anion takes place by in situ generation of a preorganized cavity via cooperative H-bonding and C−H···π interactions in solution with reduced conformational flexibility.

Once the interior cavity is formed by protonated tripodal receptors, rotation of N-terminal aromatic ring around C−N bond creates an identical environment for all the halide-substituted tripodal receptors **1b**−**4b**, and hence no particular selectivity is expected for anions with different size and shape. However, steric requirement for rotation of dansyl moiety around C−N bond in receptor **5** will allow the differentiation of the encapsulation of only anions with appropriate size and shape within the in situ formed cavity of the protonated receptor. It is likely that the aromatic protons of dansyl moiety cause steric hindrance and hence do not allow spherical anions to bind inside the cavity of receptor **5** as effectively as nitrate anions. Thus, although chloride is comparable to nitrate anions in terms of its size and hydration energy, the trigonal planar geometry and matching C_3-symmetry of nitrate anions with the receptor allows its encapsulation and selective sensing by receptor **5**. The proposed mechanism of encapsulation of nitrate anions in solution is summarized in Figure 6. The encapsulation of nitrate anions with neutral receptor **5** occurs through its zwitterionic form as shown in Figure 3. The available donor (sulfonic acid group) and acceptor (centrally bridged N-atom) moieties in the same molecule are capable of preorganizing its branches in a cone conformation and reduce the molecular flexibility with the formation of the interior cavity, which is suitably matched for encapsulation of trigonal planar nitrate anion.

Reversible Binding of Nitrate Anion. The reversible binding of nitrate anions can also be easily modulated by acid−base titration. The aliphatic C−H proton signal adjacent to the central bridged N-atom shifted back to the original position of receptor **2** upon treating the nitrate complex **2a** with 1 equiv of KOH in a DMSO-d_6 solution. After addition of excess KOH (4.5 equiv), the peak for amide N−H protons disappeared, and the solution became orange, which is attributed to either the fast proton exchange that causes a significant broadening of the signal or partial deprotonation of the amide N−Hs (see Figure S55 in the Supporting Information). The peak for amide N−H protons reappeared after acidifying the same solution mixture by trifluoroacetic acid, and the final spectrum was merged with the original spectrum of the nitrate complex **2a**, which was also confirmed by HRESI mass spectrum.

Fluorescent Sensing of Nitrate Anion. The effective encapsulation of nitrate anion by receptor **5** suggests the possibility of fluorescent sensing of nitrate anion. Fluorescence titration experiments of neutral receptor **5** with nitrate and hydrogen sulfate anions were performed in DMSO solutions with various amounts of water. Figure 7 shows the fluorescence titration spectra of receptor **5** with nitrate anion in a DMSO solution. Binding constants of different anions with receptor **5** calculated from a 1:1 binding stoichiometry are summarized in Table 3. Similar to the ^{1}H NMR titration studies, the binding constants of receptor **5** derived from fluorescence titrations showed a higher binding constant for nitrate than hydrogen sulfate. The binding constants for nitrate anion in pure DMSO

dx.doi.org/10.1021/jo202502f | J. Org. Chem. 2012, 77, 1880−1890

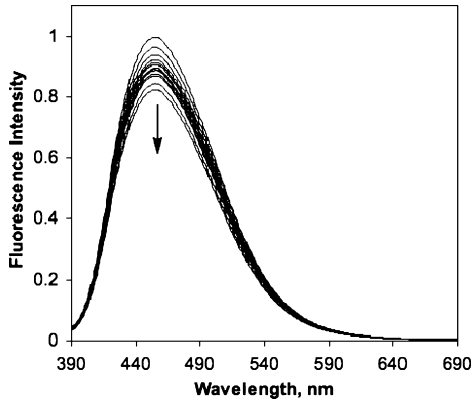


Figure 7. Fluorescent titration spectra (λ_{ex} = 375 nm) of neutral receptor **5** (2.1×10^{-6} M) with nitrate anion in a DMSO solution.

