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Host–Guest Complexes

Halide Recognition by Tetraoxacalix[2]arene[2]triazine Receptors: Concurrent Noncovalent Halide–π and Lone-pair–π Interactions in Host–Halide–Water Ternary Complexes[**]

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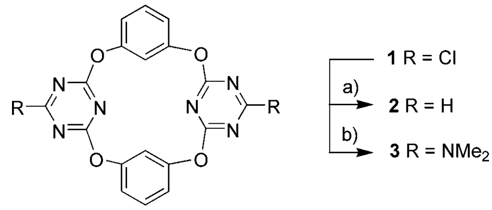
Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday

Anion recognition has attracted much attention because of its importance in biological and environmental sciences.[1–3] A large number of synthetic host molecules have been synthesized for the purpose of anion complexation. Noticeably, almost all synthetic anion receptors were designed to exploit hydrogen bonding, electrostatic interactions, hydrophobic effects, and coordination to metal ions.[1–3] In recent years, however, there has been a growing interest in anion–π interactions, the interaction between an anion and an electron-deficient π-arene species.[4–6] A number of theoretical studies,[4–10] for example, have reported the noncovalent interactions of anions with aromatic compounds such as perfluoro-, nitro-, and cyano-substituted benzene, pyridine, pyrazine, and triazine derivatives. Experimental evidence to support the purely noncovalent anion–π interaction with charge-neutral arenes, however, is very rare.[6,10–12] A recent study indicated indeed that the noncovalent anion–π interaction contributed less significantly than hydrogen bonding to the formation of the complex chloride–π-$C_6F_nH_{6-n}$ ($n = 0$–5).[13]

Heteroatom-bridged heteroaromatic calixarenes are an emerging type of novel macrocyclic molecules.[14] Because of their electronic nature, some heteroatoms, such as nitrogen, can adopt different configurations to form varying degrees of conjugation with adjacent heteroaromatic rings, resulting in macrocyclic heteroatom-linked heteroaromatic calixarenes with conformations and sizes different to those of conventional calixarenes. They have recently been utilized as versatile host molecules in supramolecular chemistry.[15] As a typical example of heteroatom-bridged heteroaromatic calixarenes, tetraoxacalix[2]arene[2]triazine **1** (Scheme 1) has been reported to adopt a pre-organized 1,3-alternate conformation, yielding a cleft formed by two π-electron deficient triazine rings.[14c,16] We envisioned that this π-electron-deficient cavity would act as a receptor to interact with anions through π–anion interactions. Herein, we report halide recognition by tetraoxacalix[2]arene[2]triazine host molecules, and considerable substituent effects of the triazine on the halide–π interaction. Most astonishingly, X-ray crystallography revealed the concurrent formation of noncovalent π–halide and π–lone-pair electron interactions between water, chloride, or bromide, and the dichloro-substituted tetraoxacalix[2]arene[2]triazine host.



Scheme 1. Dichloro-substituted tetraoxacalix[2]arene[2]triazine **1** and its transformations into **2** and **3**. a) H_2, Pd/C, NaOAc/HOAc, 50°C, 12 h, 82%. b) $Me_2NH{\cdot}HCl$, K_2CO_3, THF, 70°C, 9 h, 65%.

By means of spectrophotometric measurements, we examined the interaction of halides with dichloro-substituted tetraoxacalix[2]arene[2]triazine **1**, a macrocycle readily accessible in large scale and good yield from the coupling of resorcinol and cyanuric acid chloride, under very mild conditions.[14c] As illustrated in Figure 1 (top), a new absorption band formed at 302 nm in the UV/Vis spectrum of **1** upon titration with tetrabutylammonium fluoride. Interaction of **1** with tetrabutylammonium fluoride also led to quenching of the host molecule emission signal at 304 nm with the concomitant emergence of a new fluorescence emission at 452 nm (Figure 1 (bottom)). These spectral changes were not caused by the cation or by moisture in the sample, as the control experiments using tetrabutylammonium perchlorate or water as a titrant showed no influence on either the absorption or the emission spectrum of **1**. We then investigated the spectrophotometric titration of **1** with tetrabutylammonium chloride and tetrabutylammonium bromide. Under identical conditions, the outcomes of titration with chloride and bromide were very different to that for the titration with fluoride. For example, addition of chloride or bromide did not affect the UV/Vis spectrum of the host

