

Synthesis and Molecular Recognition of Pyrenophanes with Polycationic or Amphiphilic Functionalities: Artificial Plate-Shaped Cavitant Incorporating Arenes and Nucleotides in Water

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Water-soluble pyrenophanes possessing polycationic or amphiphilic side chains have been developed as synthetic host molecules to investigate hydrophobic and/or π -stacking interactions. By utilizing ω -acetalic alkyl side chains to retain solubility and versatility, water-soluble macrocyclic pyrenophanes could be easily obtained by Stille coupling, followed by conversion of the acetal groups to hydrophilic substituents. Among the pyrenophanes synthesized, hexaammonium-, bis(diazoniacrown)-, and tetrakis[octa(oxyethylene)]-derived ones showed enough solubility in pure water. The former two cationic pyrenophanes strongly recognized anionic arenes including nucleotides, while the latter neutral one associated with monopyrenyl guests regardless of their electric natures. The strength of recognition for nucleotides by bis(diazoniacrown)pyrenophane depended on the number of phosphate moieties, decreasing in the following order: triphosphate \gg diphosphate \sim monophosphate.

Introduction

Bondings are the most essential factor for the existence of compounds and work in natural and artificial environments. The molecular recognition chemistry has focused on noncovalent bonding and has succeeded in mimicking various phenomena in nature.¹ Among the noncovalent bondings, hydrophobic and π -stacking interactions are important ones for aromatic components, especially for each plane of base pairs in DNA and RNA helices.² Intercalation of some kinds of arenes into those planes of a nucleic acid are also driven by π -stacking interaction. For studying the π -stacking interaction, it is better to apply such host molecules bearing a plate-shaped cavity fitting the plane of guest arenes. In the field of hostguest chemistry, there have been numerous studies about synthetic hosts with a hydrophobic cavity to accommodate various kinds of guests.³ In most cases, however, the shape of the cavity was spherical or cylindrical, while host molecules bearing a plate-shaped cavity have been relatively rare.

Cyclophane is representative of a class of versatile macrocyclic compounds on which various functionalities could be conferred by the proper choice of arenes, bridges, and substituents.⁴ These compounds have attracted much attention from their moderately rigid cavity, especially as hydrophobic host molecules.^{4–8} Some of them are constructed by use of polycyclic arenes such as acridine,⁹ phenanthridine,¹⁰ quinacridine,¹¹ ethanoanthracene,¹² or flavin units,¹³ and proper arrangement of the polyaromatics produced a plate-shaped cavity on the cyclophanes. During the course of our study about molecular

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FIGURE 1. Macrocyclic pyrenophanes with cationic and amphiphilic side chains.

recognition, 14,15 we have developed a macrocyclic *pyrenophane* structure **1a** (Figure 1), in which two planes of pyrene are facing arranged across a pair of bridging spacers.¹⁴

Pyrenophane is a class of cyclophanes composed of one¹⁶ or more¹⁷ pyrene units which possess attractive optical characteristics. A single pyrene nucleus often gives a typical monomer emission, usually blue-colored, on its fluorescence spectrum. Once the excited pyrene

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meets another pyrene inter- or intramolecularly, the interaction induces structureless broad excimer emission, usually green-colored, in a longer wavelength area.¹⁸ Therefore the interaction between pyrenophanes and guest molecules can be readily followed up by monitoring the changes of the monomer and/or the excimer emissions. Furthermore, on the absorption spectra, significant hypochromism is often observed according to the complexation. Thus our pyrenophane 1a could efficiently sandwich various aromatic compounds in the plateshaped hydrophobic cavity, accompanied by such characteristic spectral changes.¹⁴ However, we could not examine the binding affinities of **1a** in pure 100% water, an ideal solvent for the hydrophobic interaction, because **1a** scarcely dissolved in it.¹⁹ This frustration made us decide to develop pyrenophanes soluble in pure 100% water with the expectation of drawing out the full potential of their hydrophobic cavities. Apart from their molecular recognition abilities, the precoordinated pyrenophanes are also interesting from the viewpoint of photophysics for their intramolecular excimer or exciplex formation.²⁰

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(19) Pyrenophane ${\bf 1a}$ was soluble in the mixture of water and ethylene glycol (3:1), in which complexations with guest molecules were studied. 14

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The solubility of the pyrenophane nucleus is inherently poor not only in water but also in most organic solvents, so some devices are necessary for improving its solubility. This also will facilitate their synthetic and analytical operations. To improve water solubility, hydrophilic functionalities such as polyammonium and polyoxyethylene groups are introduced on the molecule. However, the existence of highly polar functional groups frequently brings about serious drawbacks for manipulations such as reaction, isolation, and purification. Herein we report the development of pure-water-soluble pyrenophanes possessing a plate-shaped cavity that can incorporate various aromatic compounds including biologically important nucleotides (Figure 1). The refined synthetic strategy for overcoming insolubility problems and the molecular recognition abilities of the pyrenophanes are described.

