ORGANIC LETTERS

2005
Vol. 7, No. 18
3993−3996

Participation of Benzene Hydrogen Bonding upon Anion Binding

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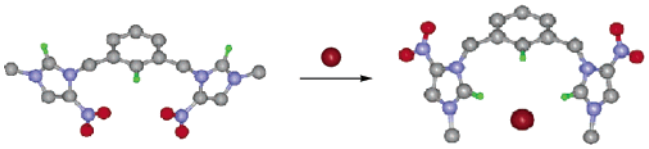
Received June 30, 2005

ABSTRACT



A *m*-xylene-bridged imidazolium receptor, 1, has been designed and synthesized. The receptor 1 utilizes two imidazole (C–H)$^+$- - -anion hydrogen bonds and one benzene hydrogen- - -anion hydrogen bond. The major driving force of complexation between the receptor 1 and anions comes from two imidazole (C–H)$^+$- - -anion hydrogen bonds. However, both NMR experiments and ab initio calculations show that the benzene hydrogen attracts the anion guests, clearly indicating benzene (C–H)- - -anion hydrogen bonding.

Hydrogen bonds are important anion recognition elements due to their directionality. As anions display a wide range of geometries, directionality of hydrogen bonds is frequently utilized to achieve complementarity between anions and receptors. Most hydrogen bonding anion receptors utilize a N−H- - -anion or O−H- - -anion hydrogen bond,[1] and C−H- - -anion hydrogen bonds are rarely utilized for anion binding even though C−H- - -anion hydrogen bonds play an important role in nature.[2] Only recently have 1,3-disubstituted imidazolium groups been introduced as new anion binding hydrogen bond moieties by forming a (C−H)$^+$- - -anion hydrogen bond between C(2)−H in the imidazolium ring and the guest anion.[3] In addition, aromatic C−H- - -anion hydrogen bond interactions are also reported even though the interaction energy is expected to be much smaller than that of imidazole (C−H)$^+$- - -anion hydrogen bonds. Jeong et al. showed that the 1-alkylpyridinium receptor has a high affinity for carboxylate ion in polar solvents. They attributed the high affinity to aromatic C−H hydrogen bonding to the carboxylate ion.[4] Gale et al. found that one of the ferrocene hydrogens participates in anion binding when a ferrocene moiety is attached to one of the *meso*-positions of calix[4]-pyrrole.[5] Abouderbala et al. reported that aromatic hydrogens adjacent to anions formed hydrogen bonds with anions when two or three hydrogen bonding arms attached to aryl core.[6] Lee et al. also demonstrated that a strapped calix[4]pyrrole that contained not only four pyrrole hydrogens but also an aromatic hydrogen in a strap form hydrogen bonds with fluoride and chloride ions.[7] In addition, Yoon et al. reported

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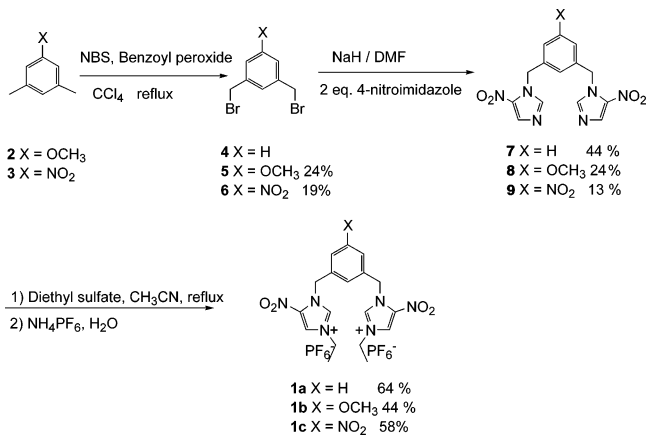
10.1021/ol0515309 CCC: $30.25
Published on Web 08/06/2005

that 9-H of anthracene in which two phenyl urea groups are immobilized on the 1,8-positions formed a strong hydrogen bond with anions.[8] We have synthesized *m*-xylene-bridged imidazolium receptor **1**, which utilizes two imidazole $(C-H)^{+}$- - -anion hydrogen bonds and one aromatic hydrogen- - -anion hydrogen bond. We report herein the synthesis and binding properties of *m*-xylene-bridged receptor **1** with various anions.

