An Imidazolium-Based Fluorescent Cyclophane for the Selective Recognition of Iodide

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The development of anion receptors and their application in chemical sensors are of current interest because of the need for biological and environmental analysis.[1] Many anions have diverse geometries that require shape-selective recognition. Therefore, many researchers have used hydrogen bonds as a selective recognition tool as they are directional, i.e., the correct orientation of hydrogen bonding can differentiate anionic guests by different geometries. Iodide is recognized as an ion of significant physiological and biological importance due to its essential role in the normal growth, development, and functioning of the brain and body.[2] Either deficiency or abundance of iodide in the thyroid gland can cause major health concerns. In fact, the World Health Organization (WHO) has stated that iodine deficiency is the biggest cause of mental retardation on a global scale.[3] Furthermore, elemental iodine has been frequently used in many areas of chemistry for synthesizing valuable molecules such as drugs and dyes. Several analytical methods have been developed for iodide analysis in various samples such as seawater, drinking water, milk, seaweed, and salts.[4] Since the pioneering work of Czarnik[4] in the detection of analytes using fluorescent chemosensors,[5] anion sensing by anion-responsive optical sensors has been developed during the last decade.[6] With regard to the iodide ion only a few reports with fluorescent sensors can be found in the literature.[7] Therefore, developing receptors that can bind iodide selectively is strongly desired.

In contrast to well-known types of hydrogen bonding for anion binding such as amide, pyrrole, urea, etc.,[8] the imidazolium group can make a strong interaction with anions through a (C–H)+···X− ionic hydrogen bond because the charge–charge electrostatic interaction dominates. In recent years, we have studied anthracene-, pyrene-, pyridine-, and benzene-based receptors with imidazolium units that bind effectively with anionic species through ionic hydrogen bond interactions.[9] Herein, we report the new imidazolium-based fluorescent cyclophane 1 bearing four imidazolium groups as well as two bridged methine groups. It has been systematically designed and synthesized for recognition of anions through imidazolium (C–H)+···X− ionic hydrogen bond as well as bridge methine C–H···X− hydrogen bond formation. Cyclophane 1 displayed a highly selective fluorescence quenching effect upon addition of iodide compared to other anions in 10 mM HEPES-buffered (pH 7.0) CH₃CN/H₂O (9:1, v/v), which was examined by fluorescence measurements, ¹H NMR spectroscopy, and theoretical calculations. In this study, we found a new anion recognition site (bridged methine C–H···X−) for sensing anions in the cyclic form.

For the synthesis of cyclophane 1 (Scheme 1), 1-pyrene carboxaldehyde (2) was treated with di(imidazol-1-yl)methylene (3) in the presence of a catalytic amount of CoCl₂ to afford 4 in 70% yield. Compound 4 was then reacted with α,α′-dibromo-m-xylene (1 equiv) to afford a bromo salt that was directly dissolved in DMF and added to a saturated aqueous NH₄PF₆ solution to give 1 in 50% yield. Cyclophane 1 displays peaks typical for pyrene moieties in the fluorescence spectra. The peak at 381 nm can be attributed to the monomeric emission while the peak at 472 nm is due

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to intermolecular excimer formation in 10% aqueous CH₃CN of pH 7.0. The excimer state arises from intermolecular π–π stacking between the pyrene rings as evidenced by the increase in the excimer to monomer intensity ratio (I₄₇₂/I₃₈₁) over the concentration range 0.01–0.002 mM (Figure S1 in the Supporting Information).

Figure 1a shows the fluorescence spectra of 1 in 10% aqueous CH₃CN of pH 7.0 in the absence and presence of the n-tetrabutylammonium salt of CH₃COO⁻, Br⁻, Cl⁻, F⁻, I⁻, NO₃⁻, H₂PO₄⁻, HSO₄⁻, and ClO₄⁻ (100 equiv each). Cyclophane 1 displayed a significant quenching of monomer and excimer emission upon addition of I⁻ but little chelation-enhanced fluorescence quenching (CHEQ) of monomer and slightly enhanced excimer emission upon addition of CH₃COO⁻, Br⁻, Cl⁻, and F⁻. On the other hand, receptor 1 also displayed a relatively small chelation-enhanced fluorescence (CHEF) effect of monomer and quenching of excimer emission for H₂PO₄⁻. Nearly no fluorescence changes of 1 were observed when NO₃⁻, HSO₄⁻, and ClO₄⁻ were added. The selectivity for iodide becomes apparent at plotting the (Iₒ/I) ratio at 381 nm for each particular anion examined. The selective fluorescence quenching upon addition of iodide to 1 can be seen by the naked eye, as shown in Figure 2.

