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UV–vis and fluorescence detection by receptors based on an isophthalamide bearing a phenylethynyl group

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ABSTRACT

We have successfully prepared 5-(2-phenylethynyl)isophathalilc acid as a signaling unit and the corresponding derivatives for an anion receptor **2** and a barbiturate receptor **4**. Receptor **2** showed characteristic UV–vis changes and dramatic fluorescence quenching upon the addition of anions and receptor **4** showed UV–vis and an OFF-ON fluorescence changes upon the addition of dibutylbarbituric acid based on the diphenylethyne moiety.

In the field of the molecular recognition, an isophthalamide amide moiety has been a key component for construction of an effective recognition site for guest species such as neutral barbiturates[1–3] and anions[4–9] due to the convergent hydrogen bonds formed by the cleft like structure. However, isophthalamide spacer is less versatile for a chromophore and a fluorophore due to the ineffective electronic perturbation on the ground and excited states during the recognition process, therefore a fluorescence signaling unit was generally appended to a receptor as a peripheral group. In order to overcome this disadvantage, an introduction of substituents on an isophthaloyl skeleton to form a practical chromofluorophore would make beneficial spacer to construct various kinds of receptors including anion and barbiturate receptors. However, fluorescence spacer groups bearing cleft-like bisamide have been less explored. Gale et al. reported anthracene-1,3-dicarboxyamide as anion receptors.[10] Jurczak and co-workers reported that bisamides based on azulene-1,3- and -5,7-dicarboxylic acids were used as colorimetric anion receptors.[11,12] Berlin et al. reported synthesis of Hamilton receptors bearing perylene diimides via ethyne as a spacer.[13] It is well known that 1,2-diphenylethyne (commonly known as diphenylacetylene and tolan) and its derivatives show fluorescence emission and widely applied to building blocks for organic materials[14–17] due to these easy preparation by well-studied Sonogashira coupling.[16] In addition, 5-ethynylisophthalamide derivatives have been reported as supramolecular materials.[18,19] We have designed and synthesized receptors based on isophthalamide for anions as shown in Scheme 1, for instance, isophthalamide-based receptors bearing pyridyl,[20] quinolyl, and isoquinolyl groups[21] for dihydrogen phosphate selective receptors. We have also prepared an isophthalamide-based receptor **1** bearing 1-pyrenylmethyl moieties for the ratiometric detection by fluorescence spectral changes for anions.[22,23] Receptor **1** showed potent binding ability for anions by six hydrogen bonds with four amide N–H and two hydroxy groups of serine residues.[23] These receptors consist of three parts, i.e. isophthalamide spacer, amino acids, and terminal amide groups. All these parts can be decorated with substituents to provide functionalities on the receptors. In this report, we demonstrate the design and preparation of 5-(2-phenylethynyl) isophthalamide and the derivatives as new class of fluorophores. It should be pointed out that the phenylethynyl group shows no photoisomerization unlike phenylethenyl and phenyldiazenyl groups which show *cis–trans* photoisomerization during photo irradiation. Receptor **2** based on this unit was prepared and evaluated for anion receptors as shown in Scheme 1. Four amide N–H and two hydroxy groups of serine residues would make effective binding site for anionic species as similar to receptor **1**.[23] As a result, UV–vis and drastic fluorescence responses of **2** can be observed during the binding process with anions.

A historical receptor **3** for barbiturate reported by Hamilton et al. has also an isophthaloyl moiety for the construction of the convergent binding site (Scheme 2).[1] We also demonstrate preparation and off–on fluorescence sensing of receptor **4** in which

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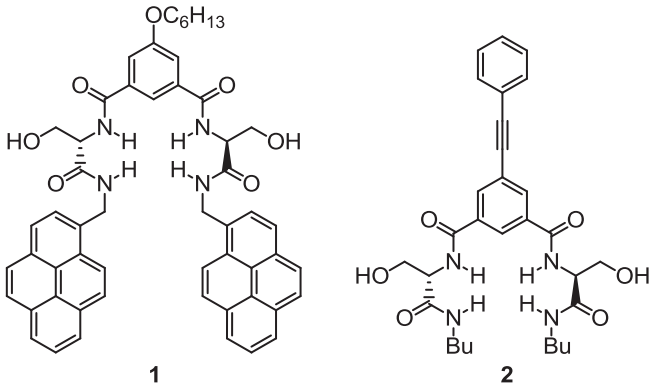
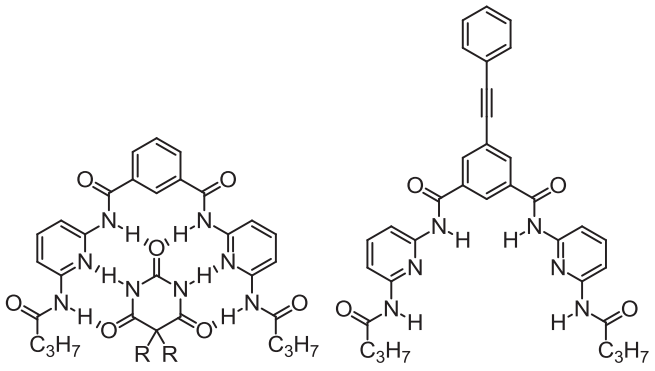


