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Improved recognition of alkylammonium salts by ion pair recognition based on a novel heteroditopic pillar[5]arene receptor

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ABSTRACT

A novel pillar[5]arene-based heteroditopic receptor for ion pair recognition of alkylammonium salts with different alkyl chain lengths and different counterions was prepared, which showed the best association constant enhancement (71 times) to *n*-$BuNH_3^+Cl^-$ compared with monotopic receptor 1,4-dimethoxypillar[5]arene over corresponding Br^- and CF_3COO^- salts in chloroform.

The research on cation receptors based on host–guest chemistry has attracted considerable interest in supramolecular chemistry due to their great importance in biological, analytical, catalytic, environmental applications, drug delivery, molecular machines, and so on.[1] When the cation recognition processes occur in apolar solvents, most recognition studies of cation guests were carried out with their low-coordinating counterions such as tetrafluoroborate and hexafluorophosphate where the counterion effect could be neglected, ascribed to their good solubility and weak ion-pairing binding affinity in apolar solvents. However, those low-coordinating counterions were hardly observed in our nature environment and real life system, and as a matter of fact, cation guests usually exist with Cl^-, PO_4^{3-}, HCO_3^- etc. as counterions,[2] where the coordinating power of the counterions could not be neglected due to their Coulomb interaction with the cation guests. As a consequence, it is quite important to study the recognition of cation guest with competitive coordinating counterions in apolar solvents for well understanding the role of counterions in recognition.[3]

In the cation recognition process in apolar solvents, the counterion can inhibit the cation recognition. However, on the other hand, the binding affinity can be improved by employing heteroditopic receptors, which consist of two different binding sites, thus capable of binding two ionic partners of an ion pair simultaneously.[4] In 1991, Reetz and co-workers[5] firstly reported a good example of heteroditopic receptors for potassium associated ion pairs. Due to the superior recognition ability and selectivity to ion pairs, heteroditopic receptors have been applied for helping salt dissolution, extraction, and transportation.[6] Nevertheless, to the best of our knowledge, heteroditopic receptors based on macrocycles for organic cation recognition especially with the improved binding affinity by ion pair recognition are rarely reported and most of them are based on crown ethers or calixarenes.[7] For instance, Huang and co-workers[8] reported dibenzo-24-crown-8 derivatives for the improved recognition of dibenzylammonium salts. So we are interested in developing a novel heteroditopic receptor based on new-type macrocycle host for organic cation recognition with improved binding affinity by ion pair recognition.

Recently, a new class of macrocycle host named pillar[n]arene[9] has attracted much attention of supramolecular chemists, and the emergence of monofunctionalized pillar[5]arene has expanded the application of pillar[n]arene in the areas of molecule recognition, self-assembly, supramolecular polymer construction, and so on.[9j,k,p] Unlike basket-shaped calix[n]arene, this novel host is para-bridged and displays perfectly symmetric architecture. Because of the column-shaped and π-electron rich cavity, pillar[n]arene can form inclusion complexes with organic cations like paraquats,[9a,d] alkylammoniums,[9g,n] and bis(imidazolium) derivatives.[9f] Among those organic cation guests, the recognition of alkylammoniums is rather significant and also full of challenge, because of their physiological activity[10] and applications in many fields such as herbicide detection.[11]

Therefore, in order to prove that the new designed pillar[5]arene based heteroditopic receptor could improve the recognition of the alkylammounium salts compared to monotopic one,

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the urea unit that is well known as a good anion receptor was introduced to the pillar[5]arene host to achieve a novel heteroditopic pillar[5]arene receptor **1**. With two different binding sites, a π-electron rich cavity and a urea group, it was desired that heteroditopic pillar[5]arene receptor **1** could bind both the ionic partners of alkylammonium salts (**G**) cooperatively, leading to dramatically improved recognition of the alkylammoniums (Fig. 1). On the other hand, this is also the first example of heteroditopic pillar[5]arene receptor designed for ion pair recognition of alkylammonium salts. Herein, we studied the complexation between heteroditopic receptor **1** and several alkylammonium salts with different counterions and different alkyl chain lengths, demonstrating that heteroditopic receptor **1** showed much more improved binding affinity to alkylammoniums by ion pair recognition than monotopic receptor 1,4-dimethoxypillar[5]arene (**DMP5**) which was synthesized for comparison.

