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Tripodal Nitro-Imidazolium Receptor for Anion Binding Driven by (C–H)$^{+}$- - -X^{-} Hydrogen Bonds

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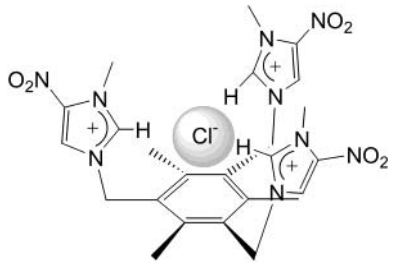
ABSTRACT



A positively charged tripodal receptor with nitro groups in the imidazolium rings was designed, synthesized, and characterized for its anion binding strength. The receptor shows strong affinity and high selectivity for Cl^- through (C–H)$^+$- - -X$^-$ hydrogen bonds wherein charge–charge and charge–dipole electrostatic interactions dominate. The association constant with chloride anion in a 9:1 mixture of acetonitrile-d_3 and DMSO-d_6 is measured to be 1.1×10^6 M^{-1}. The receptor also shows reasonably high affinity toward $H_2PO_4^-$.

The development of receptors for recognizing cation, neutral, and anion species has attracted much interest in molecular recognition study and supramolecular chemistry.[1,2] In particular, the design and synthesis of receptors capable of binding anionic guests is of crucial importance due to its potential applications in environmental and biological processes.[3] In general, most positively charged anion receptors have amide, pyrrole, urea, ammonium, or guanidinium groups as binding sites, which form N−H- - -anion hydrogen bonds.[4] In contrast to this well-known type of hydrogen bonding for the anion binding, Sato et al.[5] and Alcalde et al.[6] have recently reported that receptors with 1,3-disubstituted imidazolium groups bind anions by forming C−H- - -X$^-$ hydrogen bonds between the imidazolium rings and the guest anion. In a more clear expression, the bond is

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the $(C-H)^{+}\cdots X^{-}$ type, wherein the charge−charge electrostatic interaction dominates, and thus this novel type of charged hydrogen bonding is very intriguing in comparison with many other types[7] of hydrogen bonding. To enhance the anion binding strength, it would be desirable to increase the positive charge in the imidazolium ring. However, this enhanced anion binding strength (in the absence of solvents) could often decrease the practical anion binding in polar solvents, because the increase in simple charge−charge electrostatic interaction results in a drastic increase in the binding energy of the anion with solvent molecules (which can be easily noted in salts in polar solvents). Recently, we have addressed the importance of charge−dipole interactions in ion recognition.[8] Thus, it is important to increase the dipole moment toward the C−H direction in addition to increasing the positive charge in the imidazolium ring. This can be accomplished by attaching a nitro group (which is the electron withdrawing group with a high dipole moment along the C−H direction) to the C(4) position of the imidazolium ring. Furthermore, the structure of the tripodal receptor containing three imidazolium groups helps preorganization of the anion binding. Therefore, we here report the anion binding utilizing enhanced $(C-H)^{+}\cdots X^{-}$ interactions, especially for the recognition of a halide ion. We find that host **1**, which is obtained by adding a nitro group to the imidazolium sidearm, shows enhanced anion affinity compared to those of hosts **2** and **3**[5] (Figure 1).

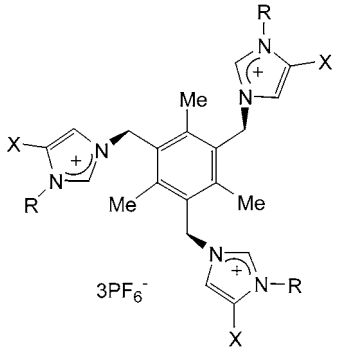

Figure 1. Schematics of tripodal receptors: (**1**) R = Me, X = NO_2, (**2**) R = Me, X = H; and (**3**) R = *n*-Bu, X = H.

