Heteroassociation of Anions with Acidic Functionalities in Acetonitrile

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Simple aromatic acids showed successive 2:1 (acid:anion) and 1:1 heteroassociation with anions in polar CH_3CN. The formation of 2:1 heteroassociate was rationalized from their sigmoidal titration profiles of acids by anions and ESI-MS measurement. Boronic acid and sulfonamide derivatives having different acidic functionalities also exhibited similar titration profiles.

Acid (HA) and its conjugate base (A^-) interact with each other to afford *homoassociate* (homoconjugate, $A^- \cdots HA$), when they are treated in aprotic solvents, such as DMF, acetonitrile, and benzonitrile.[1] However, *heteroassociate* (heteroconjugate, $B^- \cdots HA$) is given instead in the combination of acid (HA) and nonconjugate base (B^-),[2] the formation of which is applied for separation of acidic compounds in non-aqueous capillary electrophoresis.[3] In this connection, we reported a very simple methodology for anion recognition by means of anion-triggered deprotonation of aromatic acids via heteroassociation between anions and aromatic acids.[4] During the studies, simple 4-(dimethylamino)benzoic acid (**1**) showed not a plain 1:1 association behavior but a successive 2:1 (acid:anion) and 1:1 association behavior with SO_4^{2-} resulting in a sigmoidal response in UV–vis and fluorescence titration experiments. Herein we report the generalization of the successive association phenomenon of aromatic compounds bearing acidic functionalities, such as **1**, 1-pyrenecarboxylic acid (**2**), 2-quinolinecarboxylic acid (**3**), 1-pyrenylboronic acid (**4**), 5-(dimethylamino)-1-naphthalenesulfonamide (**5**), and a liquid crystalline compound 4′-octyloxy-4-biphenylcarboxylic acid (**6**), with anions to show the possibility of successive 2:1 and 1:1 heteroassociation between anions and aromatic acids (Figure 1).

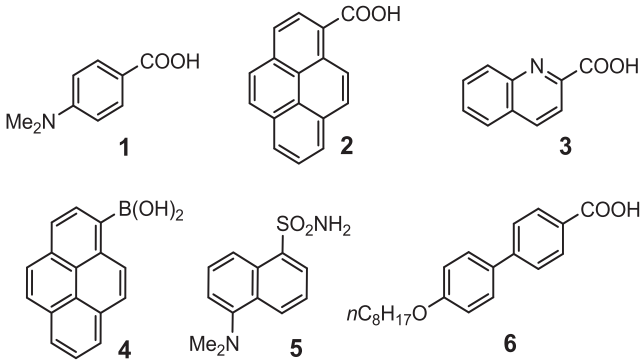

Figure 1. Chemical structures of simple aromatic acids, boronic acid, and sulfonamide.

The association was investigated by UV–vis and fluorescence titrations in CH_3CN (Figure 2). All anions were used as tetrabutylammonium (TBA) salts. Acids **1** and **2** showed absorption maxima at 309 and 350 nm, respectively. Addition of divalent HPO_4^{2-} led to a significant increase of new absorption at 275 and 348 nm, respectively. The observed absorption maxima are the same as those of the mixture of acid **1** or **2** with (TBA)OH, respectively, indicating that anion-triggered deprotonation occurred to afford anion species of corresponding acids. Both acids **1** and **2** showed a linear response to HPO_4^{2-} concentration until the molar ratio of HPO_4^{2-} to acid reached 0.5 (Figure 2A). A similar linear titration profile was obtained for acid **2**, when up to 1 equiv of divalent SO_4^{2-} was added to the acid (Figure 2B). In contrast, a sigmoidal response was observed for acid **1** upon SO_4^{2-} addition.[5] Addition of monovalent $H_2PO_4^-$ resulted in a sigmoidal response from acid **2** but no response from acid **1** (Figure 2C).