Heteroditopic receptor **1** was prepared by the simple modification of monofunctionalized pillar[5]arene **2**[9k] (Scheme 1). With the attachment of urea, pillar[5]arene **1** was expected to bind both alkylammonium and its counterion, forming a neutral ternary system consequently. Initially, ^{1}H NMR was employed to investigate the complexation between heteroditopic pillar[5]arene **1** and *n*-butylammonium salts with Cl^-, Br^-, CF_3COO^-, and PF_6^- as different counterions, respectively. Figure 2 showed the ^{1}H NMR spectra of **1**, *n*-butylammonium trifluoroacetate (**G4c**), and an equimolar mixture of them, respectively, in $CDCl_3$. In the presence of **1**, all peaks of **G4c** shifted upfield obviously and it only exhibited one set of peaks, indicating fast-exchanging complex on the NMR time scale. By 2D COSY spectrum of the mixture (Fig. S11, ESI), the peaks for **G4c** were accurately assigned. Therefore, the chemical shift changes of protons H_α, H_β, H_γ, H_δ, and NH_3 of **G4c** were −2.12, −2.88, −2.35, −0.83, and −2.30 ppm, respectively. Meanwhile, more importantly, urea protons H_a and H_b of **1** shifted downfield significantly from 5.04, 7.19 ppm to 6.58, 8.07 ppm, respectively, indicating the hydrogen bonding between urea and the counterion, CF_3COO^-. The cooperative binding between **1** and **G4c** also gave rise to lower resonances of the peaks for H_1, H_2, H_3, H_4, H_5, and H_6 of **1**, while no obvious chemical shift changes were observed for H_7 and H_8 of **1**. These results provided strong and direct evidence that linear *n*-$BuNH_3^+$ fully threaded into the cavity of **1**, and multiple noncovalent interactions such as urea–anion hydrogen bonding, cation–π, C–H···π, and N–H···π interactions[9n,12] may contribute to the stabilization of the complex of heteroditopic receptor **1** with **G4c**. Moreover, similar complexation phenomena by ion pair recognition between heteroditopic pillar[5]arene **1** and *n*-butylammonium salts with Cl^- and Br^- (**G4a** and **G4b**) as counterions in $CDCl_3$ could also be observed from the ^{1}H NMR spectra of their mixtures, respectively (Figs. S7–S8, ESI). However, in these two cases, some peaks for methylene protons and urea protons could not be clearly observed because of the broadening effects[9e,9t] that occurred due to complexation dynamics where those protons were located in the cavity of pillar[5]arene and shielded by π-electron rich cyclic pillar[5]arene. What is more, due to the poor solubility of *n*-$BuNH_3^+PF_6^-$ in chloroform, the investigation of the complexation between **1** and *n*-$BuNH_3^+PF_6^-$ by ^{1}H NMR was limited.

Because of the relatively less remarkable broadening effect in the ^{1}H NMR spectra of heteroditopic receptor **1** mixed with **G4c**, the complexation between **1** and **G4c** was selected for further study by 2D NOESY NMR. From the spectrum (Fig. S12, ESI),