As shown in Figure 3, a significant CHEQ effect of both monomer and excimer emission is exhibited by 1–I⁻, which can be attributed to the complementarity in size of iodide probably due to photo-induced electron transfer (PET) mechanism. The small fluorescent CHEQ effect of receptor 1 upon addition of anions such as Br⁻, Cl⁻, F⁻, and CH₃COO⁻ (see the Supporting Information, Figures S2d, S2g, S2j, and S2m) gradually lessens the fluorescence intensity. On the contrary, we observed a small CHEF of monomer and excimer emission, with a small hypsochromic shift of monomer emission, upon addition of 2 equiv of H₂PO₄⁻ to receptor 1. However, when more than 2 equiv of H₂PO₄⁻ were added, we also observed quenching of both monomer and excimer emission (see Figure S3 in the Supporting Information).

Figure 1. a) Fluorescence emission changes of 1 (0.01 mM) upon addition of n-tetrabutylammonium salt of CH₃COO⁻, Br⁻, Cl⁻, F⁻, I⁻, NO₃⁻, H₂PO₄⁻, HSO₄⁻, ClO₄⁻, and (I⁻+other anions) (100 equiv) in 10 mM HEPES-buffered (pH 7.0) CH₃CN/H₂O (9:1, v/v) with excitation at 348 nm. b) Corresponding bar graph of (Iₒ/I) at 381 nm for the different anions.

Figure 2. Photograph of receptor 1 (0.5 mM) in the absence (host) or presence of various anions (100 equiv each), as indicated.

Figure 3. Changes in fluorescence intensity of the receptor 1 (0.01 mM) upon addition of n-tetrabutylammonium iodide at different concentrations (0 mM to 7 mM). The inset shows a plot of the fluorescence emission at 381 nm as a function of iodide concentration (0 to 700 equiv).
Next, the binding constants for $I^-$, $\text{Br}^-$, $\text{Cl}^-$, $\text{F}^-$, and $\text{CH}_3\text{COO}^-$ were derived (Table 1) from plots of $I/I_0$ against the anion concentration (see the Supporting Information, Figures S2c, S2f, S2i, and S2l, and S2o; errors < 10%). In addition, Job-plot analysis at monomeric emission (381 nm) indicates the formation of 1–2I complexes (see the Supporting Information). The detection limits estimated (based on the criteria of fluorescence quenching) from the titration results are $98 \times 10^{-5}$ and $1 \times 10^{-5}$ M for 1–2I. The data shown in Table 1 ($K_1$ values) suggest that $I^-$ is 5.7–28.8 times more selective for $I^-$ than for $\text{Br}^-$, $\text{Cl}^-$, $\text{F}^-$, and $\text{CH}_3\text{COO}^-$. The complementarity of a receptor to an anion is a critical factor for achieving selectivity due to the diverse geometry of anions. The complementarity for halides is generally achieved by varying the size of the receptor binding site, as halides are spherically shaped. The selectivity of 1 for iodide suggests that the flexible pod in receptor 1 is more compatible to the size of iodide than to the size of other anions. Fluoride and $\text{H}_2\text{PO}_4^-$ anions are more basic than $\text{Cl}^-$, $\text{Br}^-$, and $I^-$. However, there are many examples in which halides, with the exception of $\text{F}^-$, have been shown to bind predominantly because of the complementary size of the pseudocavity formed by the receptor binding sites. Thus, the quenching of emission observed in our study is likely due to the complementarity in size of iodide with the binding site of receptor 1.