Results and Discussion

Synthesis of Water-Soluble Pyrenophanes. Polyammonium pyrenophane was the first target toward purewater-soluble compounds. The major issues in their synthesis were how to construct the macrocyclic pyrenophane ring, when to introduce hydrophilic functionalities, and how to handle highly polar intermediates. One route (Scheme 1; $\mathbf{4} \rightarrow \mathbf{5} \rightarrow (\mathbf{6} \text{ and } \mathbf{7}) \rightarrow \mathbf{8} \rightarrow \mathbf{1c}$) was planned following our previously reported synthesis of 1a, which includes the Stille-type coupling reaction as the key macrocyclization.¹⁴ Phenolic diacetylene **4**¹⁴ prepared from 3.5-bis(hydroxymethyl)phenol was condensed with triamino alcohol by the Mitsunobu reaction²¹ to give **5**. The triaminated derivative 5 was converted to a pair of counterparts for Stille-type macrocyclization, i.e., one is acetylenic stannane 6 by lithiation-transmetalation, and the other is the iodopyrene derivative 7 by Sonogashira coupling. After cyclization to pyrenophane 8, quarternarization of each amine with methyl triflate afforded hexaammonium pyrenophane 1c. The water solubility of 1c was actually increased compared to that of 1a because of the increment of the number of cationic centers. However, the low accessibility of 1c, such as low yields and troublesome handling of each polyaminated intermediate, spured us to develop a more convenient route.

In a new synthetic scheme, introduction of polar moieties was followed by macrocyclization to make the handling easier (Scheme 1; $4 \rightarrow 9 \rightarrow (10 \text{ and } 11) \rightarrow 12 \rightarrow 13$). Triisopropylsilyl(TIPS)-protected pyrenophane 12 was smoothly prepared via Stille coupling between TIPS-protected 10 and 11. But once it was deprotected to 13, the solubility tragically decreased, so any further manipulations ended in failure.

 ω -Acetalic alkyl chains opened the door to the successful route to hydrophilic pyrenophanes with synthetic versatility and easy handling (Scheme 1; **14** \rightarrow (**15** and **16**) \rightarrow **17** \rightarrow (**18** and **3**)). The key intermediate **14** was prepared from 3,5-bis(hydroxymethyl)phenol via subsequent Williamson synthesis with 1-bromo-4,4-dimethoxybutane and propargyl bromide. Both the acetylenic ends of **14** were stannylated to **15** and pyrenylated to **16**, which are two counterparts for the following macrocyclization. Stille coupling of **15** and **16** gave pyrenophane





^{*a*} Reagents: (a) $[Me_2N(CH_2)_3]_2N(CH_2)_3OH$, Ph₃P, DEAD, THF; (b) *i*-Pr₃SiCl, DMAP, Et₃N, CH₂Cl₂; (c) Br(CH₂)₃CH(OMe)₂, NaI, 18-crown-6, K₂CO₃, acetone; (d) propargyl bromide, NaH, THF, DMF; (e) *n*-BuLi, *n*-Bu₃SnCl, THF; (f) 1,6-diiodopyrene, PdCl₂(PPh₃)₂, CuI, morpholine; (g) Pd(PPh₃)₄, toluene; (h) MeOTf, CH₂Cl₂; (i) *n*-Bu₄NF, H₂O, THF; (j) CF₃CO₂H, H₂O, CHCl₃; (k) octa(ethylene glycol), 10-camphorsulfonic acid.