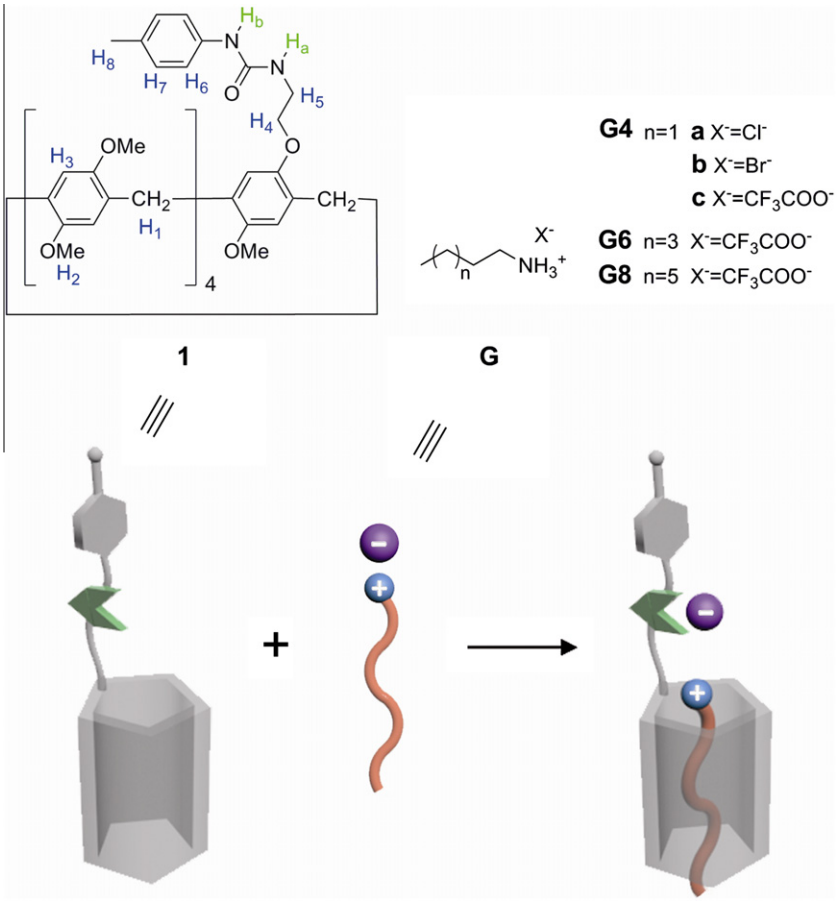
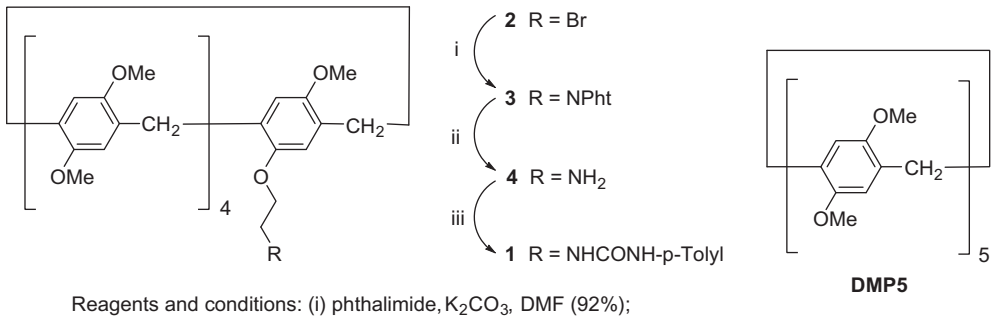


Figure 1. The cartoon representation of the complexation between heteroditopic receptor **1** and **G**.



Reagents and conditions: (i) phthalimide, K_2CO_3, DMF (92%); (ii) NH_2NH_2, THF (94%); (iii) p-tolyl isocyanate, CH_2Cl_2 (85%).

Scheme 1. Synthesis of pillar[5]arene **1** and structure of **DMP5**.