1 2

Scheme 1.

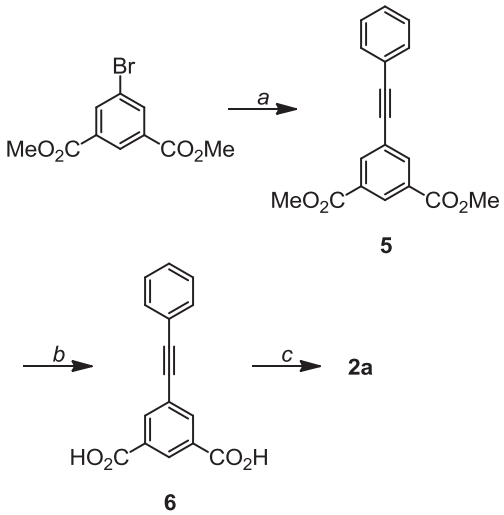


3 4

Scheme 2.

diamidopyridine moieties was used as recognition sites for barbiturates.

Receptor **2** was successfully prepared as shown in Scheme 3. Sonogashira coupling of dimethyl 5-bromoisophatalate[24] with ethynylbenzene by $Pd(PPh_3)_4$ in the presence of zinc chloride, DBU, and NaI in DMF afforded a key intermediate, dimethyl 5-(2-phenylethynyl)isophthalate **5** in 83% yield. After hydrolysis by KOH in EtOH/water, the produced dicarboxylic acid **6** was condensed with l-serine butyl amide trifluoroacetic acid salt in the presence of WSCD, HOBt, and triethylamine in DMF to give the target receptor **2** in 75% yield. The structure of **2** was confirmed by ^1H, ^{13}C, COSY, HMQC, and HMBC NMR techniques and HRMS.



5 6

Scheme 3. (a) PhC≡CH, $Pd(PPh_3)_4$, $ZnCl_2$, DBU, NaI, DMF, 83%; (b) KOH, EtOH/H_2O, 31%; (c) H_2N-Ser-NHBu, WSCD·HCl, HOBt, Et_3N, DMF, 75%.

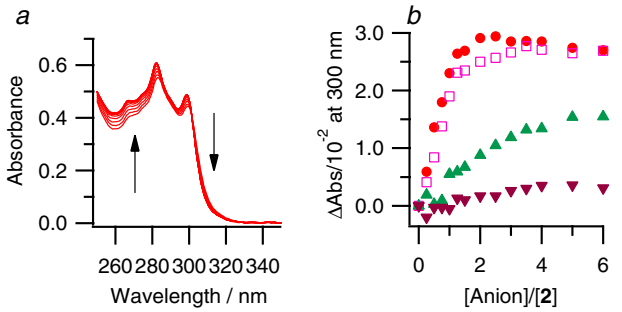


Fig. 1. (a) UV–vis spectral titration of **2** with AcO^- in MeCN. (b) Absorbance change of **2** at 280 nm upon the addition of anions in MeCN. AcO^- (●), $H_2PO_4^-$ (□), Cl^- (▲), and Br^- (▼). [**2**] = 2.0×10^{-5} mol dm^{-3} at 298 K.

The UV–vis spectrum of **2** in MeCN (typical solvent used for anion recognition) showed typical structured but slightly red-shifted spectrum for diphenylacetylene due to the intramolecular charge transfer (ICT) of the phenylethylisophthaloyl moiety as shown in Fig. 1a. The absorbance maxima at 299.5 and 283.0 nm were slightly hypsochromic shifted to 298.5 and 282.0 nm, respectively through an isosbestic point at 301 nm upon the addition of AcO^- (tetrabutylammonium was used as a counter cation for all anionic guests). The similar shift was observed upon the addition of $H_2PO_4^-$, and less significant shifts were also observed by the addition of Cl^- and Br^-. Fig. 1b shows UV–vis spectral changes of **2a** at 280 nm upon the addition of various anions in MeCN. Addition of I^-, NO_3^-, and ClO_4^- caused no spectral changes of **2a** suggesting weak interaction with these anions.