Table 3. Effect of Solution Polarity on Equilibrium Constants (K_a, M^{-1}) Determined by Fluorescence Titration (λ_{ex} = 375 nm) of Receptor 5 (2.1×10^{-6} M) with Anions as Their Tetrabutylammonium Salts in DMSO Solution with Various Amounts of Water (v/v)

	DMSO only	10% H_2O in DMSO	20% H_2O in DMSO
NO_3^-	550 ± 40	570 ± 20	290 ± 70
HSO_4^-	100 ± 30	140 ± 30	40 ± 10

solution and DMSO solution with 10% water are comparable within the experimental error. Upon further increasing the water content in DMSO solution to 20%, the binding affinity for nitrate decreased nearly to half. This result is in full agreement with the observation in ^{1}H NMR titration experiments. The very minor difference observed for binding constants in DMSO and 10% water in DMSO may be attributed to the dilution effect in typical fluorescence experiments where receptor **5** might have dissociated well at concentration of 2.1×10^{-6} M even in absence of water.

CONCLUSION

In summary, we have disclosed the protonation-induced in situ formation of an interior cavity by highly flexible and unpreorganized tripodal receptors, which selectively recognize and encapsulate the trigonal planar and C_3-symmetry nitrate anion. Apart from physical characterization, crystal structures of **2a**, **3a**, and **4a** confirmed the formation of discrete nitrate anion complexes. Receptor **5** represents a unique example of neutral receptor for encapsulation of highly hydrated and weakly coordinated nitrate anion in polar solvent media. Since these receptors do not have preorganized structural framework and the degree of freedom was much larger than previously reported examples of bicyclic receptors, selective recognition and sensing may be attributed to a combination of electrostatic attraction and optimal directionality of multiple hydrogen bonding interactions. Moreover, effective trapping of nitrogen oxide upon hydrolysis in aqueous solution by these receptors provides a proof-of-concept method for monitoring the environmental concern of atmosphere smog. Current work is underway to prepare abiotic receptors to enhance the fluorescence signal after binding with nitrate anions.

EXPERIMENTAL SECTION

Materials and General Procedures. 4-Hydroxybenzoic acid, 5-aminonaphthalene-1-sulfonic acid, triethanolamine, thionyl chloride, and all *para*-haloamines were commercially available and used as received. All solvents were purified by standard procedures. NMR spectra were recorded with a 400 MHz spectrometer. Chemical shifts are reported on the δ scale relative to tetramethylsilane. Emission spectra were recorded in an air-equilibrated solution according to reported procedures.[28] Single crystal data were collected with a CCD diffractometer. CCDC-754903 and CCDC-754904 contain the supplementary crystallographic data for nitrate complexes **2a** and **4a**, respectively, and CCDC-819453 for nitrate complex **3a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

^{1}H NMR titrations of all samples were measured on a 400 MHz spectrometer, and deuterated solvents were used from freshly opened bottle. Samples were prepared just prior to titration experiments, and all anions were used in the form of tetrabutyl ammonium salts. Titration experiments for protonated receptors **1b**−**4b** were performed in acetone-d_6 solutions, and binding constants were calculated from shifting of amide N−H protons (except for **4b** with tetrabutylammonium bromide, where the binding constant was calculated from the shifting of N-terminal aromatic C−H protons, as in this case the amide N−H proton disappears after addition of 1 equiv of bromide anion). Titration experiments of neutral receptor **5** with different anions were performed in DMSO-d_6, and binding constants were calculated from the shifting of aromatic (dansyl moiety) C−H protons.