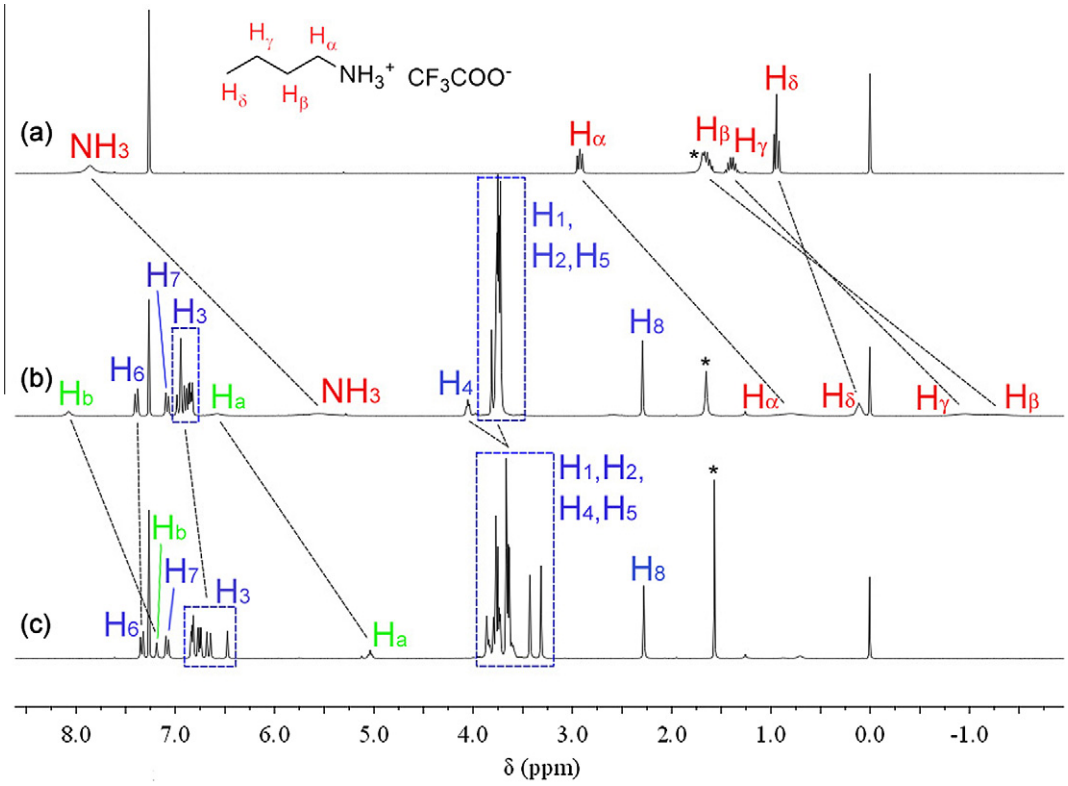


Figure 2. ^{1}H NMR spectra (300 MHz, $CDCl_3$, 298 K) of (a) **G4c** (8 mM); (b) **1** (8 mM) + **G4c** (8 mM); (c) **1** (8 mM). Asterisk = water.

correlation peaks can be clearly observed between H_1, H_2, and H_3 of **1** and H_α, H_β, H_γ, H_δ, and NH_3 of **G4c**, suggesting that *n*-$BuNH_3^+$ threaded into the cavity of **1**. Job's plot (Fig. S13, ESI) revealed that **1** and **G4c** formed 1:1 complex in chloroform. Furthermore, the 1:1 binding complex between **1** and **G4a**, **G4b**, and **G4c** was confirmed by ESI-MS, respectively (Figs. S14, S16–S17, ESI). As for the complexation of **1** and **G4c**, in the positive ion mode, the spectrum exhibited a peak at m/z = 986.3, which is corresponding to $[\mathbf{1} + \mathbf{G4c}–CF_3COO]^+$. Meanwhile, a peak at m/z = 1025.3 corresponding to $[\mathbf{1} + \mathbf{G4c}–n\text{-}BuNH_3]^-$ could be observed in the negative ion mode.