Diphenylethyne shows a structured fluorescence spectrum at around 300–330 nm in 3-methylpentane.[25] However, receptor **2** showed strong and structureless fluorescence at 355 nm in MeCN excited at 301 mm, which is the isosbestic point described above, in the absence of anions as shown in Fig. 2a. The quantum yield of **2** in MeCN was determined to be 0.075 by comparing with quinine sulfate in 0.5 mol dm^{-3} sulfuric acid. The fluorescence intensity was gradually decreased and blue shifted to 347 nm upon the addition of AcO^- as shown in Fig. 2a. In the presence of excess amount of AcO^-, fluorescence intensity of **2** was efficiently quenched ($F/F_0 \sim 0.2$). Addition of $H_2PO_4^-$ caused the similar spectral changes with AcO^-, however, Cl^- induced smaller spectral changes as shown in Fig. 2b. Interestingly, addition of Br^- induced larger quenching, which may due to bound Br^- be able to act as effective quencher of **2**. Almost no fluorescence changes were observed upon the addition of less basic anions, such as I^-, NO_3^-, and ClO_4^- suggesting weak interaction with **2**. Job's plot analyses of **2** with AcO^- and $H_2PO_4^-$ are shown in Fig. 3. The minima at mole fraction 0.5 strongly suggest complexation of receptor **2** and these anions as 1:1 stoichiometries, respectively.

The association constants of **2** with anions were calculated from the UV–vis and fluorescence titrations by non-linear curve fitting analysis to the theoretical 1:1 complexation model and the results are collected in Table 1. Basic oxoanions such as AcO^- and $H_2PO_4^-$ were strongly bound and less basic halogen anions such as Cl^- and Br^- were weakly bound (one or two orders of magnitude smaller than those for AcO^- and $H_2PO_4^-$) with **2**. The association constants with other anions, including I^-, NO_3^-, and ClO_4^- were not determined due to the negligible spectral changes even upon the excess addition of such anions. These association constants for all anions were slightly smaller than those of **1** due to the more

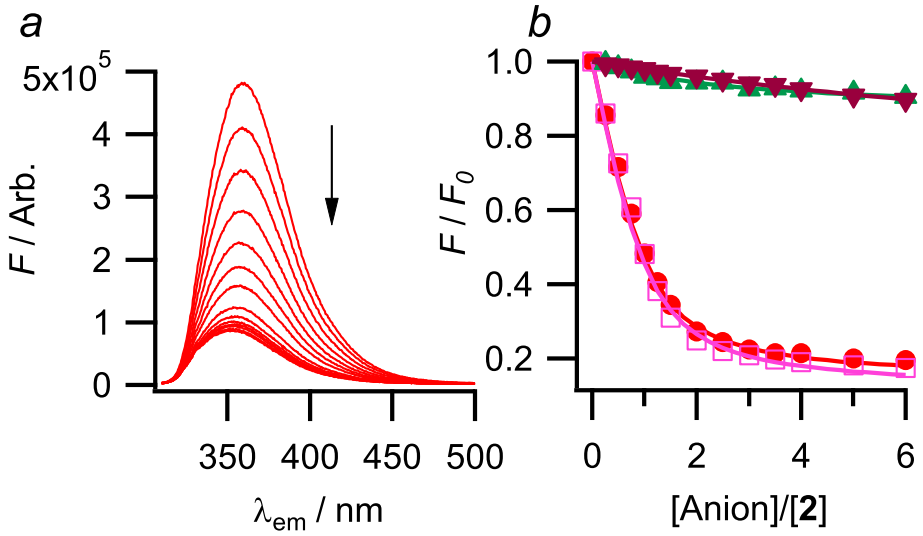


Fig. 2. (a) Fluorescence spectral titration of **2** with AcO^- in MeCN. (b) Fluorescence intensity changes of **2** at 358 nm upon the addition of anions in MeCN. AcO^- (●), $H_2PO_4^-$ (□), Cl^- (▲), and Br^- (▼). [**2**] = 1.0×10^{-5} mol dm^{-3}, λ_{ex} = 301 nm at 298 K.

