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Ion pair receptors based on anion– π interaction⁺

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A novel type of ditopic ion pair receptors based on anion– π interaction is reported. Oxacalix[2]arene[2]triazine azacrowns were synthesized efficiently from a one-pot reaction between 2,4-dichloro-4-methoxytriazine and 3,5-dihydroxybenzaldehyde followed by condensation with a diamine and reduction of bisimine; they acted as selective ditopic receptors to recognize ion pairs.

Ion pair recognition is one of the central themes in supramolecular chemistry.¹ The sophistication of the design and synthesis of novel ditopic ion pair receptors based on noncovalent bond interactions enables the selective interaction of various ion pairs.^{2–7} Among the ion pair receptors reported, crown ether moieties,² multidentate N- or O-ligands,³ and electron-rich aromatic rings⁴ are usually utilized as the cation binding sites while the anion binding sites are mainly composed of hydrogen bond donors,^{2a,b,3b,4a,5} Lewis acids^{2d-f,4b,6} or halogen bonding elements.⁷

As a new supramolecular motif, anion- π interaction has attracted growing interest in recent years.^{8,9} However, experimental evidence to support "pure" anion $-\pi$ interactions between an anion and a charge-neutral electron-deficient arene is still very rare.¹⁰ We^{10b} have reported recently that oxacalix[2]arene[2]triazine, a conformation and cavity tunable macrocyclic host molecule, using its electron-deficient V-shaped cleft of two triazine rings, recognizes halides in solution and forms ternary complexes with halide and water in the solid state due to the formation of typical anion- π interaction between chloride, bromide and one triazine ring, and lone-pair electrons- π (lpe- π) interaction between the included water molecule and the other triazine ring. Very recently, we^{10e} have also observed weak σ -interaction between chloride and the triazine ring that is incorporated into a conformationally rigid bis(oxacalix[2]arene-[2]triazine) cage molecule. Our continuous interests in the supramolecular chemistry of heteroatom-bridged calixaromatics and

in anion– π interactions lead us to undertake the current study. We envisioned that the fabrication of oxacalix[2]arene[2]triazine parent macrocyclic molecules with cation binding sites would give rise to a novel type of ditopic ion pair receptors in which anion recognition is wholly based on anion– π interactions. We report herein the expedient and efficient synthesis of oxacalix[2]arene[2]triazine azacrown molecules. Fluorescence and ¹H NMR titration studies have shown that the calixazacrowns synthesized are novel ditopic ion pair receptors able to selectively interact with ion pairs.

Scheme 1 illustrates the synthesis of oxacalix[2]arene[2]triazine azacrowns 5 and 6. In the presence of K_2CO_3 , aromatic nucleophilic substitution reaction of 3,5-dihydroxybenzaldehyde 1 with 2,4-dichloro-4-methoxytriazine 2 proceeded rapidly in refluxing acetone to afford the desired oxacalix[2]arene[2]triazine 3 in 75% yield. The efficient formation of macrocyclic product 3 in a one-pot reaction fashion is probably due to a thermodynamic controlled reaction process.¹¹ Taking the advantage of dynamic formation of an imine bond from the reaction of an aldehyde and an amine, the pre-functionalized oxacalix[2]arene[2]triazine 3 was treated with diamine 4 directly in solution. As we expected, the reaction at room temperature in



Scheme 1 Synthesis of oxacalix[2]arene[2]triazine azacrowns 5 and 6.

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acetonitrile took place efficiently to produce bisimine compound **5** in high yield. The formation of a macrocyclic bisimine ring did not necessarily require a highly diluted solution, as all reactions performed in the substrate concentration of 5–25 mmol L^{-1} either in acetonitrile or in chloroform were found to afford product **5** in comparably high chemical yields (90–94%). To have the azacrown ether moiety that may bind selectively for alkali and alkaline-earth metals, the imine bonds of compound **5** were reduced. Surprisingly, under various conditions, the C==N bond of **5** was not reduced (Table S1 in ESI†). Finally, we were pleased to find that bisimine **5** was reduced efficiently to calixazacrown ether **6** by NaHB(OCOMe)₃ at room temperature when *dichloromethane* was used as solvent.

The structures of oxacalix[2]arene[2]triazine bisimine **5** and azacrown **6** were established on the basis of spectroscopic data and microanalyses (ESI[†]). It was noteworthy that the two ditopic receptors show a single set of proton and carbon signals in their ¹H and ¹³C NMR spectra, respectively, indicating the symmetric structure in solution (Fig. S17–S23, ESI[†]). The calixcrown structure was further proved unambiguously by the X-ray single crystal structure of **6**.[‡] As shown in Fig. S1 (ESI[†]), the oxacalix[2]arene[2]triazine moiety of **6** adopts a 1,3-alternate conformation, similar to most of the heteracalix[2]arene[2]triazines.¹² Two triazine rings, which are conjugated with the bridging oxygen atoms, form a V-shaped electron-deficient cleft. On the upper-rim positions of two benzene rings, there is a macrocyclic azacrown ether loop.