In addition, the ion pair recognition between heteroditopic receptor **1** and alkylammonium trifluoroacetate salts with different alkyl chain lengths (**G6** and **G8**) in chloroform was further studied by the ^{1}H NMR spectroscopy (Figs. S9–S10, ESI). The proton signals for NH_3 of three types of alkylammonium trifluoroacetate salts (**G4c**, **G6**, and **G8**) showed similar upfield shifts (−2.30, −2.18, and −2.07 ppm, respectively), indicating the formation of threading structure for all alkylammonium trifluoroacetates. As for *n*-$HexNH_3^+CF_3COO^-$ (**G6**), only one peak corresponding to terminal methyl H_δ of **G6** exhibited no obvious shift (red dashed line in Fig. S9, ESI), while all other methylene protons shifted upfield. And in the case of *n*-$OctNH_3^+CF_3COO^-$ (**G8**), the proton chemical shifts of only terminal three alkyl groups had no significant change (red dashed line in Fig. S10, ESI), which agreed well with **G6**, indicating only first five methylenes connecting to the ammonium end of **G** could thread into the cavity of **1** with others outside the cavity. Furthermore, the complexation between heteroditopic receptor **1** and **G6** and **G8**, respectively, was also studied by ESI-MS spectra (Figs. S18–S19, ESI), which revealed the same 1:1 cooperative binding between them.

Because heteroditopic receptor **1** could form 1:1 complexes with all *n*-butylammonium salts **G4a–c** by ion pair recognition, ^{1}H NMR titration was carried out to investigate their recognition process and measure their association constants. The ^{1}H NMR titration spectra of **1** into **G4c** (Fig. S20, ESI) in $CDCl_3$ showed that only

Table 1
Association constants (Ka/M^{-1}) for the complexation of host (**1** and **DMP5**) and guest (**G4a**, **G4b**, and **G4c**), respectively, in $CDCl_3$ at 298 K

	G4a	G4b	G4c
1	$(2.01 \pm 0.72) \times 10^3$	$(4.61 \pm 1.68) \times 10^3$	$(2.62 \pm 0.73) \times 10^4$
DMP5	$(2.81 \pm 0.28) \times 10$	$(3.54 \pm 1.16) \times 10^2$	$(6.76 \pm 1.16) \times 10^2$

the peaks for H_δ of **G4c** could be recognizable when less than 1 equiv **1** was added. Nevertheless, the peaks for H_α, H_β, and H_γ of **G4c** became sharper and the peaks for H_δ of **G4c** returned to be triplet peaks from broad peaks with more than 1 equiv addition of **1**. It could also be observed that with the addition of **1**, the peak for H_δ of **G4c** shifted upfield gradually, and showed no significantly shift change after the addition of 1.6 equiv **1**. By employing the nonlinear curve-fitting of H_δ of **G4c** (Fig. S21, ESI), the association constant of the complexation between **1** and **G4c** was calculated to be $(2.62 \pm 0.73) \times 10^4$ M^{-1}. Similarly, the association constants of the complexation between **1** and **G4a** and **G4b** were also obtained under the same conditions (Table 1).

In order to prove that heteroditopic receptor **1** formed by the introduction of an urea moiety could enhance the cation recognition by ion pair recognition, monotopic receptor 1,4-dimethoxypillar[5]arene (**DMP5**) was prepared and employed for comparison with heteroditopic receptor **1** in the recognition of *n*-$BuNH_3^+$ with different counterions. The ESI-MS spectrum of **DMP5** with **G4c** was conducted and it only showed [**DMP5** + **G4c**–CF_3COO]$^+$ (m/z = 824.3) in the positive ion mode (Fig. S15, ESI), suggesting 1:1 binding stoichiometry between **DMP5** and *n*-$BuNH_3^+$, while no corresponding peak was observed in the negative mode to identify the binding between **DMP5** and the counteranion of **G4c** as expected. Furthermore, the ^{1}H NMR titration between **DMP5** and **G4a**, **G4b** and **G4c** was performed under the same condition as that between **1** and **G4a–c**, and their association constants were obtained and listed in Table 1. As for the complexation of **DMP5** and **G4c** (Fig. S22, ESI), the peak for H_δ of **G4c** shifted upfield much less upon addition of **DMP5** than addition of **1** (Fig. S21, ESI), suggesting the less stable complexation between **DMP5** and **G4c** compared to that between **1** and **G4c**.