The differences observed in these titration profiles can be rationalized by the combination of i) differences in basicity between anions and conjugate bases of acids, ii) effects relative to anion charge valences, and iii) potential hydrogen bonding between acids and anions. The inflection point observed upon addition of 0.5 equiv divalent HPO_4^{2-} to acids **1** and **2** clearly indicates 2:1 acid–anion interaction. HPO_4^{2-} ($pK_b = 6.8$)[6] is a stronger base compared to the conjugate bases of acids **1** ($pK_b = 9.0$)[7] and **2** ($pK_b = 10.3$).[7] Therefore, this strong basicity, combined with a divalent negative charge, should effectively generate negative charges on the acid moieties of the resulting 2:1 heteroassociates. Such clear spectral intensity change observed should be derived from the formation of complete anion species, while we suppose that the resulting carboxylate and conjugate acid of anion would not be separated by solvent fully to form a complete ion species but would make a pair through hydrogen bonding(s) which should be a *heteroassociate* between acids and base in CH_3CN as shown in Scheme 1.[8] In the combination of divalent SO_4^{2-} and acid **2**, the basicity difference between SO_4^{2-} ($pK_b = 12.0$)[6] and the conjugate base of acid **2** ($pK_b = 10.3$) is not enough to effectively create negative charges on the aromatic moiety of acid **2**. In contrast, the divalent charge of SO_4^{2-} may generate partial negative charge in 1:1 heteroassociate, resulting in an inflection point at 1 equiv addition. On the other hand, proton transfer from acid **1** to SO_4^{2-} with an effective electronic state change on the aromatic moieties should be quite difficult, because the conjugate base of acid **1** ($pK_b = 9.0$) is a much stronger base than SO_4^{2-} ($pK_b = 12.0$). Instead, the divalent charge of SO_4^{2-} causes a 2:1 heteroassociate with little electronic change on the aromatic moieties. As shown in Scheme 1, further addition of SO_4^{2-} cleaves the 2:1 hetero-

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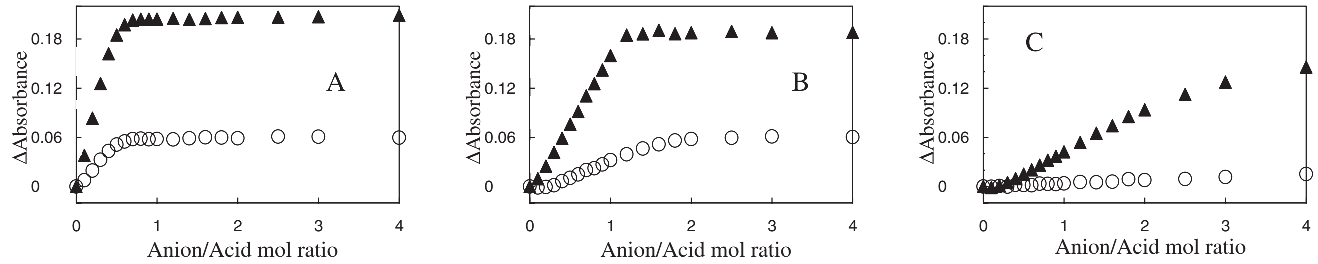
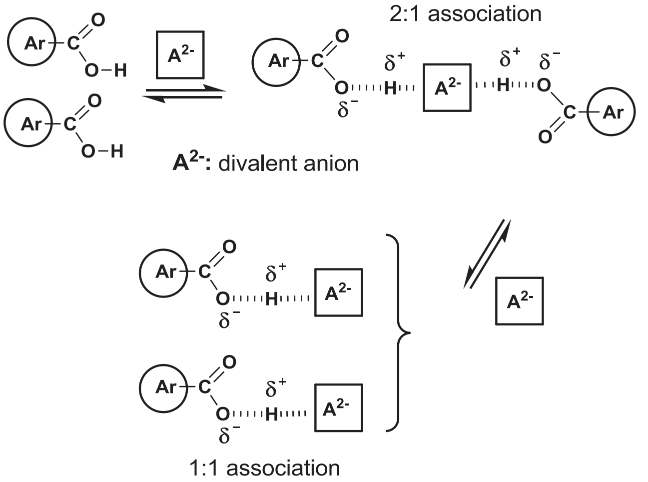


Figure 2. Titration profiles of acids **1** (○, 4.46 × 10^{-6} mol L^{-1}) and **2** (▲, 2.0 × 10^{-5} mol L^{-1}) by HPO_4^{2-} (A), SO_4^{2-} (B), and $H_2PO_4^-$ (C) monitored at 275 nm (**1**) and 348 nm (**2**).



