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Anion Recognition by 1,3-Benzenedisulfonamide Derivatives Bearing Phenolic Hydroxy Groups in MeCN-d_3

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The halide anion recognition by 1,3-benzenedisulfonamides derived from 2-aminophenols was studied by ^{1}H NMR titrations in MeCN-d_3. The results demonstrated that the receptors achieved high recognition ability with chloride anion.

The design of neutral anion receptors has been of current interest due to their application in medicinal and environmental areas of chemistry.[1] Although the hydrogen-donating effects of N–H's of amide, sulfonamide, urea, and thiourea on anion binding have been extensively investigated, anion receptors bearing hydroxy group(s) have been less explored. We have recently reported that the disulfonamide bearing alcoholic hydroxy groups (**1**) shows remarkable anion binding ability, particularly for acetate anion ($K_{11} = 2.38 \times 10^4$ dm^3 mol^{-1}) in acetonitrile-d_3.[2] It is well known that a phenolic hydroxy group is more acidic than an alcoholic one in aqueous solution and even in polar aprotic solvents such as DMSO.[3] Therefore, the phenolic hydroxy group is expected to be a more strong hydrogen bond donor than the alcoholic one. In addition, the benzene ring bearing phenolic hydroxy group can be easily modified by the introduction of various substituted groups to tune up the absorption region in UV–vis spectroscopy and the fluorescent properties. Moreover, introduction of electron-withdrawing groups would give a strong effect on hydrogen bondings due to increasing acidity.[4] In naturally occurring enzymes and receptors, a phenolic hydroxy group incorporated in a tyrosine residue acts as a hydrogen bond donor for binding anionic species. For instance, the binding site of chloride channels from *Salmonella typhimurium* and *Escherichia coli* consists of two backbone NH's and hydroxy groups of serine and tyrosine residues, as depicted in Fig. 1.[5] However, only a limited number of efforts have been conducted on anion receptors bearing phenolic hydroxy groups.[6] Recently, Kavellieratos et al. reported that simple 1,3-benzenedisulfonamide derivatives associate anions in apolar solvents such as dichrolomethane-d_2 and 1,2-dichloroethane-d_4.[7] We designed 1,3-benzenedisulfonamides bearing 2-hydroxyaniline moieties **3**, as a new class of anion receptor. These receptors are expected to bind anionic guests by two NH groups of sulfonamides and two phenolic hydroxy groups in a structure similar to the binding sites of chloride channels (Scheme 1).

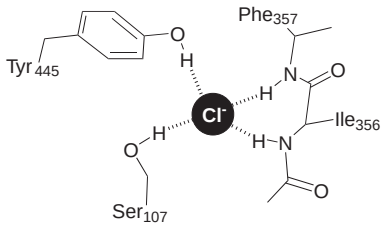
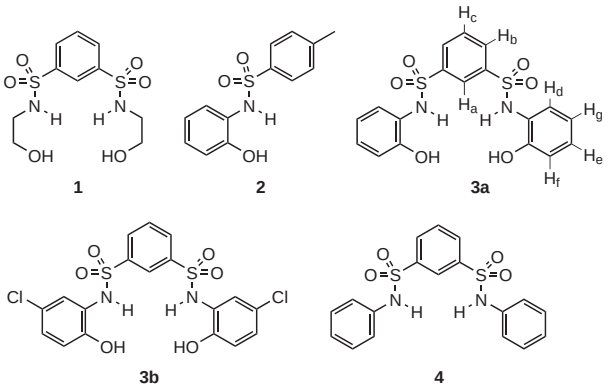


Fig. 1. Schematic representation of the binding site of chloride channel from *Salmonella typhimurium* generated from PDB data (1KPL).



Scheme 1.

Receptors **3a** and **3b** were prepared from 2-aminophenol and 2-amino-4-chlorophenol with 1,3-benzenedisulfonyl dichloride in the presence of pyridine in CH_2Cl_2 at rt under nitrogen atmosphere in 13 and 14% yields, respectively. Half receptor **2** was also prepared from 2-aminophenol with *p*-toluenesulfonyl chloride in 70% yield.[8] The products were characterized by ^{1}H NMR and elemental analyses.

To elucidate the anion complexation ability of **2** and **3**, we studied ^{1}H NMR titrations with tetrabutylammonium salts of halide anions such as Cl^-, Br^-, and I^- in MeCN-d_3. Figure 2 shows the ^{1}H NMR spectral changes of **3a** upon the addition of Br^- in MeCN-d_3. Both NH ($\Delta\delta_{max} = 1.27$ ppm) and OH ($\Delta\delta_{max} = 0.63$ ppm) peaks showed large downfield shifts upon the addition of Br^-, indicating the hydrogen bonding formation of these groups with Br^-. The spectral change can be fitted onto the 1:1 binding isotherm; the association constant (K_{11}) was then calculated to be 600 dm^3 mol^{-1} by curve fitting analysis.

