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Carboxylate anion selective receptor with glycoluril molecular scaffold ☆

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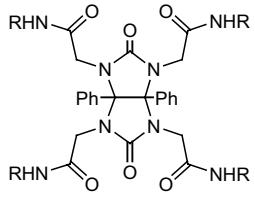
Abstract—Glycoluril based tweezer-type receptor has been designed and synthesized. Anion binding studies carried out using ^{1}H NMR and UV–vis revealed that this compound displays good affinities for Y-shaped anions such as acetate and benzoate, while binding spherical-shaped anions and tetrahedral-shaped anions only weakly.

While the selective recognition of cations was one of the main challenges in the early days of supramolecular chemistry,[1] the recognition of anions by artificial receptors became another goal of supramolecular chemistry.[2] As anions display wide range of geometries, a host–guest complementarity is required for the design of anion receptor. Therefore, hydrogen bonds are frequently used by many researchers as recognition elements due to their directionality. Correct orientation of hydrogen bonds can differentiate among anionic guests with different geometries. Nature also utilizes neutral amide N–H group to achieve anion binding by proteins.[3] For synthetic receptor with amide group, the amide groups are arranged through a space in a rigid and convergent manner. This has been achieved by incorporating amide group inside macrocycle[4] or utilizing molecular scaffold to arrange amide groups. Benzene ring,[5] pyrrole,[6] cyclohexane,[7] cholic acid,[8] tris(aminoethylamine),[9] and calixarenes[10] have been utilized as molecular scaffolds to arrange amide bonds. Recently, we have introduced glycoluril as a new molecular scaffold to arrange four amides at the corner of glycoluril. This anion receptor **1** utilizes four amide hydrogen bonds cooperatively to bind spherically-shaped halide ion with 1:1 stoichiometry and has a high affinity for fluoride ion.[11] We also synthesized glycoluril based tweezer-type receptor **2**, which has only two amide hydrogen bonds. Anion binding studies carried out using ^{1}H NMR and UV–vis revealed that this compound displays good affinities for Y-shaped anions such as acetate and benzoate, while binding spherical-shaped anions and tetrahedral-shaped anions only weakly.



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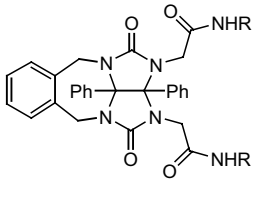

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The synthesis of the receptor **2** was achieved as depicted in Scheme 1. The synthesis stared from the reaction between 10 equiv of excess diphenyl glycoluril and α,α′-dibromo-*o*-xylene in the presence of potassium *tert*-butoxide. This reaction gave the one side protected glycoluril **3** in 40% yield. Then the compound **3** treated with potassium *tert*-butoxide was reacted with methyl-bromoacetate in DMSO to give the compound **4** in 46% yield. Hydrolysis of the compound **4** with 10 equiv of lithium hydroxide in methanol afforded the compound **5** in 84% yield. Treatment of the compound **5** with oxalyl chloride gave diacyl chloride **6** in quantitative yield. Finally the reaction with 4-nitroaniline, 4-fluoroaniline or butylamine with diacyl chloride **6** gave the desired

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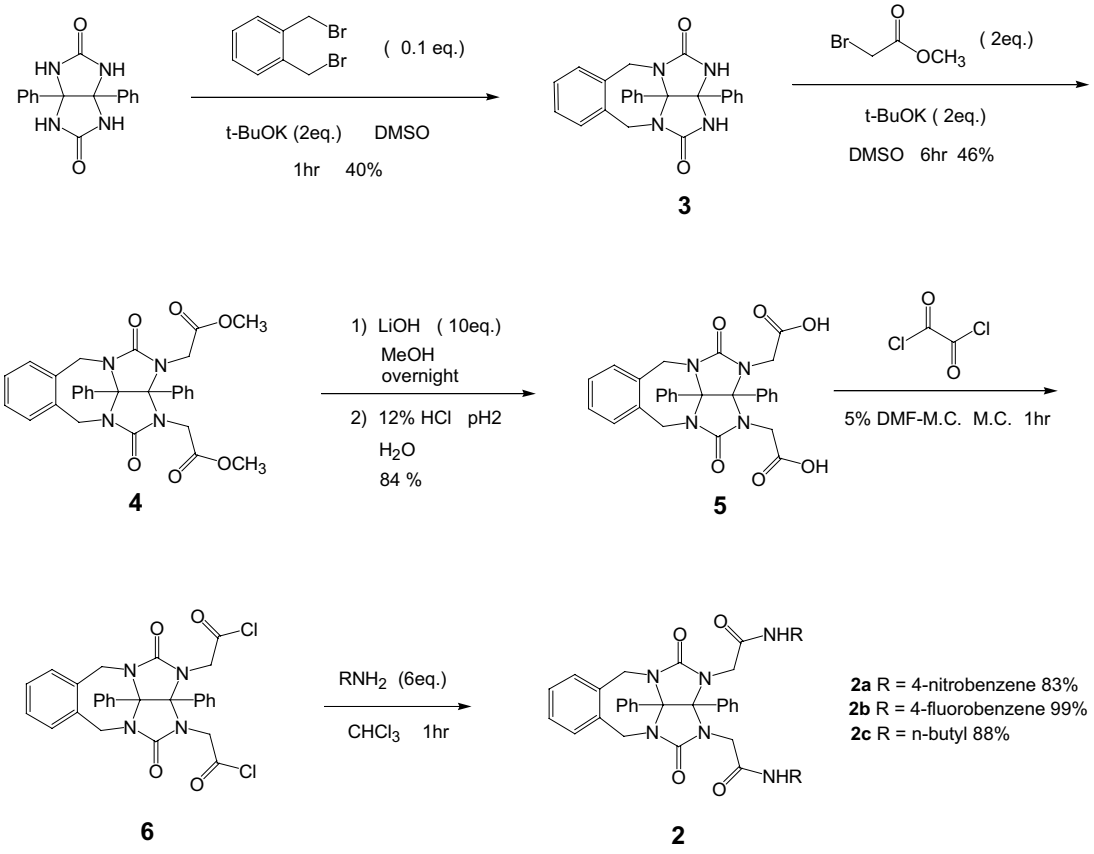

