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2,6-Bis(benzoxazoyl)pyridine (bzpybox) as a new dialkylammonium cation receptor

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Abstract—2,6-Bis(2-benzoxazoyl)pyridine (bzpybox) ligand is reported as a new artificial receptor for secondary dialkylammonium.

Molecular recognition of cationic species has been of much interest since the discovery of crown ethers.[1,2] The complexes of the crown ethers with secondary dialkylammonium cations have been often used as supramolecular building blocks to construct topologically unique supramolecular assemblies such as pseudo-rotaxanes and catenanes toward molecular switches and machinery.[3] However, there has been only a limited number of the receptors specific to the secondary dialkylammonium cations in spite of their importance as a building block. In the previous report, we demonstrated that 2,6-bis(2-oxazolin-2-yl)pyridine (pybox) ligands act as receptors for the secondary dialkylammonium cations by two complementary $N^+H\cdots N$ hydrogen bonds between them.[4] Utility of commercially available C_2 chiral pybox ligand as a chiral shift reagent has been also reported.[5] However, the 2-oxazoline rings of the pybox ligands are not stable in an acidic condition, and easily hydrolyzed to *N*-(2-hydroxy-ethyl)amide or polymerized via ring opening.[6] Thus, we can use limited organic reactions to modify the pybox ligands after formation of the oxazoline rings. This reactivity hampered us to use the pybox ligand as the supramolecular building block to construct more complicated supramolecular assemblies such as oligomeric and functionalized pybox ligands. Therefore, we designed a new receptor based on 2,6-bis(2-benzoxazoyl)pyridine (bzpybox) that is expected to be much more stable than the pybox ligand due to replacement of the reactive aliphatic 2-oxazoline ring to the inert aromatic 2-benzoxazol ring. In this report, we demonstrate formation of 1:1 complexes of the bzpybox ligand with some secondary dialkylammonium salts.

The bzpybox ligand (**1**) was prepared according to the reported method.[7] The resulting ligand was investigated as a receptor for secondary dialkylammonium cations by ^{1}H NMR and ESI MS. ^{1}H NMR titration in CD_2Cl_2–CD_3CN 4:1 (v/v) with dibenzylammonium tetraphenylborates (**2a**) provided the chemical shift changes of all the protons as shown in Figure 1. Addition of the salt into the solution of **1** illustrated that the resonance of the benzoxazol proton at the 6-position marked with f moved from 7.46 to 7.53 ppm due to the deshielding from the phenyl groups of **2a**. The other

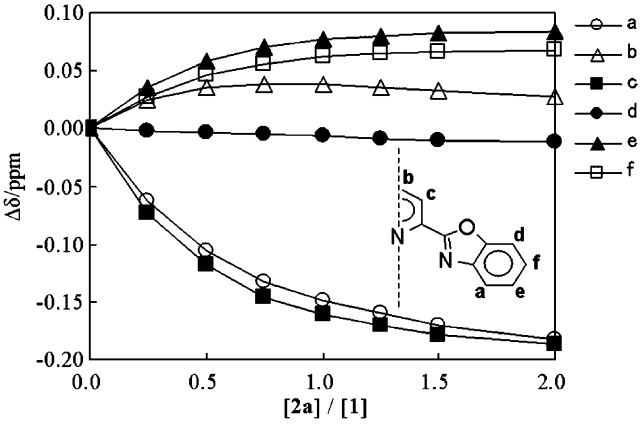

Figure 1. ^{1}H NMR titration of **1** with **2a** in CD_2Cl_2–CD_3CN 4:1 (v/v) at room temperature.

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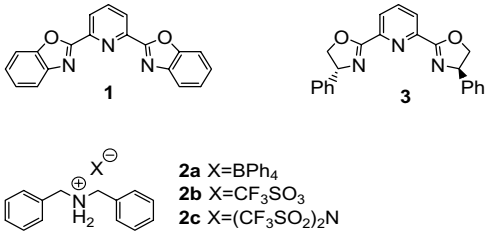
benzoxazol protons showed the downfield shifts. On the other hand, the doublet protons assigned to the protons at the 3-position of the pyridine ring marked with c exhibited an upfield shift from 8.53 to 8.34 ppm. This shift indicates the complexation by the complementary two hydrogen bonds between the imino group of **1** and the secondary ammonium cations. Addition of the secondary dialkylammonium cations suppressed the rotation between the pyridine ring and the benzoxazol ring by complexation, and the fixation of the orientation weakens the anisotropic shielding effect by the imino groups. As the result, the upfield shift of the pyridine protons was observed. These complex-induced shifts in the ^{1}H NMR spectra were quite similar to those observed in the complexes with the pybox ligands reported previously.[4] The chemical shift change was saturated at nearly a 1:1 ratio, which suggests formation of a 1:1 complex between **1** and **2a**. The bind constants between **1** and **2a** were estimated by nonlinear curve fittings in the titration experiment data, resulted in the averaged bind constant by using protons a, c, e, and f was $K = 1.1 \times 10^4$ (M^{-1}). This value is in the similar magnitude to those of the complex of the pybox ligand with the dibenzylammonium salt. The 1:1 complexation in the solution was also confirmed by ESI MS in CH_3CN (10 μM). An equimolar mixture of **1** and **2a** provided the corresponding 1:1 complex at $m/z = 511.2$. This confirmed the 1:1 complex between **1** and **2a**.