In this study, the idea of addition of a nitro group to the C(4) position of an imidazolium ring was initially based on the theoretical understanding of the $(C-H)^{+}\cdots X^{-}$ hydrogen bonding interaction and the charge−dipole interaction in molecular recognition. To clearly demonstrate the enhancement in the anion binding strength by the nitro group, we carried out ab initio calculations.[9] The calculated structure of host **1** with chloride anion demonstrates a stable feature of interaction between C(2) hydrogens of the imidazolium ring and chloride anion (Figure 2). In the gas phase, the

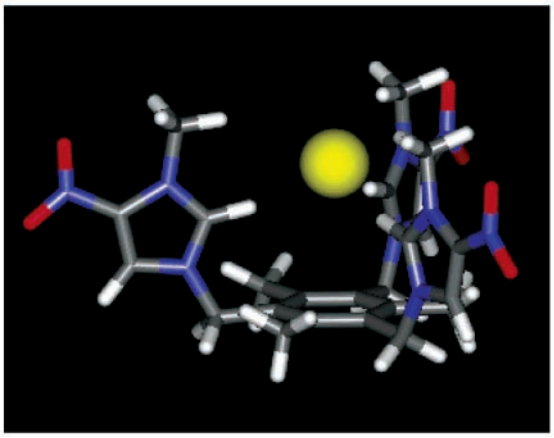

Figure 2. Calculated structure of host **1** with chloride anion (yellow in the middle).

binding energy of host **1** with Cl^{-} is 6.2 kcal/mol larger than that with Br^{-}, and 11.7 kcal/mol larger than the binding energy of host **2** with Cl^{-}. This clearly shows the effective binding of host **1** with Cl^{-}. In the acetonitrile and DMSO solutions, the binding energy gains of host **1** in favor of Cl^{-} over Br^{-} are 1.4 and 1.3 kcal/mol, respectively, which correspond to the selectivity ratios of 11 and 9 times, respectively. With increasing dielectric constant, the selectivity ratio tends to decrease.

Since the ab initio results are supportive for the enhancement in anion binding strength by the nitro group of host **1**, we demonstrate it with experiments. Host **1** was synthesized according to Scheme 1. 2,4,6-Tris(bromomethyl)mesitylene[10] was reacted with 4-nitroimidazole treated with NaH in DMF to give **4**, which was then methylated with dimethyl sulfate

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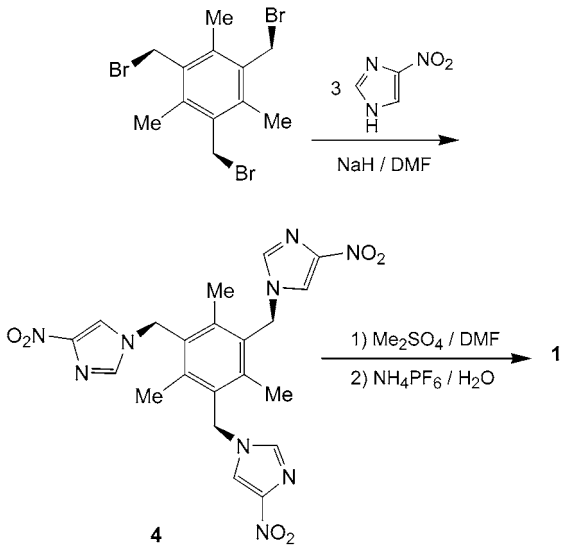
(9) The geometry optimization was done at the Hartree−Fock (HF) level of theory using 6-31+G* for halide anions and 6-31G* for all other atoms (Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998). The self-consistent reaction field (SCRF) calculations in solvent media (dielectric constant $\epsilon = 36.6$ for acetonitrile and 46.7 for DMSO) were carried out using (static) the isodensity surface polarized continuum model (IPCM) at the HF/6-31G* optimized geometries. The charges of (C, H) atoms in hosts **1** and **2** are (0.42, 0.27) and (0.40, 0.26) au, respectively. The dipole moments of hosts **1** and **2** are 9.89 and 1.68 D, respectively. Compared with the binding energy of host **2** with Cl^{-} (95.81 kcal/mol), the binding energy of host **1** with Cl^{-} (89.98 kcal/mol) increases (by 7.83 kcal/mol) in the gas phase due to the increased charges of (C, H) atoms and the increased dipole moment.