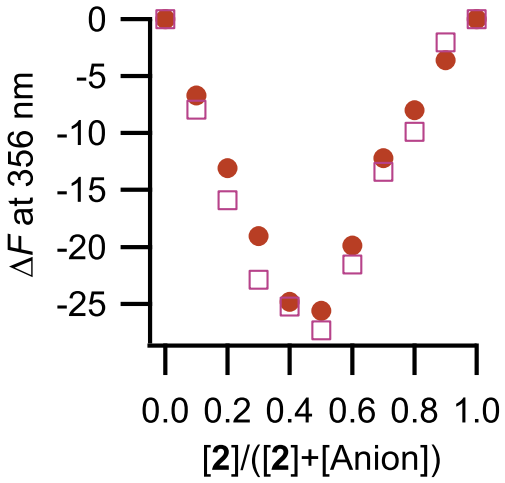
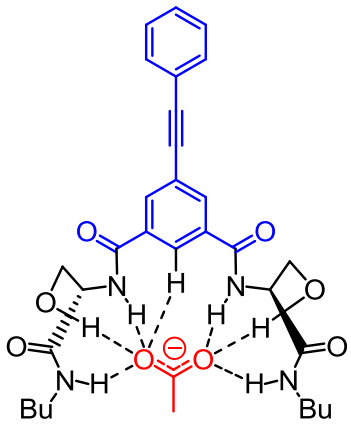


Fig. 3. Job plots of **2** with AcO^- (●) and $H_2PO_4^-$ (□) in MeCN. [**2**] + [anion] = 1.0×10^{-5} mol dm^{-3}.



Scheme 4. Proposed structure of **2**·AcO^-.

Table 1
The association constants of **2** with anions.

Anion	K_{11}/mol^{-1} dm^3	
	UV–vis[a]	Fluorescence[b]
AcO^-	$5.42 \pm 0.50 \times 10^5$	$4.96 \pm 0.43 \times 10^5$
$H_2PO_4^-$	$1.51 \pm 0.08 \times 10^5$	$3.59 \pm 0.30 \times 10^5$
NO_3^-	ND[c]	ND[c]
ClO_4^-	ND[c]	ND[c]
Cl^-	$2.44 \pm 0.51 \times 10^4$	$4.28 \pm 0.56 \times 10^4$
Br^-	$4.15 \pm 0.62 \times 10^3$	$1.16 \pm 0.19 \times 10^4$
I^-	ND[c]	ND[c]

[a] Measured in 0.3% DMSO–MeCN (*v*/*v*) at 298 K. [**2**] = 2.0×10^{-5} mol dm^{-3}.
[b] Measured in 0.2% DMSO–MeCN (*v*/*v*) at 298 K. [**2**] = 1.0×10^{-5} mol dm^{-3}. λ_{ex} = 301 nm.
[c] Not determined due to small spectral changes.

flexible terminal butyl groups of **2** than rigid 1-pyrenylmethyl groups of **1**.

The proposed structure of the complexation of **2** with AcO^- is shown in Scheme 4. The association constants with AcO^- listed in Table 1 suggest that the anion was coordinated by six point hydrogen bonds, i.e. four amides and two hydroxy groups of serine residues comparing with our previous studies.[23] In addition, a weak hydrogen bond with 2-CH of the isophthaloyl group induced the reduction of electron-withdrawing nature of the isophthaloyl moiety resulting in the diminishment of the intramolecular charge transfer of the diphenylethynyl moiety. Therefore, the UV–vis absorption of **2** was hypsochromic shift and the fluorescence spectrum was also blue shifted during the complexation with anions. TD-DFT calculations (B3LYP/6–31+G(d) level of theory) of free **7** (butyl groups of **2** were replace to methyl groups to reduce the computer resource), **7**·Cl^-, and **7**·AcO^- revealed that UV–vis absorption maxima at 312 (HOMO→LUMO), 307 (HOMO−2→LUMO), and 307 nm (HOMO−2→LUMO), respectively (Supplementary material) due to the reduction of ICT nature of **2** by complexation with anionic guest species support observed UV–vis spectral changes.