17, which was deprotected by trifluoroacetic acid to **18**. Aldehyde **18** was easily soluble in CH_2Cl_2 and was reductively aminated with 2 equiv of secondary amine by using tetra-*n*-butylammonium cyanoborohydride (*n*-Bu₄NBH₃CN)²² to afford the corresponding hexa-, tetra-, and diaminated pyrenophanes **19b**, **19d**, and **19e** (Table 1). The complete quarternarization by methyl triflate gave targeted polyammonium pyrenophanes **1b**,²³ **1d**, and **1e**. Purification of **1d**,**e** was carried out by a preparative HPLC in a reverse phase. Azacrown and azoniacrown rings were also introduced on the pyreno-

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TABLE 1. Synthesis of Pyrenophanes Possessing Amino or Ammonium Groups



^a Not determined.

phane (Table 1). Indeed, diaza- and monoaza-18-crown-6 were condensed with **18** to afford **20a** and **20b**, respectively. The quarternarization of **20a** yielded a diazonia-crown derivative **2a** quantitatively.

Next was designed a neutral hydrophilic pyrenophane **3** possessing four octa(oxyethylene) side chains (Figure 1). The poly(oxyethylene) chain has been utilized for its favorable amphiphilicity:²⁴ affinity for both organic and aqueous media. Fortunately, octa(oxyethylene) chains could be directly introduced by acid-catalyzed transacetalization of diacetal **17** with octa(ethylene glycol)²⁵ under reduced pressure to remove methanol (Scheme 1). Thus, **17** is a versatile common intermediate for synthesizing various functionalized pyrenophanes. This ap-



FIGURE 2. Virtues of ω -acetalic alkyl branches.

proach utilizing ω -acetalic alkyl chains generally would be applicable for various compounds of poor solubility in order to attach hydrophilic substituents (Figure 2).

Water Solubility of Pyrenophanes and Guest Molecules. The pyrenophanes synthesized above were studied for their water solubility. Each of the pyrenophanes 1-3 and 20 was suspended into Milli-Q pure water and passed through a membrane filter, and the filtrate was irradiated with UV light (365 nm). The water solubility was judged from the presence or absence of excimer emission. Among the pyrenophanes examined,

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FIGURE 3. Guest molecules.

hexaammonium **1b** and **1c**, bis(diazoniacrown)-substituted **2a**, and poly(oxyethylene)-substituted **3** showed pure-water solubilities, whereas tetraammonium **1d**, diammonium **1e**, and azacrown-substituted **20a** and **20b** did not. Interestingly, amphiphilic **3** also dissolved into organic solvents such as dichloromethane and ether. For studying the recognition abilities of the pyrenophanes, several types of guest molecules were subjected: those include monomeric pyrenes **21** (neutral), **22**¹⁴ (cationic), and **23** (anionic), disulfonate **24**, adenosine, and twelve kinds of nucleotides. Figure 3 shows a series of guest molecules used in this study.

UV-Visible and Fluorescence Spectra of Pyrenophane 3. In the absorption spectrum of 3 (Figure 4a), broadening of the bands slightly red-shifted and a significant hypochromism, compared with that of the monopyrenyl reference 21 were observed. These differences indicate transannular interaction between two pyrene planes in $\mathbf{3}$.^{17e,h,i,20} As mentioned above, the optical properties of pyrenophanes are well-characterized in their fluorescence spectra. In a water solution, 3 almost exclusively exhibited excimer emission ($\lambda_{max} = 520$ nm) even at the concentration of 8×10^{-7} M, while monomer emission was hardly observed (Figure 4b). Thus, the excimer emission is obviously due to intramolecular π -stacking on the precoordinated structure of **3**, not due to intermolecular stacking which should depend on the concentration. On the other hand, monomeric pyrene 21 showed both monomer ($\lambda_{max} = 395$, 416 nm) and excimer (λ_{max} = 520 nm) emissions at the concentration of 2 imes 10^{-5} M in water, and the proportion of these two emissions depended on the concentration of 21. The excimer emission of 21 disappeared under a diluted



FIGURE 4. (a) The absorption spectra of **3** (1.5×10^{-5} M, –) and **21** (3×10^{-5} M, …) in water. (b) The fluorescent spectra of **3** (1×10^{-5} M, –) and **21** (2×10^{-5} M, …) in water. The excitation wavelength was 370 nm.

condition, indicating the feature of the intermolecular interaction.