(10) van der Made, A. W.; van der Made, R. H. *J. Org. Chem.* **1993**, *58*, 1262.

Scheme 1



and anion-exchanged with a saturated aqueous solution of NH_4PF_6 to afford **1** in good yield.[11] For comparison, hosts **2** and **3** (which was already synthesized by Sato et al.)[5] were synthesized by reaction of the corresponding 1-alkyl-substituted imidazole and 2,4,6-tris(bromomethyl)mesitylene. The methyl group in the 2,4,6-trimethylbenzene spacer was expected to prohibit conformational flexibility of the imidazolium sidearm.

To investigate anion binding properties of hosts **1**−**3**, we studied the ^{1}H NMR spectral change caused by addition of the anion as tetrabutylammonium salts to DMSO-d_6 solution containing hosts. Upon addition of chloride anion to host **1**, significantly large downfield shifts ($\Delta\delta$ > 0.94 ppm) were observed for the C(2) proton of imidazolium moieties, suggesting complexation of the anion by CH hydrogen bonds. The C(5) proton also revealed downfield shifts ($\Delta\delta$ > 0.33 ppm). However, in acetonitrile-d_3, addition of chloride anion to host **1** resulted in a white precipitate. Therefore, all experiments were performed in DMSO-d_6 solution. Figure 3 shows ^{1}H NMR titration curves of hosts **1** and **2** with chloride or bromide anion in DMSO-d_6 produced by the spectral change of the C(2) proton of hosts. The saturated curves suggest 1:1 stoichiometry and additional Job plot analysis clearly indicated formation of 1:1 complexes. The

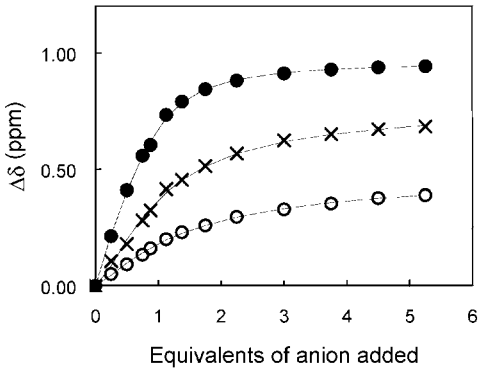


Figure 3. ^{1}H NMR titration curves of host **1** with chloride (●), host **2** with chloride (×), and host **1** with bromide (○) in DMSO-d_6 (1.0 mM). $\Delta\delta$ is the chemical shift difference of the C(2) proton of imidazolium moieties.

association constants and binding free energies were determined from their titration curves by using a nonlinear curve-fitting program[12] and are collected in Table 1. Host **1** shows

Table 1. Association Constants (K_a) and Binding Free Energies ($\Delta G°$) for 1:1 Complexes of Hosts **1**−**3** with Anions in DMSO-d_6 at 298 K[a]

hosts	anions[b]	K_a (M^{-1})	$-\Delta G°_{298}$ (kcal/mol)
1	Cl^-	4800	5.02
1	Br^-	490	3.67
1	I^-	90	2.66
1	$H_2PO_4^-$	2500	4.63
1	HSO_4^-	350	3.47
2	Cl^-	1100	4.15
2	Br^-	180	3.07
2	I^-	60	2.42
3	Cl^-	1500	4.33

[a] Estimated errors <10%. [b] Anions used in this assay were in the form of their tetrabutylammonium salts.

high affinity for the chloride anion with an association constant of 4800 M^{-1} and free energy gain of 5.0 kcal/mol. It also proved to be more highly selective for the chloride anion than for bromide and iodide, with the selectivity trend Cl^- > Br^- > I^-. The selectivity of Cl^- over Br^- is ∼10 times, in agreement with the calculated value. Host **1** also exhibits good affinity for dihydrogen phosphate with an association constant of 2500 M^{-1}, despite the fact that dihydrogen phosphate is too bulky to fit in the cavity. It presumably arises from the stronger basicity of dihydrogen phosphate.[13] A similar tendency for halide anions was observed in host **2**, which has no nitro group in imidazolium moieties. The affinity and the selectivity of host **2** for halide anions are much smaller than those of host **1** as a consequence of stronger $(C-H)^+$- - -X^- hydrogen bonds by more electron-deficient imidazolium moieties of host **1**. Host **3**,