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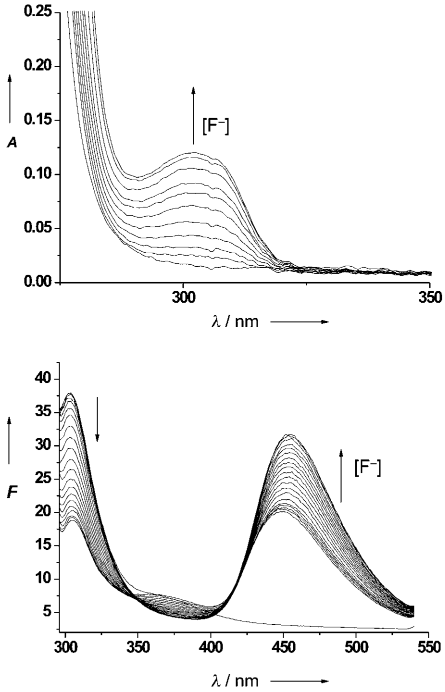

Figure 1. UV/Vis (top) and fluorescence (bottom) titrations of **1** with tributylammonium fluoride. UV/Vis titration curves of **1** (1.74×10^{-3} mol dm^{-3} in 2.5 mL acetonitrile) upon the addition of $Bu_4N^+F^-$ (0, 2.06, 2.58, 3.10, 3.61, 4.13, 4.64, 5.16, 6.19, 7.74, 9.29×10^{-3} mol dm^{-3}), respectively. Fluorescence response of **1** (1.74×10^{-3} mol dm^{-3} in 2.5 mL acetonitrile) upon the addition of $Bu_4N^+F^-$ (0, 0.0129, 0.0258, 0.0387, 0.0516, 0.0645, 0.0774, 0.0903, 0.103, 0.116, 0.129, 0.142, 0.155, 0.168, 0.181, 0.194, 0.206, 0.219, 0.232, 0.245, 0.258×10^{-3} mol dm^{-3}). The excitation wavelength was 280 nm, the excitation and emission band widths were both 10 nm and the scan speed was set at 240 nm min^{-1}.

molecule **1** at all. Whereas no change in the fluorescence spectrum of **1** occurred upon titration with bromide, the interaction between **1** and chloride gave a weak emission band at 379 nm (see Supporting Information).

To study the effect of the triazine substituent of the tetraoxacalix[2]arene[2]triazine host on the anion–π interaction, macrocyclic compounds **2** and **3**, containing, respectively, no substituents and bis(*N*,*N*-dimethylamino) groups, were prepared. Reduction of **1** by catalytic hydrogenation and an aromatic nucleophilic substitution reaction with dimethylamine afforded macrocycles **2** and **3**, respectively, in good yields (Scheme 1). Calixarene **3**, with *N*,*N*-dimethylamino groups on the triazine ring, showed no change in either the absorption or emission spectrum when titrated with fluoride, chloride, or bromide, Whereas both the absorption and emission spectra of the unsubstituted calixarene **2** remained unchanged when it was treated with chloride and bromide. Interaction between **2** and fluoride led to similar changes in the UV/Vis and fluorescence spectra as those caused by the interaction of **1** with fluoride. UV/Vis titration of **2** with fluoride, for example, led to the formation of a new absorption band at 313 nm. Fluorescence titration of **2** with fluoride resulted in quenching of the emission at 324 nm and, concomitantly, the emergence of a weak emission at 425 nm (see Supporting Information).