Scheme 1. The synthetic procedure for the anion receptor **2**.

compounds **2a**,**b** and **2c** in 83%, 99% and 88% yield, respectively (Scheme 1).

The complexation abilities of compounds **2a**,**b** and **2c** were measured by standard ^{1}H NMR titration experiments in CD_3CN using a constant host concentration (1.5–2 mM) and increasing concentrations of anions (0.1–10 equiv). The chemical shift data were analyzed by EQNMR.[12] The addition of tetrabutylammonium anion salts to the solution of **2** in CD_3CN resulted in downfield shifts in both the amide N–H hydrogen and CH_2 hydrogens next to amides. Therefore, the signals of amide NH_2 or the signals of CH_2 protons located next to amide groups were used to determine the association constants for complex **2** and anions. Whichever peaks we chose, binding constants between the receptor **2** and anions showed similar values.

As the receptor **2a** was expected to have the strongest affinity for anions, the association constants of **2a** for different anions were determined first. From the experiments, **2a** showed the highest affinities for Y-shaped anions such as acetate and benzoate. The addition of tetrabutylammonium acetate or benzoate to the solution of **2a** leads downfield shifts of the CH_2 peaks next to amides. The amide N–H peaks disappeared upon addition of acetate or benzoate. The CH_2 peaks next to amides moved downfield about 0.17 ppm for 1 equiv acetate ion and 0.27 ppm for 1 equiv benzoate ion. No further shifts were observed for both anions. The plot of induced chemical shifts versus anion concentration gave typical titration curves corresponding to the formation of a 1:1 complex (Fig. 1A). The association constants calculated from NMR titration gave $8.9\times10^4\ M^{-1}$ for acetate and $3.5\times10^4\ M^{-1}$ for benzoate. However, these values are too large to accept from ^{1}H NMR titration experiments.[13] Therefore, the binding properties of **2a** with acetate or benzoate were further assessed by UV–vis spectroscopy. Figure 1B shows the dependence of UV–vis spectra of **2a** on the concentration of acetate in CH_3CN. Increasing the concentration of acetate produced a bathochromic shift in the λ_{max} from 317 to 329 nm and clear isosbestic point appears at 321 nm. Similar spectrum was observed for the titration of **2a** with benzoate. Association constants calculated using a computer program ENZFITTER[14] gave $9.1\times10^4\ M^{-1}$ for acetate $2.4\times10^4\ M^{-1}$ for benzoate. The possible binding mode and energy minimized structure of receptor **2a** and acetate were shown in Figure 2. Receptors **2b** and **2c**, which have less acidic N–H than **2a**, showed marked decrease in association constants for the same anions, which reflects the importance of hydrogen bond in the binding event of the receptor **2** and anions. The association constants are listed in Table 1. We also investigated the associations of receptor **2a** and spherical anions such as halides, tetrahedral anions such as dihydrogenphosphate and hydrogen sulfate or linear anion such as cyanide. Job plot experiments showed 1:1 binding stoichiometry (Fig. 3) for all kinds of anions irrespective of anion shapes. The association constants