We further investigated the effect of the counter anions,[8] trifluoromethanesulfonate (**2b**) and trifluoromethanesulfonimide (**2c**) in the same solvent. They had the similar induced chemical shift changes, suggesting formation of the complexes with **1**. However, the proton resonances of **1** were not saturated by addition of a few equivalents of **2b** and **2c**, and the titration curves were bent nearly at 1:1 ratios. Therefore, we believe that the two salts form the same 1:1 complexes as **2a** with weak affinities. Nonlinear curve fitting provides that the binding constants of **2b** and **2c** with **1** were $K = 2.3 \times 10^2$ and $K = 6.0 \times 10^2$, respectively. The order of the binding constants is **2a**$\gg$**2c** $\sim$ **2b**. Difference of the observed binding constants is attributed to association of the ion pairs between the dibenzylammonium cation and the corresponding counter anion. The tetraphenylborate of **2a** is the most effective anion to bind the dibenzylammonium cation with **1**. This should be caused by the weakest interactions between them due to absence of strong hydrogen bond accepting sites in the tetraphenylborate anion. The other two anions have a sulfonate or sulfonimide group that acts as hydrogen bond acceptors for the secondary dialkylammonium cations. The order represents strength of the hydrogen bond accepting properties in the counter anions, and agrees with the results of the crown ether complexes.[9] Noncoordinating tetraphenylborates is most effective to formation of the secondary ammonium cations.

Moreover, we examined the tolerance of **1** and the pybox ligand (**3**) against an acid. Addition of one and more equivalents of triflic acid to the solution of **1** in the same solvent caused protonation of the benzoxazol ring to yield a green-yellow colored solution with downfield shifts of all the protons in the ^{1}H NMR spectrum as shown in Figure 2b. Then, addition of dibenzylamine caused to upfield shifts to move the chemical shifts (Fig. 2c). It is similar to those of the complex separately prepared by mixing **1** and **2b** (Fig. 2d). This process involves the proton transfer to dibenzylamine from the triflate salt of **1** and complexation of **1** with the resulting **2b**. There were no decomposition of the benzoxazol ring of **1**, and the bzpybox maintained the ability to bind the dibenzylammonium cation. On the other hand, under the same condition, the pybox **3** exhibited the appearance of the new sets of the resonances assigned to the opened 2-hydroxyethylamide (4.76 and 4.86 ppm) together with the downfield shifts of the oxazoline protons by the protonation. Triflic acid protonates the oxazoline ring of **3** and hydrolyzes to the open amide structure by the nucleophilic reaction at the 5-position of the oxazoline ring. Therefore, the tolerance against the strong acid is much improved by replacement from the oxazoline ring to the benzoxazol ring. The bzpybox ligand should have the advantage to construct more complex supramolecular assemblies.

In conclusion, we demonstrated 1:1 complexation of the bzpybox ligand with the secondary ammonium cation. Compared to the pybox ligand, the bzpybox ligand has similar affinity to the secondary ammonium cation and does not decompose in the strong acidic condition. This enables us to construct the complexes by simple mixing of the three components: the bzpyox ligand,

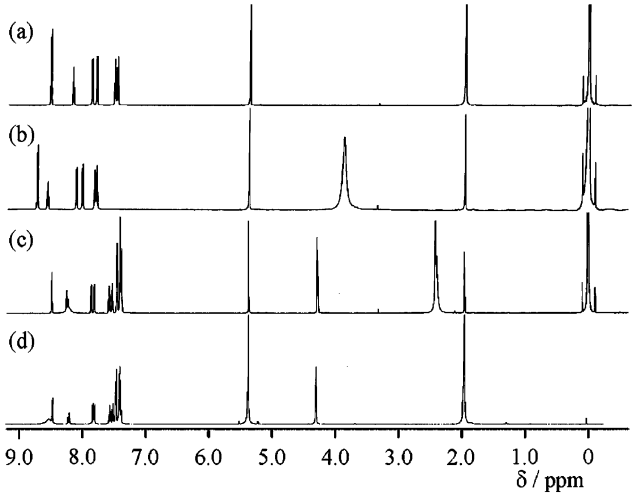


Figure 2. ^{1}H NMR spectra of (a) **1**, (b) **1** + CF_3SO_3H (1:1.4), (c) **1** + CF_3SO_3H + dibenzylamine (1:1.4:1.4), and (d) **1** + **2b** in CD_2Cl_2–CD_3CN 4:1 (v/v).

the secondary amine, and triflic acid. This access to develop molecular switches driven by protonation. Moreover, acid tolerance expands the potential of the bzpybox ligand as a supramolecular building block. A wide range of organic reactions can be applied without decomposition of the binding site. This enables us to prepare bzpybox ligands with various functional groups. In particular, preparations of the compounds with a few or more bzpybox ligands are under current investigations to construct more complex supramolecular assemblies.

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