To support this hypothesis, we synthesized compound 5 (Scheme 2, see also the Supporting Information, S6i–m), which resembles the binding site of receptor 1 but not in a closed form. However, in contrast to 1, the fluorescence emission of 5 did not change significantly upon addition of $I^-$ or the other anions (100 equiv each) in 10 mm HEPES-buffered (pH 7.0) $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (9:1, v/v) with excitation at 348 nm (see Figure S4 in the Supporting Information). This data support the assumption that iodide is bound cooperatively inside the cavity of receptor 1. As mentioned above, our experiments revealed that receptor 1 displayed a 1:2 binding mode with iodide. We therefore postulate that one molecule of receptor 1 encapsulates two iodides inside its cavity (Figure 5). The computed structure of such a complex shows a strong attraction of each iodide with imidazolium protons and bridged methine protons. These interactions may be the reason for the observed quenching of the monomer and excimer fluorescence.

![Scheme 2. Synthesis of compound 5.](image-url)

![Figure 4. Plot of $^1$H NMR spectra of receptor 1 upon addition of different amounts of $n$-tetrabutylammonium iodide.](image-url)
and aqueous solvation effects on the relative interaction energy incorporated using a polarizable continuum model (PCM). Optimized geometries for 1–2I− are depicted in Figure S5 in the Supporting Information. The most stable geometry for the 1–2I− complex is depicted in Figure 5a, in which four imidazolium protons and one bridged methine proton are oriented toward the iodide A, whereas the other bridged methine proton is oriented toward the iodide B. Receptor 1 strongly interacts with the iodide A (Figure 5b), with distances of 2.7–2.9 Å between this iodide and the four imidazolium protons and a distance of 2.9 Å between the iodide and one bridged methine proton. It also strongly interacts with the iodide B (Figure 5c), with a distance of 2.7 Å between this iodide and the other bridged methine proton. One receptor 1 molecule encapsulates two iodides interacting with four imidazolium (C–H)+−I− and two bridged methine C–H−I− protons inside the cavity, as evidenced by the significant downfield shifts in the 1H NMR data.

In conclusion, we have designed the imidazolium-based fluorescent cyclophane 1 and report a facile synthesis of this compound. It shows selective recognition of iodide, as determined by fluorescence emission spectroscopy, and results in a visual change in fluorescence in the presence of iodide but not other anions in HEPES-buffered 10% aqueous CH3CN. Receptor 1 binds iodide inside the cavity to form a 1:2 complex through imidazolium (C–H)+−I− ionic hydrogen bond and bridged methine C–H−I− hydrogen bond formation.

**Experimental Section**

**General Experimental Methods**

Solvents were dried over standard drying agents and freshly distilled prior to use. All chemicals were purchased and used without further purification. Column chromatography was performed using silica gel (230–400 mesh, Merck). Organic solutions were dried over anhydrous Na2SO4 and concentrated below 40 °C under vacuum. 1H, 13C, and HMQC NMR spectra were recorded on a Bruker Avance DPX500 (500 MHz for 1H and 125 MHz for 13C) spectrometer at 298 K in [D6]DMSO with TMS as an internal reference. The chemical shifts are reported as δ values (ppm) relative to tetramethylsilane and J values are given in Hertz. Fast atom bombardment (FAB) mass spectra were obtained from the Korea Basic Science Institute (KBSI) in Daegu. Fluorescence measurements were performed on a Shimadzu RF-5301PC spectrofluorophotometer at 298 K.

**Anion Recognition Studies**

A stock solution of compounds 1 and 5 (1 mM) was prepared in 10 mM HEPES-buffered (pH 7.0) CH3CN/H2O (9:1, v/v) medium. Stock solutions (10 mM) of n-tetraethylammonium salts of CH3COO−, Br−, Cl−, F−, ClO4−, HSO4−, SO42−, NO3−, and NO2− were prepared in the same solvent medium. To determine the anion binding ability of receptor 1, measuring flasks containing 0.01 mM of 1 and various concentrations of an n-tetraethylammonium salt mentioned above were kept at 25 ± 1 °C for 3 h under occasional shaking, followed by recording of fluorescence spectra with excitation at 348 nm. Both excitation and emission slit widths were dependent titrations.