As shown in Table 1, compared to the Ka value, $(2.01 \pm 0.72) \times 10^3$ M^{-1}, of the complexation between **1** and **G4a**, the Ka value of the complexation of **1** with *n*-$BuNH_3^+Br^-$ and with *n*-$BuNH_3^+CF_3COO^-$ increased 2 times and 13 times, respectively. Meanwhile, the Ka value of the complexation between **DMP5** and **G4a** was very low (28.1 ± 2.8 M^{-1}), and the Ka values of the complexation of **DMP5** with *n*-$BuNH_3^+Br^-$ and with *n*-$BuNH_3^+CF_3$-COO^- increased 12 times and 24 times, respectively. The results revealed that the different counterion influenced the stability of complexation between neutral hosts and organic cation guests.[13] Most importantly, binding to the same *n*-butylammonium guest, heteroditopic receptor **1** remarkably showed much higher Ka values than monotopic receptor **DMP5**, which is 71 times for *n*-$BuNH_3^+Cl^-$, 13 times for *n*-$BuNH_3^+Br^-$, and 39 times for *n*-$BuNH_3^+CF_3COO^-$, respectively. It suggested that the counterion was grabbed by the urea group of heteroditopic receptor **1** through hydrogen bonding, leading to a relatively loose ion pairing of **G**, and consequently, the synergic hydrogen bonding promoted the binding affinity between heteroditopic receptor **1** and *n*-$BuNH_3^+$.[7e] In other words, the strong binding strength of the hydrogen bonding between urea and counterion could improve alkylammonium recognition by heteroditopic receptor **1** compared to monotopic receptor **DMP5**.

Further investigation on the correlation between the selectivity of receptor **1** to *n*-$BuNH_3^+$ with different anions (Cl^-, Br^-, and CF_3COO^-) compared with **DMP5** and the binding affinity of these three anions with urea unit was carried out by the ^{1}H NMR titration experiments to determine the Ka value of the interaction between receptor **1** and three anions (Cl^-, Br^-, and CF_3COO^- as their tetrabutylammonium salts), which was 56.0 ± 4.0 M^{-1}, 42.3 ± 1.4 M^{-1}, and 31.3 ± 1.4 M^{-1}, respectively (Figs. S24–S25, Table S1, ESI). The relatively strongest binding of Cl^- with urea unit over Br^- and CF_3COO^- could lead to the most remarkable enhancement (71 times) for *n*-$BuNH_3^+$ binding to receptor **1**.[14] However, receptor **1** showed 13 and 39 times association constant enhancement for *n*-$BuNH_3^+Br^-$ and *n*-$BuNH_3^+CF_3COO^-$, respectively, compared to **DMP5**, which does not correlate with the relative binding affinity of the urea unit to Br^- and CF_3COO^-. This phenomenon could mainly result from the different size of Br^- and CF_3COO^-, and their different binding modes with urea unit.[15] Another possible reason was that compared with CF_3COO^-, the stronger urea-anion binding of Br^- makes the charge density of the anion weaker, leading to relatively weaker electrostatic interaction between Br^- and the included *n*-$BuNH_3^+$.[16]

In summary, a monofunctionalized pillar[5]arene **1** bearing one ureido group on the arm has been prepared by the simple modification of a previously reported monofunctionalized pillar[5]arene. Such a novel host is easily synthesized and acts as a heteroditopic receptor for ion pair recognition of alkylammonium salts in chloroform, with the linear guest threading into the cavity of pillar[5]arene and the counteranion binding to urea simultaneously. The uptake of counteranion by urea moiety of heteroditopic **1** weakened the ion pairing, performing a cooperative role in the recognition of alkylammoniums, and thus enhanced the recognition of alkylammoniums by heteroditopic receptor **1** in comparison with monotopic receptor **DMP5**, in which the best performance is 71 times binding enhancement for *n*-$BuNH_3^+Cl^-$. Future work will be focused on the design of more powerful pillar[n]arene based heteroditopic receptors for alkylammoniums with good selectivity and other organic cation guests and their applications in the areas of extraction and transportation.

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Supplementary data

Supplementary data (synthesis route, additional NMR spectra, ESI spectra, Job's plot and determination of association constants) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.043.

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