Complexation of Pyrenophanes with Aromatic Guests. (i) Self-Association Tendencies of Pyrenophanes 1-3 and Monomeric Pyrenes 21-23. Enough water solubility of the pyrenophanes 1b, 1c, 2a, and 3 enabled us to examine their hydrophobic interactions under a 100% aqueous condition. All binding assays must be carried out below this concentration so that the selfassociation of each substrate is negligible under the conditions of the following measurements. Therefore, selfassociation tendencies of 3 and the monopyrenyl guests 21-23 were studied in advance. From UV-vis and fluorescence spectra, the relations of the absorbance and emission intensity upon the concentration were investigated (for 3, see Figures S1 and S2 in the Supporting Information). At a lower concentration of the substrate, the absorbance fitted in proportion to the concentration, obeying Beer's law. If deviation is observed from the

 TABLE 2.
 The Concentration Ranges for 3 and 21–23 in

 Which the Absorbance and Emission Intensity Obey the

 Linear Relationship in Water

	by absorbance		by fluorescence intensity	
	λ (nm)	linearity range (M)	λ (nm)	linearity range (M)
3	391	$<\!2.5 imes10^{-4}$	520	$< 1.0 \times 10^{-5}$
21 22	370 383	$ {}^{<3.0 \times 10^{-5}} $	395 400	
23	350	$<2.5 \times 10^{-4}$	380	$<3.1 imes10^{-5}$

linearity over a certain concentration, it means selfinteraction becomes significant between two ground state molecules. On the other hand, in the fluorescence intensity, the divergence from the linearity corresponds to the interaction between one excited molecule and another, usually the ground-state one. Table 2 shows the ranges in which the absorbance and emission intensity obey a linear relationship with the concentration. In the cases of monomeric pyrenes 21-23, excimer emissions were not observed within those concentration ranges. Between the neutral substances 3 and 21, monopyrenyl 21 tends to self-associate more than pyrenophane **3**. This may be partly because the cavity inside the pyrenophane is not so large to accommodate another pyrenophane. Among the monomeric pyrenes, charged 22 and 23 showed weaker self-association than 21 probably because of the electrostatic repulsion. By analogy to that, the polycationic pyrenophanes 1b,c and 2a will be supposed to perform weaker self-association than neutral 3. On the basis of these results, all the following host-guest complexation experiments were carried out within those concentrations at which self-association is negligible.

(ii) Complexation of Poly(oxyethylene)-Substituted Pyrenophane 3. When the neutral monomeric pyrene 21 was titrated with the neutral poly(oxyethylene)-substituted pyrenophane 3, quenching of the monomer emission of 21 was observed in the fluorescence spectra (Figure 5). Curve-fitting analysis of the titration curve supported 1:1 stoichiometry, and the association constant was determined at 1.3×10^5 M⁻¹. In reverse, titration of 3 by 21 induced quenching of the excimer emission of 3 as expected. As for the cationic and the anionic monomeric pyrene guests 22 and 23, the spectral changes were also observed in a similar manner. The association constants for 22 and 23 were estimated close to that for **21** (1 \times 10⁵ M⁻¹). Thus, the poly(oxyethylene)substituted pyrenophane 3 can incorporate the monomeric pyrenes 21-23 to a similar extent, regardless of their electric natures.

The complexation mode would be depicted as a sandwich form (Figure 6).¹⁴ The other possibility is that the monomeric pyrenes merely nest on one side of **3**. However, this type of nesting association could be rejected because this mode resembles self-association of the monomeric pyrenes. Indeed, the host–guest cross-association is far preferred to the self-association. (The cross-association was observable even at [**3**] = [**21**] = 8.3 × 10⁻⁷ M as quenching of the excimer emission of **3**. Compare this with the results in Table 2.) The quenching of fluorescence during the titration means that the complexation lost the excitation energy thermally in the tripyrenyl stack, while the π,π,π -stacking excited trimer has been reported to induce a very weak broad fluores-



FIGURE 5. Fluorimetric titration of **21** (3.1×10^{-6} M) with **3** (0–12 equiv) in water. The excitation wavelength was 370 nm. Inset: The relationship between [**3**] and the decrease in intensity of the emission of **21** at 416 nm. The solid line shows the fitted curve.



FIGURE 6. The postulated triply π,π,π -stacking coordination between a pyrenophane host and a monopyrenyl guest.

cent band at longer wavelengths with dibenzoperylene^{26a,b} or triple-decked cyclophane.^{26c} In our experiments, however, such an extra emission band could not be found, so in the case of pyrene the π,π,π -excited trimer formation by spectroscopy remains to be confirmed. The investigation of trilayer or more π -stacking pyrene systems is now under way.