The isophthalic acid derivative **4** was also designed as another example of fluororeceptor. Phenylethynyl moiety was attached to the Hamilton's receptor **3** to achieve an effective fluororeceptor for barbiturates. The intermediate **6** can be easily converted to diacylchloride with thionyl chloride and the produced diacyl chloride was immediately condensed with 6-amino-2-butyrylamidopyridine in THF gave receptor **4** in 51%. Receptor **4** showed broad

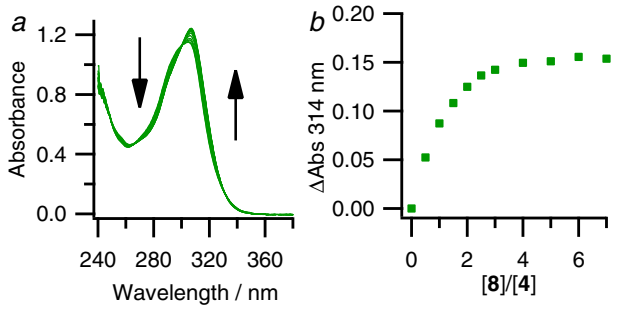


Fig. 4. (a) UV–vis spectral changes of **4** upon the addition of dibutylbarbituric acid (**8**) in $CHCl_3$. (b) Absorbance changes of **4** at 314 nm upon the addition of **8** in $CHCl_3$. [**4**] = 2.0×10^{-5} mol dm^{-3} at 298 K.

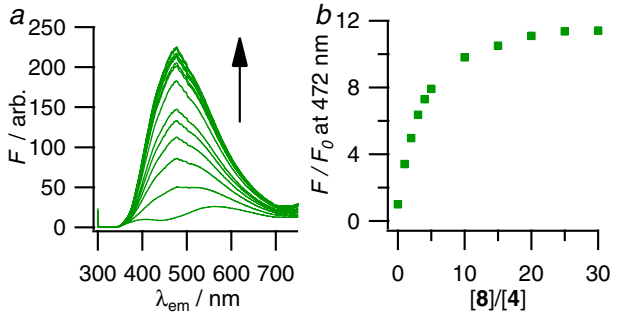
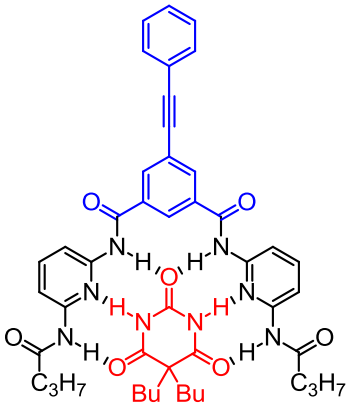


Fig. 5. (a) Fluorescence changes of **4** upon the addition of **8** in $CHCl_3$. (b) Fluorescence spectral changes of **4** at 472 nm upon the addition of **8** in $CHCl_3$. [**4**] = 5.0×10^{-6} mol dm^{-3}, λ_{ex} = 298 nm at 298 K.



Scheme 5. Proposed structure of **4**·**8**.

absorption at around 300 nm in $CHCl_3$. The UV–vis spectra of **4** were slightly sharpen upon the addition of dibutylbarbituric acid (**8**) through an isosbestic point at 298 nm as shown in Fig. 4. Receptor **4** showed low fluorescence intensity (ϕ_F = 0.0026) in the absence of guest excited at 298 nm, however, the fluorescence intensity of **4** was gradually increased upon the addition of **8** (Fig. 5). The emission maximum of the complex **4**·**8** was observed at 478 nm, which is longer wavelength than that of **2** (355 nm, Fig. 2a) due to the conjugation of diphenylethyne and diamidopyridyl groups. The titration curves showed typical 1:1 binding isotherms, therefore, the association constants of **4** with dibutylbarbituric acid were calculated to be $6.58 \pm 0.18 \times 10^4$ and $5.98 \pm 0.27 \times 10^4$ mol^{-1} dm^3 from UV–vis and fluorescence titrations, respectively. The association constant of Hamilton's receptor **3** with diethylbarbituric acid in the same solvent was reported to be 2.08×10^4 mol^{-1} dm^3 by ^1H NMR titrations,[1] which is comparable to those of **4** suggesting the same binding mode of **4** for a barbituric acid as shown in Scheme 5.

In conclusion, we have synthesized receptor **2** as an effective anion receptor. Receptor **2** showed dramatic fluorescence responses upon the addition of basic oxoanions such as AcO^- and $H_2PO_4^-$. The key skeleton, 5-(2-phenylethynyl)isophthalamide can be used for construction of various kinds of receptors, for instance barbituric acid receptor **4**, which shows an OFF-ON fluorescence response on the recognition events. Further functionalization of isophthaloyl acid bearing phenylethynyl group substituted by electron-donating, electron-withdrawing groups, and polycyclic aromatic groups showing larger spectral changes during the recognition is undertaken in our laboratory.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.09.043.

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