The job plots for these experiments indicated a 1:1 complexation between the host and the guest in solution (see Supporting Information). On the basis of the outcomes of fluorescence titrations, the binding constants were calculated, following a literature method using the Hyperquad2003[17] program (see Table 1). Macrocyclic host molecule **1** was able to form a 1:1 complex with fluoride and chloride, with binding constants of $(4036\pm36)\,\text{M}^{-1}$ and $(4246\pm83)\,\text{M}^{-1}$, respectively. To our knowledge, they represent the strongest halide–π interactions in solution reported to date. The complexation between **2** and fluoride, however, appeared weaker, yielding a binding constant of $(68\pm0)\,\text{M}^{-1}$.

Table 1: Association constants K_a [M^{-1}] for the 1:1 complexation between tetraoxacalix[2]arene[2]triazine host molecules and halides.[a]

Anion	Host[b] 1	2	3
F^-	4036 ± 36	68 ± 0	–[c]
Cl^-	4246 ± 83	–[c]	–[c]
Br^-	–[c]	–[c]	–[c]

[a] K_a was calculated on the basis of fluorescence titration data using Hyperquad2003 program.[17] [b] See Scheme 1. [c] No spectral changes occurred.

The results in Table 1 clearly indicate a considerable effect of the substituent on the π-deficient triazine ring on the halide–π interaction. The dichloro-substituted host molecule **1** exhibited much stronger binding affinity towards the same anion than the host molecule **2**, which contains no electron-withdrawing substituents on either triazine ring. This effect is most likely attributable to the electron-withdrawing nature of the chloro substituent, which renders the triazine ring more electron-deficient. Conversely, as judged by spectrophotometric titration experiments, calixarene **3** did not act as the π-deficient host to interact with halide species in solution, probably as a result of the electron-donating nature of the *N*,*N*-dimethylamino substituent increasing the electron density of the triazine ring. As a model study, the electrostatic-potential map calculated by density functional theory (DFT) indicated, as expected, that the density of positive charge at the center of triazines decreases greatly from Cl-, H-, to Me_2N-substituted dibenzoxytriazine (see Supporting Information).

Besides the dramatic variation in strength of halide–π complexation, the binding mechanism[6,10] might also differ, as a result of the different electronic natures of both host and guest species. The formation of new absorption and emission bands at longer wavelength regions in UV/Vis and fluorescence spectra, respectively, indicated the formation of a charge-transfer complex or a σ-complex of tetraoxacalix[2]arene[2]triazine compounds **1** and **2** with fluoride in solution.[6,10,11] In sharp contrast, the titration of **1** with chloride and bromide did not form any long wavelength bands in UV/Vis and fluorescence spectra, suggesting most probably a different halide–π interaction mechanism. The difference in mechanism was also reflected in ^{1}H and ^{13}C NMR spectra. For instance, the addition of chloride and bromide to the solution of host molecule **1** did not change the ^{1}H and ^{13}C NMR spectra of **1** at all. Interaction of **1** with fluoride, however, resulted in many shifted signals for aromatic protons and carbon atoms (see Supporting Information). The possible nucleophilic substitution reaction of chloro by fluoro under all titration conditions was excluded as electron impact (EI–MS) and atmospheric pressure chemical ionization mass spectrometry (APCI–MS) analyses of the mixture solutions of host **1** and fluoride gave no molecular-ion peaks and fragment peaks corresponding to the formation of C–F bonded products. In other words, it was the short-contacted interaction or σ-complexation of fluoride with the host molecule **1** that led to the conformational changes. The interaction between **1** and fluoride was further evidenced by ^{19}F NMR spectroscopy. The deshielding effect on the fluoride anion by the electron-deficient triazine ring in the host molecule effected a downfield shift of the ^{19}F signal from $\delta = -109.2$ ppm to $\delta = -39.9$ ppm, (see Supporting Information). It should be noted that no variation occurred in the NMR spectra on treating the unsubstituted calixarene **2** with fluoride, because the interaction between host and guest is very weak (see Supporting Information).