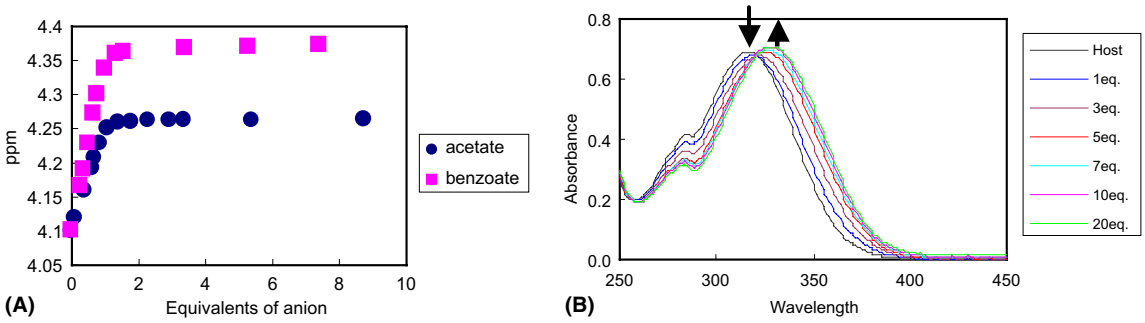

Figure 1. (A) Changes in the CH_2 protons located next to amide groups in **2a** with increasing acetate or benzoate concentration in acetonitrile-d_3. (B) Changes in UV–vis spectra of **2a** titrated with acetate (as tetrabutylammonium salt).

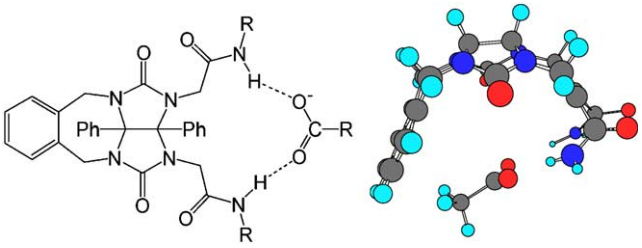

Figure 2. The energy minimized structure of 1:1 complex between receptor **2a** and acetate (Cache 3.2 MOPAC calculation); aromatic rings are omitted for clarity.

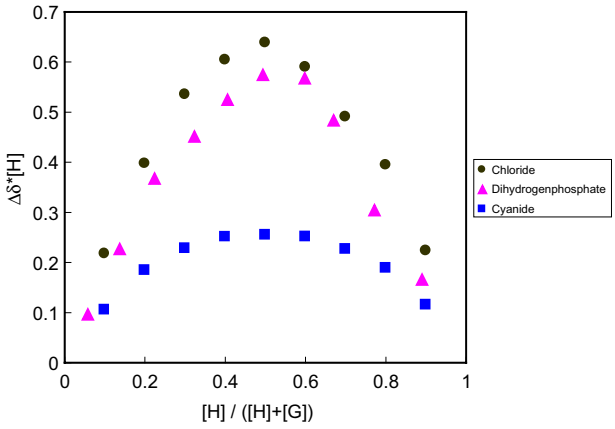

Figure 3. The Job plot of **2a** with tetrabutylammonium chloride (●), dihydrogenphosphate (▲) and cyanide (■).

calculated from NMR titration are summarized in Table 1. For receptor **2a**, the association constants were calculated as 2770 for fluoride and 1645 for dihydrogenphosphate, which are much smaller values than acetate or benzoate. The association constant for acetate is about 30–50 times higher than those of fluoride or dihydrogenphosphate. Probably the binding site of receptor **2** does not fit to the spherical halide ions, tetrahedral anions or linear cyanide anion. However, for these anions the association constants still reflect basicity of these anions.[15] Fluoride and dihydrogenphosphate are stronger hydrogen acceptor than other halide or hydrogen sulfate, respectively. Receptor **2b** and **2c** also showed smaller association constants than **2a** for the same anions as expected. However, for these anions, the differences in association constants among the receptors **2a**,**b** and **2c** are much smaller than those of carboxylate anions. The effect of amide N–H acidity does not seem to play much role for the anions, which does not fit to the binding site of receptor.

In conclusion, we have designed and synthesized new anion receptor **2** with glycoluril molecular scaffold and the receptor **2** displays selectivities for Y-shaped carboxylate anions over spherical-shaped halides, tetrahedral anions or linear anions.

Table 1. Association constants (M^{-1}) of **2** with tetrabutylammonium anions in CD_3CN from ^1H NMR titration

Anion	2a	2b	2c
$CH_3CO_2^-$	9.1×10^{4a}	6.9×10^{3b}	2.1×10^{2b}
$C_6H_5CO_2^-$	2.4×10^{4a}	5.0×10^{3b}	1.3×10^{2b}
NO_3^-	32^b	12^c	6^c
F^-	2.7×10^{3b}	2.6×10^{3b}	2.5×10^{2c}
Cl^-	2.3×10^{3c}	1.7×10^{3c}	28^b
Br^-	2.2×10^{2b}	80^b	13^b
I^-	13^c	7^c	11^c
CN^-	5.3×10^{2b}	2.3×10^{2b}	28^b
$H_2PO_4^-$	1.6×10^{3c}	1.1×10^{3c}	58^c
HSO_4^-	1.1×10^{2b}	1.1×10^{2b}	32^b

[a] Association constants were calculated from UV–vis titration.
[b] Errors in K_a are estimated to be less than 10%.
[c] Errors in K_a are estimated to be less than 20%.

Acknowledgements

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