Scheme 1. Successive 2:1 and 1:1 heteroassociation between aromatic acid and divalent anion.

associate to afford two sets of 1:1 heteroassociate and the divalent negative charge significantly changes the electronic state of the aromatic moiety in the 1:1 heteroassociate. This successive 2:1 and 1:1 heteroassociate formation between acid **1** and SO_4^{2-} leads to a sigmoidal response to SO_4^{2-} concentration.[9] The case of the monovalent $H_2PO_4^-$ is slightly different from the other anions. Specifically, the weak basicity ($pK_b = 11.9$)[6] and a monovalent charge of $H_2PO_4^-$ lead to little to almost no electronic effect on acid **1**. Similar to the combination of acid **1** and SO_4^{2-}, the sigmoidal response of acid **2** to $H_2PO_4^-$ concentration is ascribed to successive 2:1 and 1:1 heteroassociation. Actually, 2:1 and 1:1 heteroassociates were nicely confirmed by ESI-MS measurement in the case of a mixture of acid **2** and $H_2PO_4^-$ in CH_3CN (Figure 3). The 2:1 heteroassociate between acid **2** and $H_2PO_4^-$ can be formed via hydrogen bondings as shown in Figure 4. The sigmoidal response phenomenon to SO_4^{2-} concentration is not limited to simple carboxylic acids. Heteroaromatic acid **3** (UV, 238 nm) also exhibited a similar sigmoidal response to SO_4^{2-} concentration upon titrations.[10] Interestingly, boronic acid **4** (fluorescence, 378 nm) and sulfonamide **5** (fluorescence, 511 nm) bearing quite different functional groups in shape and acidity also showed sigmoidal responses to SO_4^{2-} concentration.[10]

Appearance of the clear sigmoidal responses on titration profiles (Figures 2B, 2C, 6S,[10] 8S,[10] and 10S[10]) indicates that the obtained 2:1 heteroassociates are stable under these conditions. An attempted calculation of association constants K_1 (1:1 association between acid **1** and SO_4^{2-}) and K_2 (the second association between the 1:1 associate formed and acid **1**) by curve fitting of the titration profile on UV[10] resulted in an extremely large value for K_2. As can be easily deduced from the large association constants, no temperature dependence was observed up to 70 °C in reality (Figures 11S and 12S).[10] Thus, the 2:1 heteroassociate was unexpectedly stable in CH_3CN. In order to adjust the stability of the heteroassociates to the extent exhibiting temperature dependence in the titration profile practically, we combined a liquid crystal compound **6** and divalent SO_4^{2-} in polar CH_3CN, where the stability of 2:1 associate would be reduced without loss of association driving force between acidic functionalities and anion. Namely, the resulting 2:1 heteroassociate of **6** with SO_4^{2-} should be relatively unstable in CH_3CN compared to those of simple acids, since the long alkyl chains provide the heteroassociate with a lipophilic surface which is then exposed to the highly polar solvent. When temperature is raised, the 2:1 heteroassociate would be cleaved to afford a 1:1 heteroassociate and **6** itself which are more polar, thus more stable in CH_3CN. In fact, acid **6** showed a clear sigmoidal response to SO_4^{2-} concentration monitored at 293 nm at 10 °C (Figure 5A).[11] Association constants, K_1 and K_2, were calculated to be $\log K_1 > 7$ and $\log K_2 = 7$, respectively, by curve fitting of the titration profile on UV (Figure 5A). This sigmoidal curve changed into gentle sloping lines when the temperature increased to 26 °C

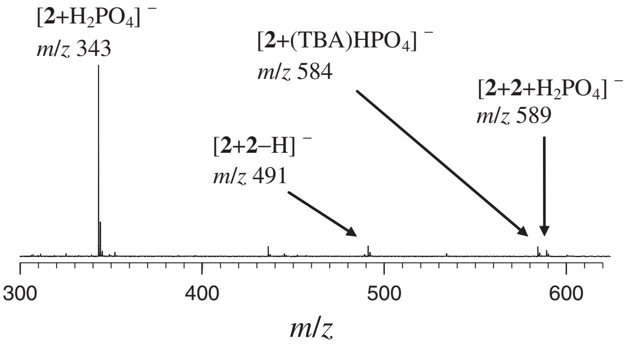


Figure 3. ESI-MS fragmentation of heteroconjugates generated from acid **2** and $(TBA)H_2PO_4$ in CH_3CN.

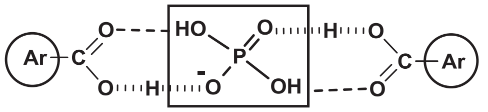


Figure 4. Postulated 2:1 heteroassociate between acid and $H_2PO_4^-$.