For the synthesis of *m*-xylene-bridged imidazolium receptor **1a**, 2 equiv of 4-nitroimidazole was reacted with α,α′-dibromo-*m*-xylene to give the compound **7** in 44% yield. Then, the xylene-bridged imidazole **7** was refluxed with 30 equiv of diethyl sulfate for 24 h. Anion exchange with ammonium hexafluorophosphate gave receptor **1a** bearing two imidazolium rings in the 1- and 3-positions of *m*-xylene in 64% yield. In the cases of receptors **1b** and **1c**, the starting materials were 5-nitro-*m*-xylene **2** and 3,5-dimethylanisole **3**. These starting materials were brominated by *N*-bromosuccinimide to give compounds **5** and **6**. Receptors **1b** and **1c** were synthesized from these materials following the same procedure used to obtain receptor **1a** (Scheme 1). All

Scheme 1. Synthetic Procedure for Anion Receptors **1**



compounds were characterized by ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry.

The complexation ability of compound **1** was measured by standard ^{1}H NMR titration experiments in 10% DMSO-d_6 in CD_3CN using a constant host concentration (4 mM) and increasing concentrations of anions (0.1−10 equiv). The chemical shift data were analyzed by EQNMR.[9] The addition of tetrabutylammonium anion salts to the solution of receptor **1** in 10% DMSO-d_6 in CD_3CN resulted in downfield shifts of the C(2) proton of imidazolium moieties along with the inner aromatic proton located between the two imidazolium groups. In the case of receptor **1a**, addition of tetrabutylammonium chloride moved the C(2) proton of the imidazolium ring ($\mathbf{H}_a$ in Figure 2) from 9.23 to 10.64 ppm. In addition, the inner aromatic proton located between the two imidazolium groups ($\mathbf{H}_b$ in Figure 2) originally resonating at $\delta = 7.54$ was shifted to $\delta = 8.14$ upon addition of chloride anions, while those of the other aromatic protons remained almost unchanged. Job plot experiments showed 1:1 binding stoichiometry (Figure 1). The association constant calculated from the chemical shift change of $\mathbf{H}_a$ was 1130 ± 97. The large downfield shift of the inner aromatic proton is consistent with the presence of a hydrogen bond interaction between the inner aromatic proton and chloride anion in addition to the expected normal hydrogen bond interaction between the $\mathbf{H}_a$ and halide anion. The two positively charged imidazolium rings would affect the sandwiched aromatic ring hydrogen to be slightly positively charged, and so the interaction between the aromatic hydrogen and anion can exist. Here, we reasoned that if a slight positive charge in the sandwiched aromatic hydrogen enabled the aromatic hydrogen to participate in hydrogen bonding with anions, variation of the partial positive charge in the sandwiched

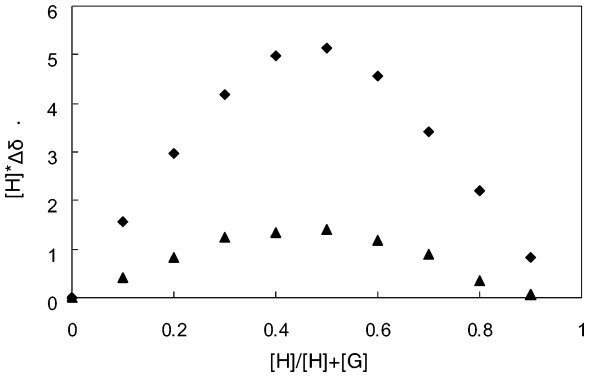


Figure 1. Job plot of **1** with tetrabutylammonium chloride (◆) and hydrogen sulfate (▲).