(iii) Complexation of Polycationic Pyrenophanes 1c and 2a with Anionic Guest 24. The complexation of the pyrenophanes 1c and 2a bearing polycationic sites was studied. These pyrenophanes were expected as multipoint recognition hosts based on collaboration of the π -stacking and the electrostatic interactions. Thus, 1c and 2a may have an advantage in recognizing such a molecule that has both aromatic and anionic moieties. When disulfonate 24 was added to a solution of the bis-(diazoniacrown)-substituted pyrenophane 2a, hypochromism in the absorption spectra of 2a was observed (Figure 7a). This should be due to the complexation, and the association constant was determined to be 1.5×10^6 M⁻¹ by curve-fitting analysis. On fluorimetric titration, quenching of the excimer emission of 2a was observed under

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FIGURE 7. (a) UV-vis titration of **2a** $(1.1 \times 10^{-5} \text{ M})$ with **24** (0-1.5 equiv) in water. (b) Fluorimetric titration of **2a** $(1.6 \times 10^{-5} \text{ M})$ with **24** (0-1.5 equiv) in water. The excitation wavelength was 370 nm.

similar conditions (Figure 7b). The branched polycationic pyrenophane **1c** also displayed a similar affinity for **24**, and the association constant between **1c** and **24** was estimated as over 1×10^{6} M⁻¹ from the fluorimetric titration. Thus, the multipoint recognition by **1c** and **2a** takes place for anionic arenes, while neutral pyrenophane **3** showed no observable interaction with **24** by both UV– vis and fluorimetric titrations.

Complexation of Pyrenophane 2a with Nucleotides. Nucleotides are the most important class of biomolecules possessing both aromatic and anionic moieties. So they are suitable guest molecules for demonstrating the host ability of the bis(diazoniacrown)substituted pyrenophane 2a. There have already been numerous studies about the development of host molecules for nucleotides.²⁷ One efficient strategy for the recognition of nucleotides is to use cationic macrocycles



FIGURE 8. Multipoint recognition of 2a for nucleotide.

which recognize phosphate moieties, for example, azoniacrowns, ^{28–30} azoniacyclophanes,⁸ and protonated sapphyrins.³¹ Lehn, Hosseini, and co-workers have reported a series of azoniacyclophanes.^{5b,9–11} Furthermore, acridinearmed azoniacyclophanes^{28d,e} associated with nucleotides as multipoint recognition hosts by both electrostatic and π -stacking interactions.

Two kinds of three recognition sites in **2a** are placed at appropriate positions, i.e., two azoniacrown sites at both ends and one pyrenophane site at the center. If these sites work synergistically, the form of the complex would be featured as in Figure 8 in expectation of effective distinction of nucleotides by size.

When **2a** was titrated with ATP in water, the UV-vis spectra changed in a hypochromic way according to

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FIGURE 9. (a) UV–vis titration of **2a** (1.0×10^{-5} M) with ATP (0–1.4 equiv) in water. (b) Fluorimetric titration of **2a** (1×10^{-5} M) with ATP (0–6.0 equiv) in water. The excitation wavelength was 370 nm.

 π -stacking coordination (Figure 9a), and the association constant was determined (1.0 × 10⁶ M⁻¹ by curve-fitting analysis) as high as the disulfonate guest **24**. The quenching of the excimer fluorescence was also observed under similar conditions (Figure 9b).³² On the other hand, the neutral host **3** showed no observable interaction with ATP on the UV–vis titration, possibly because the π -plane of adenine is not large enough to complex with **3** by only π -stacking.

These results encouraged us to investigate the recognition ability of **2a** for other nucleotides comprehensively in a similar manner as for ATP. The association constants were lined up in Table 3. Triphosphate nucleotides GTP, CTP, and UTP associated with **2a** at comparable levels

 TABLE 3. Association Constants and Free-Energy Changes for the Complexation of 2a with Nucleotides^a

nucleotide	association constant (M^{-1})	$-\Delta G_{293}$ (kJ mol ⁻¹)
ATP	$1.0 imes10^6$	34
ADP	$5.3 imes10^3$	21
AMP	$1.9 imes10^3$	18
GTP	$1.3 imes 10^6$	34
GDP^b	$4.0 imes10^3$	20
GMP	$2.7 imes10^3$	19
CTP	$2.6 imes10^5$	30
CDP	$7.7 imes10^3$	22
CMP^{b}	$4.0 imes10^3$	20
UTP	$7.7 imes10^5$	33
UDP	$2.2 imes10^4$	24
UMP	$3.0 imes10^3$	20

 a Calculated by curve-fitting analysis of hypochromism on 390 nm. Conditions: **2a** (1.0 \times 10⁻⁵ M), nucleotide, 20 °C in water. b The association constant was estimated by the Benesi-Hildebrand method.