In the titration experiment of **3a** with Cl^-, both NH and OH signals also showed downfield shifts due to hydrogen bonding with Cl^-; however, broadening of the signals prevented determination of the association constants from these signals. Then, the CH signals of the aromatic groups were followed to determine the association constants. The CH signals of **3a** showed biphasic change upon the addition of Cl^- in MeCN-d_3, as shown in Fig. 3. The spectral change could not be fitted onto the 1:1 binding isotherm, but instead could be fitted to the 1:1 and 1:2 systems (Scheme 2); all the signals can be perfectly fitted, as shown in Fig. 4.[9] The association constants, K_{11}

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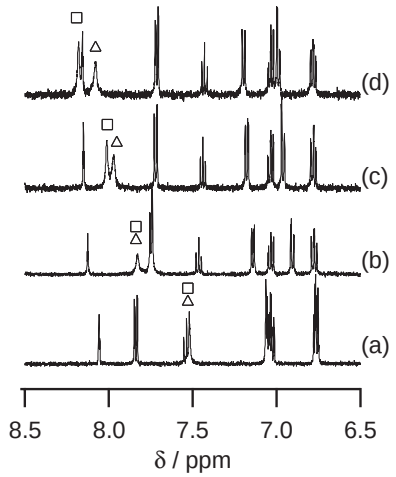


Fig. 2. Partial ^{1}H NMR spectra of **3a** in the absence (a) and the presence of 0.8 (b), 1.6 (c), and 3.0 (d) equiv of tetrabutylammonium bromide in MeCN-d_3 at 298 K. Squares and triangles indicate the peaks corresponding to hydroxy and NH groups. [**3a**] = 5.0×10^{-3} mol dm^{-3}.

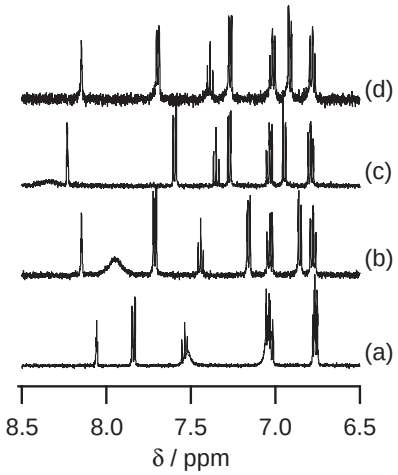
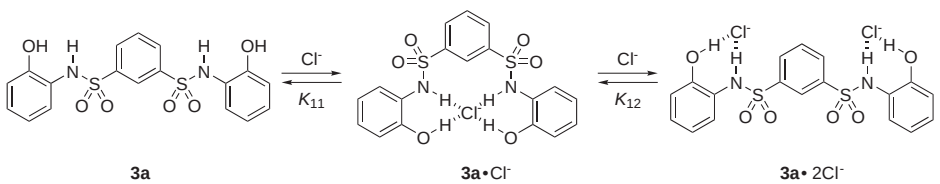


Fig. 3. Partial ^{1}H NMR spectra of **3a** in the absence (a) and the presence of 0.47 (b), 1.17 (c), and 3.50 (d) equiv of tetrabutylammonium chloride in MeCN-d_3 at 298 K. [**3a**] = 5.0×10^{-3} mol dm^{-3}.



Scheme 2.

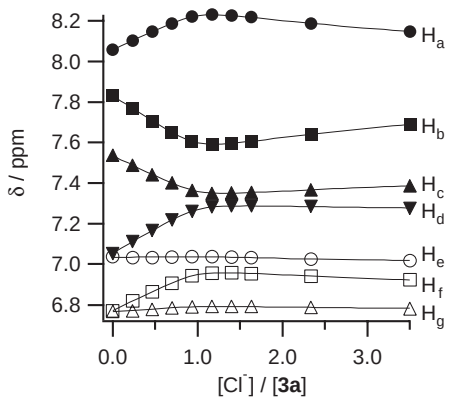


Fig. 4. Observed chemical shifts of the aromatic CH protons of **3a** upon the addition of tetrabutylammonium chloride in MeCN-d_3 at 298 K. The solid lines indicate the best-fit curves calculated by the non-linear curve fitting method.

(**3a** + Cl$^-$ ⇌ **3a**·Cl$^-$) and K_{12} (**3a**·Cl$^-$ + Cl$^-$ ⇌ **3a**·2Cl$^-$), were determined to be 14000 and 44 dm^3 mol^{-1}, respectively. The aromatic 2-CH proton of **3a** showed an initial downfield shift up to 1 equiv addition of Cl$^-$ and an upfield shift above 1 equiv. A similar biphasic shift was reported in the case of **4** with F$^-$ in CD_2Cl_2.[7a] As proposed by Crabtree et al., the spectral change suggests that unbound **3a** has the *anti-anti* conformation. Upon binding of Cl$^-$, *syn-syn* 1:1 and *anti-anti* 1:2 complexes are formed, as shown in Scheme 2. ESI-MS (negative ion mode) of **3a** and **3b** in the presence of anions in MeCN showed peaks corresponding to the 1:1 complex.