Having had synthetic ditopic receptors in hand, we first examined their ability to interact with anions by means of fluorescence titration. As illustrated in Fig. S3 and Table S2 (ESI[†]), the fluorescence spectrum of 5 was changed upon the titration of tetrabutylammonium fluoride, cyanide and acetate, and the association constants, which were calculated based on fluorescence titration curves using a Hyperquad 2003 software,¹³ were 6.59 × 10³ M⁻¹ (F⁻), 4.16 × 10³ M⁻¹ (CN⁻) and $4.52 \times 10^3 \text{ M}^{-1} (\text{CH}_3 \text{CO}_2^{-})$, respectively. Selective binding of **6** towards fluoride ($K_a = 1.11 \times 10^3 \text{ M}^{-1}$) and cyanide ($K_a =$ $5.87 \times 10^3 \text{ M}^{-1}$) was also observed. No interactions of 5 and 6 with other anions were evident (Fig. S3 and S5, ESI[†]). The interaction between 5, 6 and anions was further investigated using ¹H NMR spectroscopy. As demonstrated in Fig. S15 and S16 (ESI \dagger), no variation at all in the ¹H NMR spectra of 5 and 6 occurs with the addition of anions. It is consistent with our early reports that an ion- π interaction is responsible for the change of fluorescence spectrum of the host molecules.^{10b}

Being azacrown entities, macrocycles **5** and **6** exhibited expectedly selective interactions with metal ions. For example, titration of bisimine **5** with perchlorate salts of varied transition and heavy metal ions caused the emergence and the enhancement of a new fluorescence emission band at about 425–475 nm, whereas addition of alkali and alkaline-earth metals did not affect the fluorescence spectrum of **5** at all (Fig. S4, ESI[†]). The association constants for the complexes of **5** with metal ions ranged from 7.23 × 10³ M⁻¹ to 9.21 × 10⁴ M⁻¹ (Table S2, ESI[†]). Calixazacrown **6**, in contrast, was found to be able to complex with alkali metals in addition to transition and heavy metals. Based on the changes of fluorescence emission bands that were blue-shifted to about 320 nm upon titration, moderate ($K_a = 9.86 \times 10^2 \text{ M}^{-1}$) to strong $(K_a = 1.54 \times 10^5 \text{ M}^{-1})$ association constants were calculated (Fig. S5 and Table S3, ESI†).

After revealing the binding properties of 5 and 6 towards anions and metal cations, we then turned our attention to ion pair recognition. Since fluoride was able to form an anion- π complex with both 5 and 6 as aforementioned, it was first chosen as an anion probe to examine ion pair interaction of ditopic receptors. Upon the addition of fluoride to a solution of equimolar of 5 and ions such as Fe^{2+} , Co^{2+} , Cu^{2+} and Hg^{2+} , the fluorescence emission resulted from the 5-metal ion complex at about 425–475 nm was quenched (Fig. S6, ESI⁺). It indicated that fluoride might compete with the azacrown moiety of 5 to bind metal ions, leading to the dissociation of the complexes $[5 \cdot M]^{n+}$. Interestingly, in the case of complexes $[5 \cdot Zn]^{2+}$ and $[5 \cdot Pb]^{2+}$, however, titration with fluoride gave rise to further enhancement of intensity of the fluorescence band at 425 nm (Fig. 1 and Fig. S6, ESI[†]). The association constants for the complexes between fluoride and $[5 \cdot Zn]^{2+}$ and $[5 \text{ Pb}]^{2+}$ were $1.53 \times 10^5 \text{ M}^{-1}$ and $3.71 \times 10^3 \text{ M}^{-1}$, respectively. While the binding of $[5 \cdot Pb]^{2+}$ with fluoride was comparable with that of parent 5 ($K_a = 6.59 \times 10^3 \text{ M}^{-1}$), a more than 23-fold increase of the binding constant from $6.59 \times 10^3 \text{ M}^{-1} \text{ [5} \cdot \text{F]}^-$ to $1.53 \times 10^5 \text{ M}^{-1} \text{ [Zn} \cdot \text{5} \cdot \text{F]}^+$ was significant. Remarkably, the $[5 \text{ Zn}]^{2+}$ complex was also able to interact with some other anions that were not recognized by the parent host 5 its own. For example, chloride, bromide, and nitrate were bonded by $[5 \cdot Zn]^{2+}$, giving the association constant of 7.39×10^3 M⁻¹, 1.59×10^3 M⁻¹ and 4.25×10^3 M⁻¹. respectively. Addition of cyanide into the $[5 \cdot Zn]^{2+}$ complex, however, did not influence the fluorescence spectrum (Fig. S7, Table S4, ESI[†]). Interestingly, while most of the anions examined did not interact with complexes between 6 and metals, cyanide was found to bind $[6 \cdot M]$ (M = K⁺, Cs⁺, Ca^{2+} , Sr^{2+}) with an association constant ranging from 3.46 × 10^3 M^{-1} to $8.36 \times 10^3 \text{ M}^{-1}$ (Fig. S8 and S9, Table S5, ESI†).

