

Synthesis of Bis(2-hydroxynaphthamide) Derivatives Behaving as a Fluorophore for Anions

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Bis(2-hydroxynaphthamide) derivatives have been synthesized *via* tandem Claisen rearrangement in high yields. These compounds are found to make complexes with anions and emit luminescence, serving as anion sensing fluorophores.

Anion plays a very important role in biological processes and development of effective anion recognition system is desired. Although much effort has been paid to the construction of anion binding reagents,¹ there is much room to make improvements in selectivity and efficiency compared to cation binding reagents such as crown ethers.

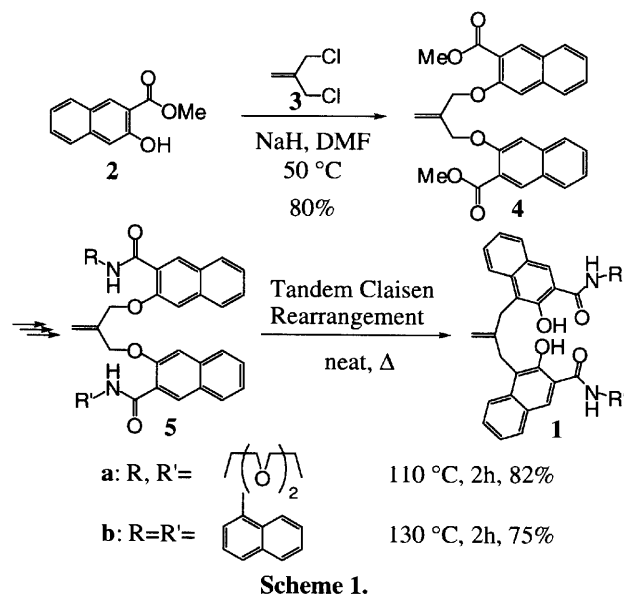
So far, cationic compounds like protonated polyamines have often been used to make complexes with anions.² Coulombic force is the main interaction between them. Such cationic anion receptors have some problems in regard to selectivity. Highly acidic condition required for protonation of these receptors makes it difficult to apply them in biological system. This leads to the wide attention to the development of neutral anion sensing reagents.³ Of these, urea or thiourea based compounds are well known.⁴ They use acidic amide protons as hydrogen bond donors. While anion receptors which use phenolic hydroxyl group as hydrogen bond donors are relatively few,⁵ they are expected to serve as good receptors as well. Besides, the use of naphthol derivatives, which have the potential of emitting luminescence, could be a way to develop fluorophores.

We report herein the synthesis of novel anion sensing luminescent compounds **1** that have plural phenolic group as hydrogen bond donors as well as their complexation ability with anions. It is not unusual that undesirable side-reaction, i.e., polymerization or oxidation reaction occur in the process of synthesizing polyphenols. We have recently developed tandem Claisen rearrangement, a useful reaction for making polyphenols in one step from corresponding polyethers bearing methallyl units.⁶ This method was successfully applied to preparing bisnaphthol derivatives **1** in a simple manner and in good yields.

Methyl 2-hydroxynaphthoate **2** was treated with methallyl dichloride **3**, using sodium hydride as a base, to give bisnaphthoate **4**, which has methallylarylether moiety as a key component for tandem Claisen rearrangement to occur. The bisnaphthoate **4** was then hydrolyzed, converted to acyl chloride, and condensed with amines to give amides **5**. Tandem Claisen rearrangement was carried out by heating **5** without solvent in vacuum for a few hours and binaphthol **1a,b** were obtained in high yields, respectively, as shown in Scheme 1.

When tetraethylammonium salt of fluoride ion was added to **1**, emission of green fluorescence was observed. The emission was also exceptionally strong. Since fluoride selective

receptors have not been so much reported as chloride or bromide selective ones,⁷ this result was interesting, which brought us into further investigation of anion binding properties of **1**.



First, the effect of anion species on the strength of fluorescence of **1a** was examined. The result is shown in Figure 1. Among halide ions, fluoride ion gave quite strong luminescence, and emission strength decreased as ionic radius becomes larger. Addition of bromide or iodide ion gave almost no response, indicating **1a** has fluoride ion selectivity. Nonspherical shaped anions were then tried. Among them, perchlorate ion gave hardly any response, while addition of oxoanions such as dihydrogenphosphate and acetate ions resulted in strong emission of luminescence.

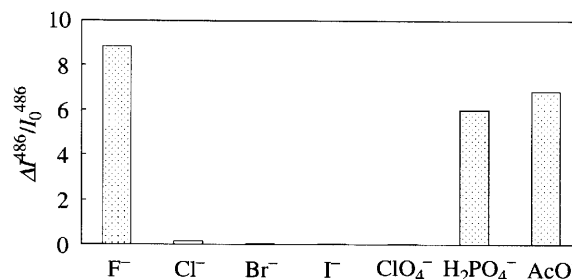


Figure 1. Fluorescence intensity dependence of **1a** on anion species in CH_3CN . [**1a**] = 1×10^{-5} M, 10 eq. anion, excitation 296 nm. $\Delta I^{486} = I^{486}_{10\text{eq.anion}} - I_0^{486}$. Anions were added as tetraethylammonium salts except for dihydrogenphosphate and acetate as tetrabutylammonium salts.