General Procedures for the Synthesis of Receptors 1−5. To a solution of 4-hydroxymethylbenzoate (16.7 g, 0.11 mol) in dry DMSO (80 mL) was added NaOH (5.98 g, 0.15 mol), and the solution was stirred at rt for 30 min. To the resulting solution, tris(2-chloroethyl)-amine hydrochloride (8.0 g, 33.2 mmol) was added at once, and the mixture was heated at 80 °C for 12 h. Thereafter, the solution was allowed to cool to rt, diluted with distilled water (100 mL), extracted with ethyl acetate (3 × 100 mL). The organic layer was washed three times with 10% K_2CO_3 solution and then two times with cold water. The organic layer was collected and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography eluted with ethyl acetate in hexane to obtain the triester B (14.3 g, 78% yield). Thereafter, 150 mL of 5 N NaOH solution was added to a suspension of triester B in 250 mL of MeOH−H_2O (1:1 in v/v) mixture solution, and the resulting solution was refluxed for overnight. After cooling to rt, the reaction mixture was acidified with 25% HCl solution and allowed to stand at rt for a further 6−7 h to precipitate the expected triacid C. The milky white precipitate was filtered out, washed with Et_2O, and air-dried (12.1 g, 92% yield). This triacid C was used for next step without further purification.

To a suspension of triacid C (5.0 g, 9.81 mmol) in dry dichloromethane (100 mL), 4.5 equiv of thionyl chloride (3.13 mL, 44.2 mmol) was added, followed by addition of a catalytic amount of DMF (1 mL), and the mixture was refluxed under guard tube for 6 h. After cooling of the reaction mixture to rt, the volatile was removed under reduced pressure to get the creamy yellow solid of corresponding acid chloride. The acid chloride was again dissolved in dry dichloromethane (100 mL) and transferred through cannula to another two-necked 500 mL round-bottom flask containing 3.6 equiv of corresponding 4-haloamine (35.3 mmol) dissolved in a 100 mL of dry dichloromethane under nitrogen atmosphere in an ice bath. The mixture solution was allowed to stir for 10−15 min in the ice bath, and then 4.5 equiv of triethylamine (44.2 mmol) was added. The reaction mixture was allowed to reach room temperature and refluxed for 8−12 h. Solvent was removed under reduced pressure, and the crude product was purified by flash chromatography with $CHCl_3$/MeOH mixture solution as the eluent to get the desired receptors in 69−95% yields. Receptor **5** was synthesized by similar procedures described above, except THF was used instead of dichloromethane, and the crude product was first recrystallized by hot THF followed by MeOH to yield receptor **5** in 65% yield.

Receptor 1. Creamy yellow solid (5.34 g, yield 69%, mp 195−197 °C): ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C) δ 3.12 (t, ^3J = 5.6 Hz, 6H), 4.18 (t, ^3J = 5.6 Hz, 6H), 7.04 (d, ^3J = 8.8 Hz, 6H), 7.16 (t, ^3J =

dx.doi.org/10.1021/jo202502f | J. Org. Chem. 2012, 77, 1880−1890

8.8 Hz, 6H), 7.76 (dd, ^3J = 8.8 Hz, 6H), 7.93 (dd, ^3J = 8.8 Hz, 6H), 10.13 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C) δ 53.6, 66.9, 114.2, 115.0, 115.3, 122.2, 126.8, 129.6, 135.7, 161.3, 164.9; HRFABMS m/z calcd for [M + H$^+$] 789.2900, found 789.2892; Elemental analysis calcd (%) for $C_{45}H_{39}F_3N_4O_6\cdot1.5H_2O$ C 66.25, H 5.19, N 6.87, found C 66.52, H 5.08, N 6.89.

Receptor **2**. White solid (7.74 g, yield 94%, mp 250−252 °C): ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C) δ 3.12 (t, ^3J = 5.6 Hz), 4.18 (t, ^3J = 5.6 Hz, 6H), 7.04 (d, ^3J = 8.8 Hz, 6H), 7.38 (d, ^3J = 8.8 Hz, 6H), 7.80 (d, ^3J = 8.8 Hz, 6H), 7.94 (d, ^3J = 8.8 Hz, 6H), 10.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C) δ 53.5, 66.9, 114.2, 121.8, 126.6, 127.0, 128.5, 129.7, 138.3, 161.3, 165.0; HRFABMS m/z calcd for [M + H$^+$] 837.2013, found 837.2017; Elemental analysis calcd (%) for $C_{45}H_{39}Cl_3N_4O_6$ C 64.48, H 4.69, N 6.68, found C 64.21, H 4.68, N 6.59.