to ATP. On the other hand, bindings of **2a** to di- and monophosphate nucleotides (ADP, GDP, CDP, UDP, AMP, GMP, CMP, and UMP) appeared much weakly than those to triphosphates. The association constants for the di- and monophosphate nucleotides were close to that between **2a** and adenosine ($6.5 \times 10^3 \text{ M}^{-1}$) rather than those for triphosphates whether the type of nucleobase had only a little effect on the binding or purine bases were slightly preferred to pyrimidine ones. Thus, the recognition selectivities of **2a** would be due to a structural reason: the distance between the pyrenophane cavity and diazoniacrown sites in **2a** may fit in with the size of the triphosphate nucleotides along with synergistic coordination.

Conclusion

To investigate the molecular recognition abilities of pyrenophanes in pure water, several types of pyrenophanes possessing various hydrophilic functionalities were synthesized. The construction of the pyrenophane nucleus was achieved by macrocyclization applying Stilletype coupling. The use of ω -acetalic alkyl chains was efficient for retaining the solubility on pyrenophane intermediates, and the side chains could be readily converted to polyammonium-, azoniacrown-, and poly(oxyethylene)substituted hydrophilic substituents. In the study of molecular recognition abilities, amphiphilic poly(oxyethylene)-substituted pyrenophane 3 showed good affinities for monopyrenyl guests, regardless of the guest being cationic, anionic, or neutral. Polycationic hexaammonium pyrenophane 1c and bis(diazoniacrown)-substituted one 2a associated well with anionic arenes. It is remarkable that 2a much preferred triphosphate nucleotides rather than di- or monophosphate ones. These pyrenophanes are the optical probe of interest, not only for recognition ability, but also for their optical uniqueness. They displayed characteristic excimer emission owing to the two precoordinated pyrene rings, which were susceptibly affected by association with guest arenes. This makes the study of its host-guest chemistry straightforward. Further development of polypyrenyl architectures for bioorganic applications is now under way in our laboratory.

Experimental Section

Evaluation of Association Constants. Milli-Q pure water was used as a common aqueous solvent. The analyses for **3**

⁽³²⁾ Similar optical behavior was observed in our previous work.¹⁴

were performed by fluorimetric titration at 25 °C, measuring the quenching of the emission at 520, 416, and 380 nm for **3**, **21**, and **23**, respectively. The analyses for **2a** were performed by UV–vis titration at 20 °C by measuring hypochromism of the absorption at 390 nm. The association constants were calculated by using iterative least-squares curve-fitting or the Benesi–Hildebrand method.³³

1-(4,4-Dimethoxybutyloxy)-3,5-bis(hydroxymethyl)benzene. To an acetone (70 mL) suspension of 1-bromo-4,4dimethoxybutane³⁴ (16 g, 81 mmol), NaI (0.61 g, 4.1 mmol), 18-crown-6 (1.1 g, 4.1 mmol), and finely ground K₂CO₃ (28 g, 203 mmol) was added an acetone (70 mL) solution of 3,5-bis-(hydroxymethyl)phenol¹⁴ (6.1 g, 41 mmol). The suspension was refluxed for 12 h and filtered, and the concentrated filtrate was purified on column chromatography (silica gel; CH₂Cl₂: MeOH 50:1) to give 1-(4,4-dimethoxybutyloxy)-3,5-bis(hydroxymethyl)benzene as a colorless oil (7.6 g, 69%). ¹H NMR $(300 \text{ MHz}, \text{DMSO-}d_6) \delta 6.81 \text{ (s, 1 H)}, 6.71 \text{ (s, 1 H)}, 5.13 \text{ (t, } J =$ 5.7 Hz, 2 H), 4.43-4.39 (m, 5 H), 3.93 (t, J = 6.2 Hz, 2 H), 3.22 (s, 6 H), 1.71-1.63 (m, 4 H); ¹³C NMR (75 MHz, DMSO d_6) δ 158.48, 143.85, 116.46, 110.57, 103.66, 66.91, 62.83, 52.42, 28.67, 24.02; IR (KBr) 3396, 2939, 2879 cm⁻¹; FABMS (3nitrobenzyl alcohol) m/z 270 (M⁺, 100).