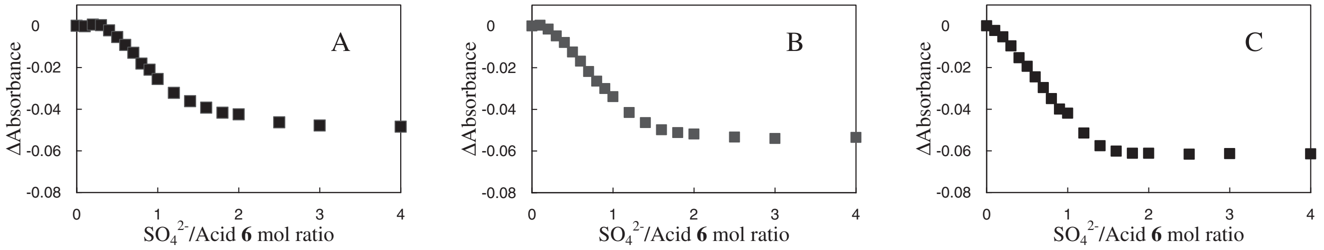


Figure 5. Titration profiles of acid **6** monitored at 293 nm using SO_4^{2-} at 10 (A), 26 (B), and 70 °C (C).

(Figure 5B) and to 70 °C (Figure 5C; $\log K_1 = 6.5$, $\log K_2 = 5.4$) as expected. Titration profiles monitored at different wavelengths showed similar trends.[10] Thus, the liquid crystal molecule showed temperature dependence in titration profiles.

Conclusion

We succeeded in observing heteroassociation phenomena between aromatic acids (and their derivatives) and anions by spectroscopic methods on UV–vis and fluorescence as well as ESI-MS measurement. Successive 2:1 and 1:1 association with SO_4^{2-} is a common feature in the combination of the compounds with acidic functionalities and anions in CH_3CN.

Experimental

General. UV–vis spectra were measured on a JASCO Ubest V-560, a Perkin-Elmer Lambda 9, and a SHIMADZU UV-2450 spectrophotometers. Fluorescence spectra were recorded on a JOBIN YVON-SPEX Fluorolog-3 spectrophotometer. ESI-MS was conducted with a JEOL 700 mass spectrometer. HPLC grade acetonitrile from Nacalai Tesque, Inc. was utilized without further purification unless otherwise stated.

UV–vis and Fluorescence Titrations of 1, 2, 3, 4, 5, and 6 by SO_4^{2-}, HPO_4^{2-}, and $H_2PO_4^-$ Anions. Solutions of **1** (4.46×10^{-6} mol L^{-1}), **2** (2.0×10^{-5} mol L^{-1}), **3** (1.0×10^{-5} mol L^{-1}), **4** (4.0×10^{-6} mol L^{-1}), **5** (2.0×10^{-5} mol L^{-1}), and **6** (8.0×10^{-6} mol L^{-1}) in CH_3CN and appropriate concentration of SO_4^{2-}, HPO_4^{2-}, and $H_2PO_4^-$ tetrabutylammonium salts solutions in CH_3CN were prepared. Then, 3.00 mL of acid solution was transferred into a quartz cell. After the UV–vis and/or fluorescence spectra were measured, an aliquot of the anion solution was added to the cell, and absorbance and fluorescence intensity were recorded; this procedure was repeated for each aliquot addition.

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Supporting Information

UV–vis and fluorescence spectra and titration profiles. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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8 Heteroassociation of SO_4^{2-} in CH_3CN with an uncharged hydrogen donor, 3,5-dinitrophenol, was also reported, see Ref. 2c).

9 UV–vis and fluorescence measurements were performed alternatively using the same sample. Fluorescence measurements required very low concentration (10^{-6} mol L^{-1}) of **1** in CH_3CN, which resulted in quite small absorbance change (Δabs < 0.02) in Job's plot. In the complexation **1** and SO_4^{2-}, two inflection points around $[\mathbf{1}]/([\mathbf{1}] + [SO_4^{2-}]) =$ ca. 0.4 and ca. 0.7 were barely recognized in the Job's plot. However, it is difficult to put a conclusive discussion for the complexation stoichiometry because of the uncertainty of the inflection points.

10 See Supporting Information.

11 Control of water content in CH_3CN is an important factor for the reproductivity of the titration profiles in the case of compound **6**. When moist CH_3CN (water:CH_3CN = 1.3:100 (v/v) by mixing distilled CH_3CN from CaH_2 and water) was used for the titrations of compound **6**, the titration profile was easily reproducible. As a preliminary experiment concerning on solvent effect, 9-anthracenecarboxylic acid exhibited spectral response in UV–vis and fluorescence to SO_4^{2-} concentration in polar CH_3CN but not in less polar CH_2Cl_2. Thus, solvent effect is critical for the heteroassociation.