Receptor **3**. White solid (9.05 g, yield 95%, mp 258−260 °C): ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C) δ 3.12 (t, ^3J = 5.6 Hz, 6H), 4.18 (t, ^3J = 5.6 Hz, 6H), 7.04 (d, ^3J = 8.8 Hz, 6H), 7.50 (d, ^3J = 8.4 Hz, 6H), 7.74 (d, ^3J = 8.4 Hz, 6H), 7.93 (d, ^3J = 8.8 Hz, 6H), 10.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C) δ 53.5, 66.8, 114.1, 115.0, 122.2, 126.6, 129.6, 131.3, 138.7, 161.3, 164.9; HRFABMS m/z calcd for [M + H$^+$] 971.0478, found 971.0431; Elemental analysis calcd (%) for $C_{45}H_{39}Br_3N_4O_6\cdot H_2O$ C 54.62, H 4.18, N 5.66, found C 54.62, H 4.03, N, 5.72.

Receptor **4**. Creamy white solid (9.83 g, yield 90%, mp 266−268 °C): ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C) δ 3.11 (s, 6H), 4.18 (s, 6H), 7.05 (s, 6H), 7.64 (m, 12H), 7.94 (s, 6H), 10.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C) δ 53.4, 87.1, 114.2, 122.5, 129.7, 137.2, 139.2, 164.9; HRFABMS m/z calcd for [M + H$^+$] 1113.0082, found 1113.0095; Elemental analysis calcd (%) for $C_{45}H_{39}I_3N_4O_6$ C 48.58, H 3.53, N 5.04, found C 48.74, H 3.57, N, 5.02.

Receptor **5**. Pale violet solid (7.18 g, yield 65%, mp 245−247 °C): ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C) δ 3.83 (s, 6H), 4.59 (t, ^3J = 4.8 Hz, 6H), 7.05 (d, ^3J = 8.2 Hz, 6H), 7.54−7.61 (m, 6H), 7.71 (d, ^3J = 8.8 Hz, 3H), 7.90 (d, ^3J = 8.8 Hz, 6H), 8.06−8.09 (m, 6H), 8.87 (d, ^3J = 8.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C) δ 52.8, 62.6, 114.6, 120.0, 123.6, 123.8, 125.2, 125.4, 125.5, 127.1, 127.4, 128.7, 129.8, 131.4, 144.2, 161.1, 166.9; HRFABMS m/z calcd for [M − H]$^-$: 1123.2200, found 1123.2201; Elemental analysis calcd (%) for $C_{57}H_{48}N_4O_{15}S_3\cdot3H_2O$ C 58.05, H 4.62, N 4.75, S 8.16, found C 57.89, H 4.52, N 4.71, S 7.96.

General Procedures for the Synthesis of Nitrate Complexes 1a−5a. To a mixture solution of the corresponding compounds **1**−**5** (1 mmol in 15 mL of $CHCl_3$/MeOH, v/v in 1:1 ratio) was added 9 drops of dilute HNO_3 (10%), and the resulting solution was stirred at room temperature for 20 min and filtered. The residue obtained was air-dried for 24 h to yield the desired nitrate complexes **1a**−**5a**.

Nitrate Complex ***1a***. Creamy yellow solid (0.61 g, yield 72%, mp 160−162 °C): ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C) δ 3.90 (s, 6H), 4.55 (d, ^3J = 4.4 Hz, 6H), 7.11 (d, ^3J = 8.8 Hz, 6H), 7.18 (t, ^3J = 8.8 Hz, 6H), 7.77 (dd, ^3J = 8.8 Hz, 6H), 7.99 (d, ^3J = 8.8 Hz, 6H), 10.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C) δ 53.4, 62.6, 114.3, 115.1, 122.2, 127.6, 129.6, 135.5, 160.1, 164.6, 206.4; HRESIMS m/z calcd for [M − H]$^-$ 850.2700, found 850.2703; Elemental analysis calcd (%) for $C_{45}H_{40}F_3N_5O_9\cdot2H_2O$ C 60.88, H 5.00, N 7.89, found C 61.14, H 4.80, N 8.13.