To shed light on the mechanism of ditopic interaction of **5** with Zn^{2+} and anion species, following experiments were conducted. To exclude the possibility that the fluorescence enhancement resulted from the binding of anions with zinc ion of the complex $[5 \cdot Zn]^{2+}$, a model bisimine compound 7 was prepared (Fig. 2) and its fluorescence titration with ion pairs was studied. Although compound 7 formed indeed a complex



Fig. 1 Left: fluorescence titration of 5 $(3.99 \times 10^{-4} \text{ M in 2 ml aceto$ nitrile) with F⁻ (up, 0–3.41 × 10⁻⁴ M) and Zn²⁺ (down, 0–9.65 × 10⁻⁴ M). $Right: fluorescence titration of 5 <math>(3.99 \times 10^{-4} \text{ M in 2 ml acetonitrile})$ with F⁻ (0–4.18 × 10⁻⁴ M) in the presence of 1 eq. Zn²⁺.



Fig. 2 Structure of 7.

with Zn^{2+} , however, addition of anions into the solution of $[7 \cdot Zn]^{2+}$ complex did not generate a similar red-shifted emission band as that observed for 5 (Fig. S10, ESI[†]). We also carefully recorded ¹H NMR spectra of 5 with the addition of zinc ion followed by the addition of Cl⁻. As illustrated in Fig. 3, interaction of 5 with one equivalent of Zn^{2+} produced complex $[5 \cdot Zn]^{2+}$ almost quantitatively. Addition of Cl⁻ up to one equivalent did not affect the ¹H NMR spectrum of complex $[5 \cdot Zn]^{2+}$. These results indicated clearly that the fluorescence enhancement upon the addition of anions such as halides and nitrate to the complex $[5 \cdot Zn]^{2+}$ (Fig. 1) is due to the interaction of anions with the electron-deficient triazine ring such as [anion–5–Zn]⁺ rather than the interaction between anions and zinc ion $[5–Zn–anion]^+$.

It should be noted that addition of more than one equivalent of anions led to the dissociation of ion pair complex [anion–**5**–Zn]⁺, this has been evidenced by the observation of the quench of fluorescence of the complex from fluorescence titration (Fig. S11–S14, ESI[†]) and the generation of free oxacalix[2]arene[2]triazine azacrown host **5** from ¹H NMR titration. Fig. 4 is a schematic illustration of interactions of ditopic receptor **5** with Zn²⁺ and anion species.

In summary, we have provided a very efficient and expedient synthesis of oxacalix[2]arene[2]triazine azacrowns 5 and 6. Bearing an azacrown moiety and an electron-deficient V-shaped cleft formed by two triazine rings, compounds 5 and 6 acted as ditopic receptors to interact with ion pairs. We have thus demonstrated for the first time that the anion $-\pi$ interaction motif can be used in the design of receptors for ion pair recognition.

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Fig. 3 Left: ¹H NMR titrations of **5** upon the addition of $Zn(ClO_4)_2$. Right: ¹H NMR titrations of $[5 \cdot Zn^{2+}](ClO_4)_2$ upon the addition of tetrabutylammonium chloride.



Fig. 4 Illustration of interactions of 5 with Zn^{2+} and anion species.

Notes and references

‡ Crystallographic data of 6: $C_{57}H_{62}Cl_2N_{16}O_{16}$, M = 1298.13, monoclinic, $P2_1/c$, a = 15.195(6) Å, b = 25.537(9) Å, c = 17.451(7) Å, $\alpha = 90.00^{\circ}$, $\beta = 114.634(4)^{\circ}$, $\gamma = 90.00^{\circ}$, V = 6155(4) Å³, Z = 4, μ (Mo-K α) = 0.71073 mm⁻¹, T = 173(2) K. The structure was solved and refined by SHELXL-97 in the WinGX package. Final residuals (871 parameters) $R_1 = 0.1380$ for 9377 reflections with $I > 2\sigma$ (*I*), and $R_1 = 0.1588$, $wR_2 = 0.2746$. GoF = 1.353 for all 11 127 data. CCDC 816915.

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