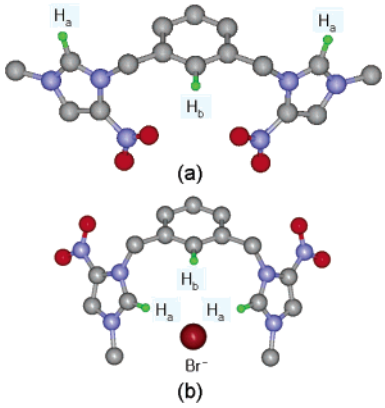


Figure 2. Optimized geometry of free host **1a** (a) and its Br^- complex (b). Imidazole moieties rotate upon complexation. All hydrogen atoms except the three shown above have been omitted for clarity. $\mathbf{H}_a$ is the hydrogen atom attached to the imidazole ring close to the anion. There are two $\mathbf{H}_a$s. $\mathbf{H}_b$ is the hydrogen atom in the benzene moiety closest to the anion upon complexation.

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inner aromatic hydrogen should affect the binding constant with anions. Furthermore, the dependence of the binding constant on the partial positive charge of the aromatic hydrogen would be good evidence of participation of the aromatic hydrogen in the binding event. Therefore, we have synthesized receptors **1b** and **1c** and measured their binding constants by standard ^{1}H NMR titration. In the cases of receptors **1b** and **1c**, the C(2) proton of the imidazolium ring moved from 9.20 to 10.68 ppm and from 9.27 to 10.72 ppm with chloride ion, respectively. In addition, the inner aromatic proton located between the two imidazolium groups originally resonating at $\delta = 7.09$ was shifted to $\delta = 7.70$ ($\Delta = 0.61$ ppm) for **1b**. In the case of receptor **1c**, the inner aromatic proton located between the two imidazolium rings showed an even larger downfield shift from $\delta = 7.96$ to $\delta = 8.76$ ($\Delta = 0.80$ ppm) upon addition of chloride anions. The association constant calculated from the ^{1}H NMR titration was 790 ± 32 for **1b** and 1908 ± 272 for **1c**. The larger downfield shift for the inner aromatic hydrogen for **1c** and the increase in K_a result in part from the increased hydrogen bond ability of $\mathbf{H}_b$. The partial positive charge in the aromatic hydrogen was increased by the nitro group in the aromatic ring and decreased by the methoxy group in the aromatic ring. We also measured the association constant for other halides and hydrogen sulfate, which showed a 1:1 binding with receptor **1**. The results are summarized in Table 1. As shown in Table 1, the magnitude of association

Table 1. Association Constants[a] (M^{-1}) of **1** with Tetrabutylammonium Anions in 10 % DMSO-d_6 in CD_3CN from ^{1}H NMR Titration

	1a	**1b**	**1c**
Cl^-	1130	790	1908
Br^-	496	420	1068
I^-	339	254	365
HSO_4^-	1260	780	1739

[a] Errors in association constants are estimated to be less than 10%.

constants is well correlated to the hydrogen acceptor ability of aromatic C−H. That is, electron withdrawing group ($-NO_2$) increase the association constant and electron donating group (−OMe) decrease the association constant.

The molecular modeling from ab initio calculation shows the details of complexation between the receptor **1** and the guest anion. All structures were fully optimized by density functional methods (Becke three parameters employing Lee−Yang−Parr functionals, B3LYP) with the basis set of 6-31G**. Calculations were carried out with the Gaussian-03 suite[10] of programs, and molecular structures were drawn using the POSMOL package.[11] Vibrational frequency analyses were performed to confirm the minima. The partial charges were calculated by both Mulliken and natural population analysis[12]

The free host (Figure 2a) has two nitro groups near the molecular center. This orientation keeps the two charged imidazole moieties apart. The center to center distance of