Nitrate Complex ***2a***. Pale yellow solid (0.77 g, yield 85%, mp 181−183 °C): ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C) δ 3.90 (s, 6H), 4.56 (s, 6H), 7.11 (d, ^3J = 8.8 Hz, 6H), 7.39 (d, ^3J = 8.8 Hz, 6H), 7.80 (d, ^3J = 8.8 Hz, 6H), 7.99 (d, ^3J = 8.8 Hz, 6H), 10.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C) δ 53.4, 62.6, 114.3, 121.9, 127.1, 127.5, 128.5, 129.7, 138.2, 160.2, 164.8; HRESIMS m/z calcd for [M − H]$^-$ 898.1813, found 898.1823; Elemental analysis calcd (%) for $C_{45}H_{40}Cl_3N_5O_9$ C 59.97, H 4.47, N 7.77, found C 59.78, H 4.59, N 7.65.

Nitrate Complex ***3a***. Pale yellow solid (1.00 g, yield 97%, mp 128−130 °C, decomposition): ^{1}H NMR (100 MHz, DMSO-d_6, 20 °C) δ 3.90 (s, 6H), 4.56 (s, 6H), 7.11 (d, ^3J = 8.4 Hz, 6H), 7.52 (d, ^3J = 8.4 Hz, 6H), 7.75 (d, ^3J = 8.4 Hz, 6H), 7.99 (d, ^3J = 8.4 Hz, 6H), 10.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C) δ 53.4, 62.7, 114.3, 115.2, 122.3, 127.4, 129.7, 131.4, 138.6, 160.2, 164.8; HRESIMS m/z calcd for [M − H]$^-$ 1034.0257, found 1034.0310; Elemental analysis calcd (%) for $C_{45}H_{40}Br_3N_5O_9\cdot3H_2O$ C 49.65, H 4.26, N 6.43, found C 49.58, H 4.19, N 6.38.

Nitrate Complex ***4a***. Creamy yellow solid (1.00 g, yield 85%, 162−164 °C): ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C) δ 3.89 (s, 6H), 4.54 (s, 6H), 7.10 (d, ^3J = 8.4 Hz, 6H), 7.61 (d, ^3J = 8.4 Hz, 6H), 7.68 (d, ^3J = 8.4 Hz, 6H), 7.98 (d, ^3J = 8.4 Hz, 6H), 10.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C) δ 53.3, 79.2, 87.1, 114.3, 122.5, 127.5, 129.7, 137.2, 139.1, 160.2, 164.7; HRESIMS m/z calcd for [M − H]$^-$ 1173.9882, found 1173.9889; Elemental analysis calcd (%) for $C_{45}H_{40}I_3N_5O_9\cdot3H_2O$ C 43.96, H 3.77, N 5.70, found C 43.74, H 3.73, N 5.93.

Nitrate Complex ***5a***. Pale yellow solid (1.03 g, yield 87%, mp 170−172 °C): ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C) δ 3.86 (s, 6H), 4.53 (s, 6H), 7.04 (d, ^3J = 8.0 Hz, 6H), 7.56−7.62 (m, 3H), 7.91 (d, ^3J = 8.0 Hz, 3H), 7.98 (d, ^3J = 8.4 Hz, 6H), 8.06−8.07 (m, 6H), 8.86−8.87 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C) δ 53.3, 62.6, 114.6, 119.9, 123.1, 123.8, 125.3, 125.5, 125.7, 126.8, 127.5, 128.5, 129.7, 131.4, 144.2, 161.0, 166.9; HRESIMS m/z calcd for [M − H]$^-$ 1188.2268, found 1188.2300; Elemental analysis calcd (%) for $C_{57}H_{49}N_5O_{18}S_3\cdot H_2O$ C 56.76, H 4.26, N 5.81, S 7.97, found C 56.80, H 4.23, N 5.78, S 8.01.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra, titration spectra, and CIF files for crystal structures of **2a**, **3a**, and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sssun@chem.sinica.edu.tw.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Council of Taiwan (Grant No 100-2113-M-001-024-MY3) and Academia Sinica for support of this research. A.S.S. thanks the postdoctoral fellowship sponsored by the National Science Council of Taiwan (Grant No 100-2811-M-001-090). Mass spectrometry analyses were performed by Mass Spectrometry facility of the Institute of Chemistry, Academia Sinica. Mr. Ting-Shen Kuo at National Taiwan Normal University is acknowledged for assistance with X-ray crystallography.