1-(4,4-Dimethoxybutyloxy)-3,5-bis(2-propynyloxymethyl)benzene (14). NaH (60% oil dispersion; 2.64 g, 66 mmol) was washed thoroughly with hexane and suspended with THF (50 mL), to which was added a DMF (65 mL) solution of 1-(4,4dimethoxybutyloxy)-3,5-bis(hydroxymethyl)benzene (4.45 g, 16.5 mmol) dropwise at 0 °C. After the solution was stirred at that temperature for 1 h, propargyl bromide (7.8 g, 66 mmol) was added dropwise at -78 °C. The mixture was stirred additionally for 12 h, being allowed to reach room temperature. After evaporation, the residue was diluted with water and extracted with CHCl₃. The CHCl₃ extract was concentrated and subjected to column chromatography (silica gel; CH₂Cl₂) to give 14 as a colorless oil (4.0 g, 70%). ¹H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 1 H), 6.84 (s, 2 H), 4.57 (s, 4 H), 4.40 (t, J = 5.2 Hz, 1 H), 4.18 (d, J = 2.4 Hz, 4 H), 3.99 (t, J = 6.0 Hz, 2 H), 3.34 (s, 6 H), 2.47 (t, J = 2.4 Hz, 2 H), 1.88 - 1.76 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃) δ 159.4, 139.0, 119.7, 113.5, 104.2, 79.6, 74.7, 71.3, 67.5, 57.2, 52.8, 29.1, 24.5; IR (KBr) 3290, 2944, 2117 cm⁻¹; FABMS (3-nitrobenzyl alcohol) m/z 345 (M - H⁻, 100); ESI-HRMS m/z calcd for C₂₀H₂₆NaO₅ (M + Na⁺) 369.1678, found 369.1637.

1-(4,4-Dimethoxybutyloxy)-3,5-bis(3-tributylstannyl-2propynyloxymethyl)benzene (15). To a THF (5 mL) solution of 14 (900 mg, 2.6 mmol) was added a hexane solution of n-BuLi (5.7 mmol) dropwise at 0 °C. After the solution was stirred at that temperature for 1 h, n-Bu₃SnCl (1.9 g, 5.7 mmol) was added dropwise. The reaction mixture was stirred additionally for 14 h, being allowed to reach room temperature. After evaporation, the residue was treated with saturated aqueous KF and extracted with Et₂O. The Et₂O extract was evaporated to give crude 15 as a colorless oil (2.25 g, 94%), which was used in the next reaction without further purification. ¹H NMR (300 MHz, CDCl₃) δ 6.90 (s, 1 H), 6.84 (s, 2 H), 4.57 (s, 4 H), 4.44 (t, J = 5.2 Hz, 1 H), 4.19 (t, J = 3.9 Hz, 4 H), 3.98 (t, J = 5.7 Hz, 2 H), 3.34 (s, 6 H), 1.83–1.77 (m, 4 H), 1.66-1.59 (m, 12 H), 1.39-1.19 (m, 12 H), 1.12-0.99 (m, 12 H), 0.96–0.84 (m, 18 H); ¹³C NMR (75 MHz, CDCl₃) δ 159.3, 139.4, 119.9, 113.5, 104.4, 90.3, 71.2, 68.2, 67.7, 58.5, 53.0, 29.2, 27.4, 27.3, 24.8, 14.0, 11.4; IR (neat) 2954, 2924, 2853, 2148 cm⁻¹; ESI-HRMS m/z calcd for C₄₄H₇₈NaO₅¹¹⁸Sn¹²⁰Sn (M + Na⁺) 947.3785, found 947.3768.