To a stirred solution of pyrene carboxaldehyde (5.0 g, 21.75 mmol), di((imidazol)yl)methane (3.5 g, 21.75 mmol) in CH3CN (20 mL) was added CoCl2 (40 mg, 0.2 mmol) as a catalyst at room temperature under N2 atmosphere. The mixture was heated at reflux temperature for 2 h, and the resulting crude product was purified by column chromatography using CHCl3/MeOH (99:1, v/v) as a pale yellow solid. M.p.: 123 °C; 1H NMR (500 MHz, [D6]DMSO): δ = 9.09 (s, 1H), 8.34–8.39 (m, 2H), 8.30–8.32 (d, 1H, J = 8.5 Hz), 8.26–8.28 (m, 1H), 8.20–8.22 (m, 1H), 8.11–8.14 (m, 2H), 7.85 (s, 2H), 7.42–7.44 (d, 1H, J = 8.0 Hz), 7.26 (s, 2H) and 7.07 ppm (s, 2H); 13C NMR (125 MHz, [D6]DMSO): δ = 137.03, 131.75, 130.70, 129.89, 129.47, 128.91, 128.76, 128.43, 127.56, 127.18, 126.78, 126.28, 126.03, 125.07, 124.00, 123.57, 

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**Pyrenyl bis(imidazol)yl methane (4)**

A stirred solution of pyrene carboxaldehyde (5.0 g, 21.75 mmol), di((imidazol)yl)methane (3.5 g, 21.75 mmol) in CH3CN (20 mL) was added Na2SO4 (40 mg, 0.2 mmol) as a catalyst at room temperature under N2 atmosphere. The mixture was heated at reflux temperature for 2 h, and the resulting crude product was purified by column chromatography using CHCl3/MeOH (99:1, v/v) to yield 2 (5.3 g, 70% yield) as a pale yellow solid. M.p.: 123 °C; 1H NMR (500 MHz, [D6]DMSO): δ = 9.09 (s, 1H), 8.34–8.39 (m, 2H), 8.30–8.32 (d, 1H, J = 8.5 Hz), 8.26–8.28 (m, 1H), 8.20–8.22 (m, 1H), 8.11–8.14 (m, 2H), 7.85 (s, 2H), 7.42–7.44 (d, 1H, J = 8.0 Hz), 7.26 (s, 2H) and 7.07 ppm (s, 2H); 13C NMR (125 MHz, [D6]DMSO): δ = 137.03, 131.75, 130.70, 129.89, 129.47, 128.91, 128.76, 128.43, 127.56, 127.18, 126.78, 126.28, 126.03, 125.07, 124.00, 123.57,
[Pyrenyl bis(N-methyl-1-himidazolyl) methane] 

A to stirred solution of pyrenyl bisimidazolyl) methane 4 (696 mg, 2 mmol) in CH₂CN (80 mL) was added dropwise α, α-dibromo-m-xylene (524 mg, 2 mmol) in CH₂CN (40 mL) at room temperature for 10 min under N₂ atmosphere. Subsequently, the mixture was heated at reflux temperature for 24 h. The resulting solid was filtered off, washed with cold CH₂CN, CHCl₃, and hot MeOH to give the bromo salt of 1. The bromide salt was dissolved in 3 mL DMP, followed by dropwise addition of saturated aqueous NH₄PF₆ (3 mL) at room temperature to afford a pale brown precipitate. This precipitate was filtered off and washed with water, methanol, and chloroform to yield pure 1 (1.48 g, 50% yield) as a pale brown solid: ¹H NMR (500 MHz, [D₆]DMSO): δ = 9.41 (m, 6 H), 8.32–8.48 (m, 10 H), 8.20 (m, 3 H), 8.13–8.15 (m, 8 H), 7.97 (s, 3 H), 7.75 (m, 2 H), 7.40–7.48 (m, 5 H), 7.21 (brs, 3 H) and 5.38 ppm (s, 8 H); ¹³C NMR (125 MHz, [D₆]DMSO): δ = 138.14, 135.53, 133.11, 130.66, 129.98, 129.79, 129.58, 128.85, 128.38, 128.23, 127.27, 127.11, 126.68, 125.46, 124.09, 123.23, 122.72, 122.53, 121.01, 70.53, and 52.20 ppm; MS (FAB): m/z [M⁺PF₆]⁺ calcd for C₃₁H₂₅N₆F₆P₁: 1139.03; found: 1139.29 and m/z [M⁺2PF₆]⁺ calcd for C₃₁H₂₅N₆F₁₂: 1194.03; found: 1194.33.

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