■ REFERENCES

(1) (a) *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., Garcia-España, E., Eds.; Wiley-VCH: New York, 1997. (b) Snowden, T. S.; Anslyn, E. V. *Curr. Opin. Chem. Biol.* **1999**, *3*, 740−746. (c) Okunola, O. A.; Santacroce, P. V.; Davis, J. T. *Supramol. Chem.* **2008**, *20*, 169−190. (d) Lundberg, J. O.; Weitzberg, E.; Cole, J. A.; Benjamin, N. *Nat. Rev. Microbiol.* **2004**, *2*, 593−602.

(2) (a) Bondy, C. R.; Loeb, S. J. *Coord. Chem. Rev.* **2003**, *240*, 77−99. (b) Kang, S. O.; Llinares, J. M.; Powell, D.; VanderVelde, D.; Bowman-James, K. *J. Am. Chem. Soc.* **2003**, *125*, 10152−10153 and references therein. (c) Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2003**, *125*, 10241−10249. (d) Kang, S. O.; Begum, R. A.; Bowman-James, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7882−7894. (e) Chen, C.-L.; Chen, Y.-H.; Chen, C.-Y.; Sun, S.-S. *Org. Lett.* **2006**, *8*, 5053−5056. (f) Chen, C.-L.; Lin, T.-P.; Chen, Y.-S.; Sun, S.-S. *Eur. J. Org. Chem.* **2007**, 3999−4010. (g) Kang, S. O.; Day, V. W.; Bowman-James, K. *J. Org. Chem.* **2010**, *75*, 277−283. (h) Amendola, V.; Bergamaschi, G.; Buttafava, A.; Fabbrizzi, L.; Monzani, E. *J. Am. Chem. Soc.* **2010**, *132*, 147−156.

(3) (a) Bisson, A. P.; Lynch, V. M.; Monahan, M. K. C.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1997**, *36*, 2340−2342. (b) Mason, S.; Clifford, T.; Seib, L.; Kuczera, K.; Bowman-James, K. *J. Am. Chem. Soc.* **1998**, *120*, 8899−8900. (c) Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 2456−2457. (d) Herges, R.; Dikmans, A.; Jana, U.; Köhler, F.; Jones, P. G.; Dix, I.; Fricke, T.; König, B. *Eur. J. Org. Chem.* **2002**, 3004−3014. (e) Arunachalam, M.; Ghosh, P. *Inorg. Chem.* **2010**, *49*, 943−951.

(4) Kavallieratos, K.; Bertao, C. M.; Crabtree, R. H. *J. Org. Chem.* **1999**, *64*, 1675−1683.

(5) Choi, K.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3912−3915.

(6) Cook, J. L.; Hunter, C. A.; Low, C. M. R.; Perez-Velasco, A.; Vinter, J. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 3706−3709 and references therein.

(7) (a) Nishizawa, S.; Bühlmann, P.; Iwao, M.; Umezawa, Y. *Tetrahedron Lett.* **1995**, *36*, 6483−6486. (b) Bühlmann, P.; Nishizawa, S.; Xiao, K. P.; Umezawa, Y. *Tetrahedron Lett.* **1997**, *53*, 1647−1654. (c) Bell, T. W.; Hext, N. M.; Khasanov, A. B. *Pure Appl. Chem.* **1998**, *70*, 2371−2377. (d) Sasaki, S.; Mizuno, M.; Naemura, K.; Tobe, Y. *J. Org. Chem.* **2000**, *65*, 275−283. (e) Lin, Z.; Chen, H.-C.; Sun, S.-S.; Hsu, C.-P.; Chow, T. J. *Tetrahedron* **2009**, *65*, 5216−5221.