To further clarify the halide–π interaction on the molecular level, single crystals of the complexes were grown. Whereas the complex of the dichloro-substituted tetraoxacalix[2]arene[2]triazine **1** and fluoride failed to crystallize, co-crystallization from a solution in dichloromethane/*n*-hexane of **1** with both tetraethylammonium chloride and bromide gave single crystals of the complexes. Single-crystal X-ray diffraction afforded molecular structures, as depicted in Figure 2 and in the Supporting Information, which revealed the formation of very similar ternary complexes incorporating the host, a halide ion and a water molecule.[18]

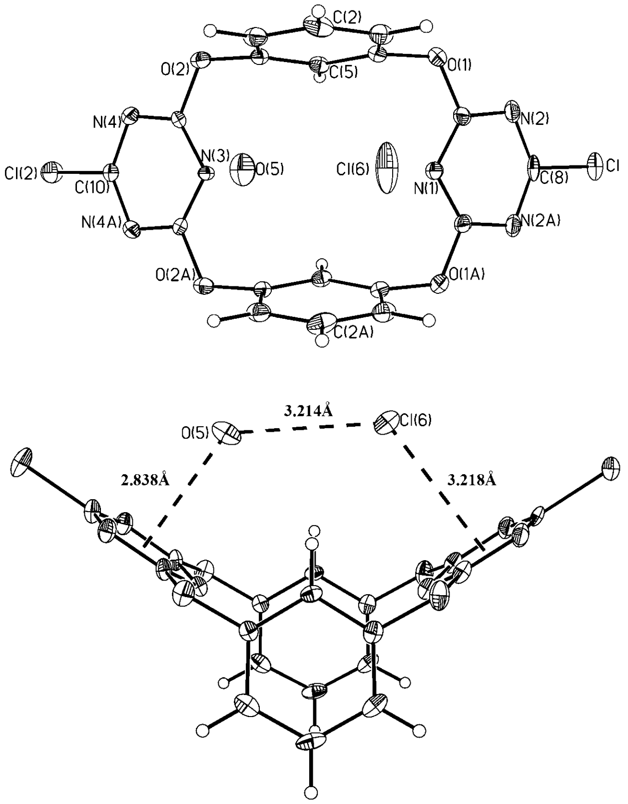

Figure 2. Molecular structure of the ternary complex of **1**, chloride and water, determined by X-ray crystallography. Thermal ellipsoids are set at 25% probability. Disordered water molecule outside the cavity is not shown and water hydrogen atoms have been removed for clarity. Selected interatomic distances [Å]: C(8)-C(10) 8.944, N(1)-N(3) 4.612, C(2)-C(2A) 5.511; C(5)-C(5A) 4.321.

Some interesting structural features are worth addressing. First of all, in both complexes, the calixarene moiety adopts a 1,3-alternate conformation, with the two benzene rings being nearly face-to-face, whereas the two π-deficient triazine rings form a V-shaped cleft. Secondly, although the conformation of the calixarene in the complexes resembled that of the parent host molecule, the V-shaped cleft formed by the two π-deficient triazine rings in the complexes was narrower than that of the pure host molecule.[14c] The upper (wider) rim distance between two triazine rings in the complexes is approximately 8.9 Å (Figure 2), while the corresponding distance for the parent host molecule is approximately 9.5 Å.[14c] The change of cavity size in complexing with guest species indicates that the flexibility of calixarene **1**, owing to the heteroatom linkages in the bridge positions, allowed the host molecule to fine-tune the size of the π-deficient cleft to maximize its interaction with the guest species. In addition, both chloride and bromide in complexes form typical non-covalent anion–π interactions with the triazine rings. In the case of the host–chloride complex, for example, the distances of chloride to the plane and to the centroid of the triazine ring are nearly same, being 3.218–3.247 Å and 3.227–3.249 Å, respectively. The bromide in the complex, on the other hand, is located almost over the centroid of the triazine ring, at a distance of 3.273–3.348 Å (see Supporting Information). The distances between the chloride or bromide and the triazine ring centroid are shorter than the sums of the van der Waals radii, and are in agreement with values obtained from theoretical calculations.[6,10] In both cases, no arene C–H hydrogen bonding occurred between the calixarene host and the halide guest. Furthermore, both host–halide complexes co-crystallized with water molecules, and one water molecule was found to form a ternary complex with halide and host (see Figure 2). As indicated by the distance between chloride and oxygen ($d_{\text{Cl–O}}$ 3.214 Å) and between bromide and oxygen ($d_{\text{Br–O}}$ 3.042–3.223 Å), the halide in both complexes formed a hydrogen bond with the water molecule. Moreover, the hydrogen-bonded water molecule in both cases formed an intriguing H_2O:–π (lone-pair–π) interaction between water oxygen and the triazine ring, as evidenced by the location of the water molecule virtually above the triazine centroid with a very short distance of 2.833–2.849 Å. Such a short distance excluded the other possible water–arene interaction model, namely an O–H···π interaction, as theoretical studies[19] have suggested a much longer oxygen-to-arene-centroid distance (3.11 Å) for this interaction. Supported by neutron diffraction studies, Fujita and co-workers[20] have recently provided one example of a lone-pair–π interaction between water and a triazine ring, in which the distance between oxygen and the triazine centroid is 3.06 to 3.09 Å. Finally, the interaction of tetraoxacalix[2]arene[2]triazine **1** with bromide and water in the solid state formed a multicomponent complex in which two bromide anions and two water molecules held together by a hydrogen-bonding network, formed anion–π and lone-pair – π interactions, respectively, with the four π-deficient triazine rings of two dichloro-substituted tetraoxacalix[2]arene[2]triazine host molecules (see Supporting Information).