Table 2. Comparison of Binding Energies[a] of Both NMR Experiments and ab Initio Calculations

	1b	**1a**	**1c**
NMR			
Cl^-	−3.95 (0.52)	−4.16 (0.31)	−4.47 (0.00)
Br^-	−3.57 (0.56)	−3.67 (0.46)	−4.13 (0.00)
HSO_4^-	−3.94 (0.48)	−4.22 (0.20)	−4.42 (0.00)
ab initio (B3LYP/6-31G**)			
Cl^-	−172.62 (2.15)	−173.30 (1.47)	−174.77 (0.00)
Br^-	−171.31 (2.12)	−171.92 (1.51)	−173.43 (0.00)
HSO_4^-	−171.57 (1.60)	−172.12 (1.05)	−173.17 (0.00)

[a] Units are in kcal/mol. Data in parentheses are relative binding energies with respect to the most stable one among three hosts (**1a**−**c**). Ab initio calculations were performed in the gas phase. The relative binding energies of hosts (**1a**−**c**) are in good correlation between NMR and calculation results. Anions are always bound most strongly by the host with the electron-withdrawing substituent (**1c**).

two imidizole rings ($\mathbf{C_{Im}}-\mathbf{C_{Im}}$) is 8.7 Å. When guest anions are present, this structure completely reorganizes to accommodate the negatively charged guest, attracting two positively charged imidazole moieties more closely. For example, the $\mathbf{C_{Im}}-\mathbf{C_{Im}}$ becomes 7.1 Å for the Br^- complex (Figure 2b). The reduction of $\mathbf{C_{Im}}-\mathbf{C_{Im}}$ is clearly observed for all three hosts for all the anion guests. The major driving force of complexation between the receptor **1** and anions should come from the two charged imidazole ring and anion hydrogen bonding. This is clearly seen in the short distance and the large positive charge of $\mathbf{H}_a$ and $\mathbf{C}_a$ (the carbon attached to $\mathbf{H}_a$) as shown in Table 3. However, as shown in

Table 3. Partial Charges[a] of Anion, Three Hydrogens, and Carbons Attached to Hydrogens

		anion	H_b	C_b	H_a1	H_a2	C_a1	C_a2
1b								
free	NBO		0.266	−0.222	0.280	0.276	0.290	0.292
	MULL		0.136	−0.134	0.219	0.226	0.339	0.338
Cl^-	NBO	−0.808	0.252	−0.240	0.296	0.296	0.307	0.308
	MULL	−0.705	0.114	−0.149	0.210	0.210	0.373	0.374
Br^-	NBO	−0.787	0.252	−0.240	0.288	0.288	0.307	0.308
	MULL	−0.675	0.112	−0.151	0.214	0.213	0.361	0.362
1a								
free	NBO		0.266	−0.183	0.282	0.284	0.291	0.291
	MULL		0.140	−0.116	0.223	0.226	0.339	0.337
Cl^-	NBO	−0.807	0.253	−0.204	0.295	0.295	0.307	0.307
	MULL	−0.704	0.120	−0.136	0.208	0.208	0.374	0.374
Br^-	NBO	−0.786	0.253	−0.204	0.287	0.287	0.306	0.306
	MULL	−0.675	0.118	−0.139	0.212	0.212	0.361	0.361
1c								
free	NBO		0.270	−0.162	0.286	0.286	0.292	0.293
	MULL		0.143	−0.088	0.228	0.229	0.340	0.339
Cl^-	NBO	−0.803	0.262	−0.180	0.294	0.294	0.307	0.307
	MULL	−0.701	0.132	−0.109	0.205	0.205	0.337	0.337
Br^-	NBO	−0.783	0.260	−0.181	0.286	0.286	0.306	0.306
	MULL	−0.673	0.128	−0.111	0.211	0.211	0.363	0.363

[a] Charges are calculated with both the Mulliken charge scheme (MULL) and natural population orbital analysis (NBO). See Figure 2 for $\mathbf{H_a}$ and $\mathbf{H_b}$. $\mathbf{C_a}$ is the carbon attached to $\mathbf{H_a}$, and $\mathbf{C_b}$ is that attached to $\mathbf{H_b}$. There are two $\mathbf{H_a}$s and two $\mathbf{C_a}$s.