(8) (a) Pflugrath, J. W.; Quiocho, F. A. *Nature* **1985**, *314*, 257−260. (b) Luecke, H.; Quiocho, F. A. *Nature* **1990**, *347*, 402−406. (c) He, J. J.; Quiocho, F. A. *Science* **1991**, *251*, 1479−1481. (d) Koropatkin, N. M.; Pakrasi, H. B.; Smith, T. J. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 9820−9825.

(9) See Chapter 3 in reference 1a.

(10) (a) Vázquez, M.; Fabbrizzi, L.; Taglietti, A.; Pedrido, R. M.; González-Noya, A. M.; Bermejo, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1962−1965. (b) Lin, Z.-H.; Zhao, Y.-G.; Duan, C.-Y.; Zhang, B.-G.; Bai, Z.-P. *Dalton Trans.* **2006**, 3678−3684. (c) Han, F.; Bao, Y.; Yang, Z.; Fyles, T. M.; Zhao, J.; Peng, X.; Fan, J.; Wu, Y.; Sun, S. *Chem.—Eur. J.* **2007**, *13*, 2880−2892. (d) Chen, C.-Y.; Lin, T.-P.; Chen, C.-K.; Lin, S.-C.; Tseng, M.-C.; Wen, Y.-S.; Sun, S.-S. *J. Org. Chem.* **2008**, *73*, 900−911.

(11) (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609−1646. (b) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486−516.

(12) (a) Starnes, S. D.; Arungundram, S.; Saunders, C. H. *Tetrahedron Lett.* **2002**, *43*, 7785−7788. (b) Amendola, V.; Boiocchi, M.; Fabbrizzi, L.; Palchetti, A. *Chem.—Eur. J.* **2005**, *11*, 120−127. (c) Lin, T.-P.; Chen, C.-Y.; Wen, Y.-S.; Sun, S.-S. *Inorg. Chem.* **2007**, *46*, 9201−9212. (d) Wu, Y.; Peng, X.; Fan, J.; Gao, S.; Tian, M.; Zhao, J.; Sun, S. *J. Org. Chem.* **2007**, *72*, 62−70. (e) Berryman, O. B.; Johnson, C. A. II; Zakharov, L. N.; Haley, M. M.; Johnson, D. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 117−120.

(13) (a) Hossain, M. A.; Kang, S. O.; Llinares, J. M.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2003**, *42*, 5043−5045. (b) Inoue, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* **2003**, *44*, 5167−5169. (c) Odago, M. O.; Hoffman, A. E.; Carpenter, R. L.; Tse, D. C. T.; Sun, S.-S.; Lees, A. J. *Inorg. Chim. Acta* **2011**, *374*, 558−565.

(14) (a) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17−55. (b) Lee, C.-H.; Na, H.-K.; Yoon, D.-W.; Won, D.-H.; Cho, W.-S.; Lynch, V. M.; Shevchuk, S. V.; Sessler, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 7301−7306. (c) Sessler, J. L.; An, D.; Cho, W.-S.; Lynch, V. M. *J. Am. Chem. Soc.* **2003**, *125*, 13646−13647. (d) Wu, C.-Y.; Chen, M.-S.; Lin, C.-A.; Lin, S.-C.; Sun, S.-S. *Chem.—Eur. J.* **2006**, *12*, 2263−2269. (e) Yoon, D.-W.; Gross, D. E.; Lynch, V. M.; Sessler, J. L.; Hay, B. P.; Lee, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5038−5042.

(15) (a) Yun, S.; Ihm, H.; Kim, H. G.; Lee, C.-W.; Indrajit, B.; Oh, K. S.; Gong, Y. J.; Lee, J. W.; Yoon, J.; Lee, H. C.; Kim, K. S. *J. Org. Chem.* **2003**, *68*, 2467−2470. (b) Chellappan, K.; Singh, N. J.; Hwang, I.-C.; Lee, J. W.; Kim, K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2899−2903.