In summary, we have demonstrated that 1,3-alternate dichloro-substituted tetraoxacalix[2]arene[2]triazine is a unique and self-tuning macrocyclic host molecule able to interact with halides in both solution and in the solid state. Through different mechanisms, it formed complexes with fluoride and chloride in solution, giving binding constants K_a of over $4000\,\text{M}^{-1}$. The V-shaped π-deficient cleft created by the two triazine planes of the macrocycle formed ternary complexes with halide and water through concurrent, non-covalent π–halide, π–lone-pair-electron interactions and hydrogen bonding in the solid state. The design of host molecules using π-deficient aromatic components for specific interaction with various anions is currently under investigation, and will be reported in due course.

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[18] Crystallographic data for $\mathbf{1}\cdot\text{Cl}^-(\text{CH}_3\text{CH}_2)_4\text{N}^+\cdot(\text{H}_2\text{O})_{1.5}$ ($\text{C}_{26}\text{H}_{31}\text{Cl}_3\text{N}_7\text{O}_{5.5}$): $M_r = 635.93$, orthorhombic, space group *Pnma*, $a = 24.168(5)$, $b = 16.852(3)$, $c = 14.967(3)$ Å, $\alpha = 90.00$, $\beta = 90.00$, $\gamma = 90.00°$, $V = 6096(2)$ Å^3, $T = 173(2)$ K, full-matrix least-squares refinement on F^2 converged to $R_F = 0.1050$ [$I > 2\sigma(I)$], 0.1688 (all data) and $Rw(F^2) = 0.2292$ [$I > 2\sigma(I)$], 0.2515 (all data), goodness of fit 1.232. Crystallographic data for $\mathbf{1}\cdot\text{Br}^-(\text{CH}_3\text{CH}_2)_4\text{N}^+\cdot\text{H}_2\text{O}$ ($\text{C}_{26}\text{H}_{28}\text{BrCl}_2\text{N}_7\text{O}_5$): $M_r = 669.35$, orthorhombic, space group *Pnma*, $a = 24.235(5)$, $b = 16.845(3)$, $c = 15.021(3)$ Å, $\alpha = 90.00$, $\beta = 90.00$, $\gamma = 90.00°$, $V = 6132(2)$ Å^3, $T = 173(2)$ K, full-matrix least-squares refinement on F^2 converged to $R_F = 0.1108$ [$I > 2\sigma(I)$], 0.1631 (all data) and $Rw(F^2) = 0.2746$ [$I > 2\sigma(I)$], 0.2906 (all data), goodness of fit 1.644. CCDC 684393 and CCDC 684394 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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