Table 1. The Association Constants of Receptors with Halide Anions in MeCN-d_3

	K_{11}/dm^3 mol^{-1} [a]		
Receptor	Cl$^-$	Br$^-$	I$^-$
1[b]	928	236	3
2	2,000	140	25
3a	14,000 (44)[c]	600	30
3b	32,100 (26)[c]	800 (34)[c]	60
4	490	130	30

a) Determined by 500 MHz ^{1}H NMR spectroscopy in MeCN-d_3 at 298 K. [Receptor] = 5.0×10^{-3} mol dm^{-3}. b) Ref. 2. c) K_{12}/dm^3 mol^{-1}.

The association constants of receptors **1**–**4** for halide anions in MeCN-d_3 at 298 K are listed in Table 1. The association constants of **3a** for Cl$^-$ and Br$^-$ are larger than those of **4** and **2**. These results indicate that four hydrogen bonds, donated from two NH and two OH groups, are important to associate Cl$^-$ and Br$^-$ with **3a**, as shown in Scheme 2. In addition, the association constants of **3a** for halide anions are larger than those of **1**, which is a 1,3-benzenedisulfonamide bearing alcoholic hydroxy groups, representing that the phenolic hydroxy group is a stronger hydrogen bond donor than the alcoholic one for the association of halide anions.

As an example for modification of phenyl rings of 2-amino-

phenol moieties of **3a**, the association constants of receptor **3b**, into which chloro groups were introduced, are shown in Table 1. The association constants of receptor **3b** for halide anions are approximately two times larger than **3a**, indicating that introduction of electron-withdrawing groups is effective to enhance the ability of hydrogen-bond donors. The receptors **3a** and **3b** bind Cl^- most strongly, followed by Br^- and I^-. This order can be explained by both the basicity and the charge density of the anions.

In conclusion, we have developed novel 1,3-benzenedisulfonamide derivatives bearing phenolic hydroxy groups, which show outstanding binding ability of halide anions, as determined by ^{1}H NMR titrations. Further functionalizations of **3a** might provide promising candidates for various applications, such as anion transports across the membrane.

Experimental

All reagents used were of analytical grade. Dry acetonitrile was purchased from Kanto Chemical Inc. ^{1}H NMR spectra were measured on JEOL AL300 (300 MHz) and λ-500 (500 MHz) spectrometers. Electrospray ionization mass spectra (ESI-MS) were recorded on an Applied Biosystems/MDS-Sciex API-100 spectrometer. Elemental analyses were performed at the Center of Instrumental Analysis of Gunma University. Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected.

***N*,*N*′-Bis(2-hydroxyphenyl)benzene-1,3-disulfonamide (3a).** Into a solution of 2-aminophenol (0.44 g, 4.04 mmol) and pyridine (0.53 g, 6.64 mmol) in dry CH_2Cl_2 (30 mL), 1,3-benzenedisulfonyl dichloride was added in 0 °C under nitrogen atmosphere. The mixture was stirred at rt overnight. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, AcOEt:$CHCl_3$ = 1:3), followed by recrystallization from AcOEt–hexane to afford 0.11 g of **3a** (13%): mp 191.1–191.8 °C; ^{1}H NMR (300 MHz, MeCN-d_3) δ 6.75 (m, 4H), 7.04 (m, 4H), 7.06 (s, 2H), 7.52 (s, 2H), 7.54 (t, 1H, J = 7.9 Hz), 7.84 (dd, 2H, J_1 = 8.2, J_2 = 1.8 Hz), 8.06 (s, 1H). Anal. Calcd for $C_{18}H_{16}N_2O_6S_2$: C, 51.42; H, 3.84; N, 6.66%. Found: C, 51.40; H, 3.84; N, 6.50%.

***N*,*N*′-Bis(5-chloro-2-hydroxyphenyl)benzene-1,3-disulfonamide (3b).** Preparation of **3b** was performed from 2-amino-4-chlorophenol (0.59 g, 4.10 mmol) in a similar manner to that described above. Purification by column chromatography (silica gel, MeOH:$CHCl_3$ = 1:30), followed by recrystallization from $CHCl_3$–hexane gave 0.28 g of **3b** (14%): mp 226 °C (decomp). ^{1}H NMR (300 MHz, MeCN-d_3) δ 6.70 (d, 2H, J = 8.9 Hz), 7.01 (dd, 2H, J_1 = 8.5, J_2 = 2.4 Hz), 7.18 (d, 2H, J = 2.4 Hz), 7.47 (brs, 4H), 7.57 (t, 1H, J = 7.9 Hz), 7.87 (dd, 2H, J_1 = 7.6, J_2 = 1.8 Hz), 8.06 (t, 1H, J = 1.5 Hz). Anal. Calcd for $C_{18}H_{14}Cl_2N_2O_6S_2$: C, 44.18; H, 2.88; N, 5.72%. Found: C, 44.18; H, 2.95; N, 5.47%.

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