(16) (a) Sisson, A. L.; Clare, J. P.; Taylor, L. H.; Charmant, J. P. H; Davis, A. P. *Chem. Commun.* **2003**, 2246−2247. (b) Boiocchi, M.; Boca, L. D.; Esteban-Gomez, D.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *Chem.—Eur. J.* **2005**, *11*, 3097−3104. (c) Brooks, S. J.; Gale, P. A.; Light, M. E. *Chem. Commun.* **2006**, 4344−4346. (d) Custelcean, R.; Remy, P.; Bonnesen, P. V.; Jiang, De-en; Moyer, B. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1866−1870.

(17) (a) Linton, B. R.; Goodman, M. S.; Hamilton, A. D. *Chem.—Eur. J.* **2000**, *6*, 2449−2455. (b) Lam, C. K.; Mak, T. C. W. *Chem. Commun.* **2003**, 2660−2661. (c) Tumcharem, G.; Tuntulani, T.; Coles, S. J.; Hursthouse, M. B.; Kilburn, J. D. *Org. Lett.* **2003**, *26*, 4971−4974.

(18) (a) Metzger, A.; Lynch, V. M.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1997**, *36*, 862−865. (b) Schmuck, C.; Schwegmann, M. *Org. Lett.* **2005**, *7*, 3517−3520. (c) Schmuck, C.; Bickert, V. *J. Org. Chem.* **2007**, *72*, 6832−6839. (d) Kuchelmeister, H. Y.; Schmuck, C. *Chem.—Eur. J.* **2011**, *17*, 5311−5318. (e) Rether, C.; Schmuck, C. *Eur. J. Org. Chem.* **2011**, 1459−1466.

(19) (a) Boiocchi, M.; Boca, L. D.; Gomez, E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507−16514. (b) Amendola, V.; Boiocchi, M.; Fabbrizzi, L.; Palchetti, A. *Chem.—Eur. J.* **2005**, *11*, 5648−5660.

(20) Singh, A. S.; Chen, B.-Y.; Wen, Y.-S.; Tsai, C.; Sun, S.-S. *Org. Lett.* **2009**, *11*, 1867−1870.

(21) Kavallieratos, K.; Sachleben, R. A.; Berkel, G. J. V.; Moyer, B. A. *Chem. Commun.* **2000**, 187−188.

(22) (a) Singh, A. S.; Bharadwaj, P. K. *Dalton Trans.* **2008**, 738−741. (b) Singh, A. S.; Sun, S.-S. *Chem. Commun.* **2011**, *47*, 8563−8565.

(23) Annunziata, R.; Benaglia, M.; Cozzi, F.; Mazzanti, A. A. *Chem.—Eur. J.* **2009**, *15*, 4373−4381.

(24) Mahoney, J. M.; Stucker, K. A.; Jiang, H.; Carmichael, I.; Brinkmann, N. R.; Beatty, A. M.; Noll, B. C.; Smith, B. D. *J. Am. Chem. Soc.* **2005**, *127*, 2922−2928.

(25) Miller, Y.; Finlayson-Pitts, B. J.; Gerber, R. B. *J. Am. Chem. Soc.* **2009**, *131*, 12180−12185.

(26) (a) Russell, K. C.; Leize, E.; Dorsselaer, A. V.; Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 209−213. (b) Olenyuk., B.; Whiteford, J. A.; Fechtenkotter, A.; Stang, P. J. *Nature* **1999**, *398*, 796−799.

(27) The binding constants for nitrate and hydrogen sulfate were calculated to be 590 ± 40 and 220 ± 40, respectively, by fitting the changes of proton "*h*".

(28) (a) Hung, C.-Y.; Singh, A. S.; Chen, C.-W.; Wen, Y.-S.; Sun, S.-S. *Chem. Commun.* **2009**, 1511−1513. (b) Chen, K.-F.; Chang, C.-W.; Lin, J.-L.; Hsu, Y.-C.; Yeh, M.-C. P.; Hsu, C.-P.; Sun, S.-S. *Chem.—Eur. J.* **2010**, *16*, 12873−12882.