(11) Analytical data for **1**: ^{1}H NMR (500 MHz, CD_3CN) δ 8.41 (br s, 3H), 8.30 (s, 3H), 5.59 (s, 6H), 4.12 (s, 9H), 2.31 (s, 9H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$) δ 142.49, 138.66, 138.22, 128.13, 124.23, 49.10, 37.42, 16.42; MS (FAB) *m*/*z* 830.33 $[M - PF_6]^+$. Anal. Calcd for $C_{24}H_{30}O_6N_9F_{18}P_3$: C, 29.55; H, 3.10; N, 12.92. Found: C, 29.94; H, 2.95; N, 12.66.

(12) Conners, K. A. *Binding Constants, The Measurement of Molecular Complex Stability*; Wiley: New York, 1987. WinEQNMR was used as a curve-fitting program (Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311).

(13) In the case of a much stronger basic anion such as fluoride and acetate anions, we have found that basic anions act as the nucleophile capable of attacking the methylene group of the mesitylene unit and producing 4-nitroimidazole in the ^{1}H NMR titration condition as a consequence.

(14) Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 3910.

which contains *n*-butyl groups in imidazolium moieties, shows no significant enhancement in chloride anion binding compared to host **2**, which means that N-substituents in imidazolium moieties do not directly affect complexation of anions.

The association constant of host **3** for chloride anion was reported to be 75 000 M^{-1} in acetonitrile-d_3[5] while its value in DMSO-d_6 decreased to 1500 M^{-1} probably due to the high dielectric constant of DMSO. Therefore, we measured the association constants of hosts **1** and **2** for chloride anion in various solvent mixtures of acetonitrile-d_3 and DMSO-d_6 as shown in Table 2. It was difficult to determine the exact value of the association constant of host **1** in 10% DMSO-d_6 in acetonitrile-d_3 by using the ^{1}H NMR titration experiment, due to a strong binding equilibrium (which is estimated to be $K_a > 10^6$ M^{-1}). To overcome this difficulty, a competitive method was used to give an extremely high association constant of 1.1×10^6 M^{-1} in the same solvent mixture. In a 50% DMSO-d_6 mixture, the association constant of host **1** was found to be 65 000 M^{-1}, showing a drastic increase compared to the value in DMSO-d_6 only, whereas that of host **2** increased moderately to 8300 M^{-1}. As expected, in a more polar solvent of 75% DMSO-d_6, the binding affinity of host **1** decreases depending on the polarity of the solvent.

Table 2. Association Constants (K_a)[a] and Binding Free Energies ($\Delta G°$) for 1:1 Complexes of Hosts **1** and **2** with Chloride Anions[b] in Various Solvent Mixtures of DMSO-d_6 and Acetonitrile-d_3 at 298 K

hosts	DMSO-d_6 (%) in acetonitrile-d_3	K_a (M^{-1})/10^4	$-\Delta G°_{298}$ (kcal/mol)
1	10	110.8[c]	8.24
1	50	6.50	6.56
1	75	2.19	5.92
1	100	0.48	5.02
2	10	7.10	6.61
2	50	0.83	5.34
2	100	0.11	4.15

[a] Estimated errors <10%. [b] Tetrabutylammonium salt was used. [c] Determined by competitive binding experiment.[14] K_{rel} of host **1**/host **2** is 15.6.

In summary, we have shown that host **1** recognizes effectively and selectively the chloride anion over other halide ions in highly polar solvent. These complexes are formed by $(C-H)^+ \cdots X^-$ hydrogen bonds which are highly strengthened by the nitro groups that enhance the positive charge in the C−H group in the imidazolium ring and increase the dipole moment along the C−H bond. In addition, host **1** shows reasonably high affinity toward the biologically important diphosphate anion.

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Supporting Information Available: Chemical syntheses and characterization of compounds **1**, **2**, and **4** and experimental procedures for measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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