Now that it was clear that **1** have selectivity for particular anions, we tried to carry out titration and determine association constants of **1** for each anion. A couple of problems have occurred in the process. The one was that a sigmoidal curve was obtained as a result of the titration of **1** with fluoride ion by fluorescence spectroscopy. Since inclusion of more than two fluoride ions in single **1** molecule is unlikely, drastic change of ionic strength of the solution due to the high electronegativity of fluoride was considered to be the reason. Addition of excess perchlorate, already known not to interact with **1** at all, for the purpose of stabilizing the polarity of solution solved the problem as expected, and a normal titration curve was obtained. Dihydrogenphosphate still gave sigmoidal curve under this condition, however. The other one was that when acyclic compound **1b** was added with more than about 2 equimolar amounts of fluoride ion, red-shift of the maximum emission wavelength and significant increase of emission strength, as shown in Figure 2, were observed. This spectral change indicates that proton transfer from the host compound **1b** to the guest anion took place.⁸ This fact was confirmed by the existence of HF_2^- observed with ^{19}F NMR⁹ and reproduction of the phenomenon by adding sodium hydroxide to **1b**. From the titration curve, it is clear that 1:1 complex was formed before hydrogen transfer took place.¹⁰ Addition of acetate or dihydrogenphosphate ion caused **1b** to do the same behavior.

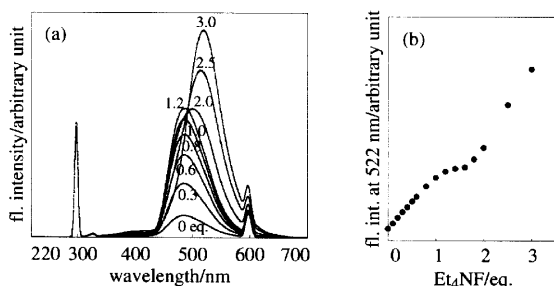


Figure 2. Change in the fluorescence spectrum of **1b** upon addition of tetraethylammonium fluoride (a) and plot of emission intensity against the amount of fluoride (b) in CH_3CN . [**1b**] = 1×10^{-5} M, 100 eq. Et_4NClO_4 , excitation 296 nm.

Table 1 shows association constants of **1** for various anions determined by fluorescence spectrum titration using non-linear regression method. From this result, it became clear that acyclic compound **1b** has a considerable preference for fluoride, well over 100 times than chloride, 10000 times than bromide, among halide ions. **1b** showed excellent selectivity as an acyclic receptor, indicating a good induced-fit for fluoride ion was realized. Cyclic **1a** was found to form host:guest = 2:1 complex with fluoride ion by Job's plot.¹¹ Though the exact reason is yet to be known, the ring size of **1a** may be not large enough to fully incorporate a fluoride ion. For acetate ion **1a,b** showed more affinity than for fluoride ion. Association constants for dihydrogenphosphate ion, the other oxoanion examined here, were not able to be calculated because both **1a** and **1b** gave sigmoidal curves upon titration. Since multiple binding of dihydrogenphosphate ion, much larger than acetate ion in size, to **1** is implausible, this probably indicates that this anion is slightly too large to fit into the cavity of **1**, requiring

Table 1. Association constants for **1** with various anions in CH_3CN at 298 K^a

Anion ^b	Association constant K_a/M^{-1}	
	1a	1b
fluoride	(H:G=2:1) ^c	$2.6 \times 10^{5(d)}$
chloride ^e	4.0×10^1	4.5×10^2
bromide ^e	— ^f	1.2×10^1
iodide	— ^f	— ^f
dihydrogenphosphate	— ^g	— ^g
acetate	5.9×10^6	$1.7 \times 10^{7(d)}$

^aAssociation constants were determined by fluorescence spectrum titration using non-linear regression method. [**1**] = 1×10^{-5} M, 100 eq. Et_4NClO_4 . ^bHalide ions were added as tetraethylammonium salts. Dihydrogenphosphate and acetate ions were added as tetrabutylammonium salts. ^cDetermined by Job's plot. ^d K_a was calculated within the concentration range at which proton transfer did not occur. ^e 1×10^{-3} M solution of **1** was used. ^f K_a was too small to be determined. ^gTitration gave sigmoidal curves.

higher concentration of the anion to move the equilibrium for complex formation.

In conclusion, we have synthesized a new type of anion sensing compounds which emit luminescence upon complexation with certain anions, promising feature for practical application as anion sensors. Determination of the structure of the complexes are currently in progress.

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- ^1H -NMR (500 MHz, $\text{DMSO}-d_6$) δ = 16.1 ppm (t, $J=121$); ^{19}F -NMR (270 MHz, $\text{DMSO}-d_6$) δ = -216.3 ppm (d, $J=121$).
- 1:1 complex of **1b**- Et_4NF was obtained by recrystallization from CHCl_3 . For **1b**- $\text{Et}_4\text{NF} \cdot 2\text{H}_2\text{O}$: Anal. Calcd for $\text{C}_{54}\text{H}_{58}\text{N}_3\text{FO}_6$: C, 75.06; H, 6.77; N, 4.86%. Found: C, 74.94; H, 6.76; N, 5.13%.
- The possibility that formation of 2:1 complex was the reason for strong emission in Figure 1 could be excluded because maximum emission wavelength and spectrum profile were same with those of 1:1 complexes.