Figure 2, the distance of $\mathbf{H}_b$- - -bromide is small (3.3 Å) enough for hydrogen bonding. Furthermore, the partial charge of hydrogen is also significantly positive (0.27 for NBO

Table 4. Distances of Anion, Three Hydrogens, and Carbon Attached to Hydrogen

	1b	1a	1c
anion−$\mathbf{H_b}$			
Cl^-	3.249	3.238	3.163
Br^-	3.297	3.258	3.250
anion−$\mathbf{C_b}$			
Cl^-	3.930	3.900	3.803
Br^-	4.052	4.023	3.952
anion−$\mathbf{H_a1}$			
Cl^-	2.154	2.143	2.123
Br^-	2.310	2.305	2.289
anion−$\mathbf{H_a2}$			
Cl^-	2.148	2.143	2.123
Br^-	2.317	2.305	2.289
center (imidazole 1)−center (imidazole 2)			
free	8.435	8.681	8.756
Cl^-	7.030	7.094	7.195
Br^-	7.036	7.068	7.209
HSO_4^-	6.457	6.468	7.454

[a] Units are in Å.

charge and 0.14 for Mulliken charge). This suggests that not only two $\mathbf{H_a}$- - -anion interactions but also a $\mathbf{H_b}$- - -anion interaction contribute to the binding of the anion and the receptor.

To further demonstrate the existence of a $\mathbf{H_b}$- - -anion interaction upon anion binding, we calculated both electron-withdrawing group (**1c**) and electron-donating group (**1b**) effects at the para position of $\mathbf{H_b}$. It is expected that **1b** will have a less positive $\mathbf{H_b}$ compared to **1a**, while that of **1c** is more positive than that of **1a**. NMR titration experiments clearly show this substituent effect. As the benzene ring becomes more positive, the absolute value of binding free energy increases. In Table 2, the binding energies for both NMR and ab initio calculations are compared. It is clear that the relative binding energies for both NMR experiments and ab initio calculation are in good correlation.[13] That is, both experiments and theory indicate that the electron-withdrawing substituent makes the host a stronger binder of anions. In Table 3, the electronic effect of substitution is also clear. For example, the charge of chloride ion is −0.808 for methoxy group substitution (host **1b**). This means that the charge of −0.192 is transferred to this electron-deficient host. The magnitude of charge-transfer becomes slightly higher for host **1a**, while for nitro substitution (host **1c**), this transfer becomes −0.197. Likewise, we can see that electron depletion occurs for $\mathbf{H_b}$ and $\mathbf{C_b}$ with an electron-withdrawing group. Because of the enhanced positive character for $\mathbf{H_b}$ and $\mathbf{C_b}$, for host **1c**, there is more attraction between the anion and $\mathbf{H_b}$, and the distance becomes shorter. For example, the $\mathbf{H_b}$- - -Cl^- distance is 3.25 Å for host **1b**, 3.24 Å for host **1a**, and 3.16 Å for host **1c**.

In conclusion, although it may be small, the attraction between $\mathbf{H_b}$ and anion exists. The effect of para substitution to $\mathbf{H_b}$ demonstrates the contribution of $\mathbf{H_b}$ and anion hydrogen bonding interaction to the complexation.

Supporting Information Available: Optimized geometries and energies of complexes in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Absolute binding energies are very different between experimental and theoretical results. This should come from the phase difference. The experiments were performed in a mixed solvent system, while calculations were performed in the gas phase. The discrepancy between theory and experiment over the preference of the anion guest should also come from this complicated solvation effect.