1-(4,4-Dimethoxybutyloxy)-3,5-bis[3-(6-iodopyren-1yl)-2-propynyloxymethyl]benzene (16). A morpholine (120 mL) suspension of 14 (1.1 g, 3.2 mmol), 1,6-diiodopyrene³⁵ (5.25 g, 11.6 mmol), Pd(PPh₃)₄ (370 mg, 0.32 mmol), and CuI (30 mg, 0.16 mmol) was stirred at 110 °C for 5 h. After evaporation, the residue was diluted with brine and extracted with CHCl₃. The CHCl₃ extract was concentrated and purified by repeated column chromatography (silica gel; CH₂Cl₂:MeOH 100:1) to give **16** as a solid (1.0 g, 32%). Mp 154–158 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.43 (d, J = 5.4 Hz, 2 H), 8.36 (d, J= 8.3 Hz, 2 H), 8.15 (d, J = 9.3 Hz, 2 H), 8.01 (d, J = 8.1 Hz, 2 H), 7.96-7.67 (m, 6 H), 7.24 (s, 1 H), 7.00 (s, 2 H), 4.85 (s, 4 H), 4.65 (s, 4 H), 4.43 (t, J = 5.5 Hz, 1 H), 4.04 (t, J = 6.1 Hz, 2 H), 3.32 (s, 6 H), 1.87-1.76 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃) δ 159.6, 139.2, 137.0, 132.3, 131.7, 131.6, 131.0, 130.9, 130.2, 128.9, 127.9, 126.3, 125.7, 124.8, 124.7, 123.4, 120.4, 117.7, 113.8, 104.2, 97.0, 91.1, 85.5, 71.5, 67.6, 58.1, 52.8, 29.1, 24.5; IR (KBr) 2929, 2873, 2834, 2215 cm⁻¹; FABMS (2nitrophenyl octyl ether) m/z 998 (M⁺, 100); ESI-HRMS m/z calcd for C₅₂H₄₀I₂NaO₅ (M + Na⁺) 1021.0863, found 1021.0817.

Acetalic Pyrenophane 17. Stille-Type Macrocyclization. To a toluene (500 mL) solution of 16 (2.6 g, 2.6 mmol) and Pd(PPh₃)₄ (300 mg, 0.26 mmol) was added a toluene (100 mL) solution of 15 (2.6 g, 2.9 mmol) at room temperature, and the mixture was stirred at 60 °C for 2 days. After evaporation, the residue was diluted with brine and extracted with CHCl₃. The CHCl₃ extract was concentrated and subjected to column chromatography (silica gel; CH₂Cl₂:MeOH 50:1) to give 17 as a solid (0.23 g, 8%). Mp 169-171 °C; 1H NMR (300 MHz, CDCl₃) δ 8.20 (d, J = 9.0 Hz, 4 H), 7.84 (d, J = 7.8 Hz, 4 H), 7.54 (d, J = 9.3 Hz, 4 H), 7.50 (d, J = 8.1 Hz, 4 H), 7.44 (s, 2 H), 7.04 (s, 4 H), 4.94 (s, 8 H), 4.63 (s, 8 H), 4.48 (t, J = 5.5Hz, 4 H), 4.09 (t, J = 6.1 Hz, 2 H), 3.37 (s, 12 H), 1.94–1.81 (m, 8 H); 13 C NMR (75 MHz, CDCl₃) δ 159.9, 138.9, 131.6, 130.4, 129.5, 127.6, 125.5, 124.7, 123.0, 121.6, 117.1, 114.3, 104.2, 90.5, 85.8, 71.0, 67.7, 57.4, 52.8, 29.1, 24.5; IR (KBr) 2929, 2873, 2838, 2215 cm⁻¹; FABMS (2-nitrophenyl octyl ether) m/z 1088 (M⁺, 100); ESI-HRMS m/z calcd for C₇₂H₆₄- NaO_{10} (M + Na⁺) 1111.4397, found 1111.4349.

Aldehydic Pyrenophane 18. To a CHCl₃ (5 mL) solution of 17 (50 mg, 0.046 mmol) was added aqueous 50% CF₃CO₂H (2.5 mL) dropwise at 0 °C, and the mixture was stirred at that temperature for 18 h. To the mixture was added aqueous K₂- CO_3 at room temperature until no more CO_2 evolved. The reaction mixture was extracted with CH₂Cl₂, and the CH₂Cl₂ extract was concentrated and subjected to column chromatography (silica gel; CH₂Cl₂:MeOH 20:1) to give **18** (45 mg, 95%). Mp > 240 °C dec; ¹H NMR (300 MHz, \breve{CDCl}_3) δ 9.88 (s, 2 H), 8.20 (d, J = 9.0 Hz, 4 H), 7.78 (d, J = 8.1 Hz, 4 H), 7.59 (d, J= 9.0 Hz, 4 H), 7.51 (d, J = 8.5 Hz, 4 H), 7.44 (s, 2 H), 7.03 (s, 4 H), 4.93 (s, 8 H), 4.63 (s, 8 H), 4.11 (t, J = 6.0 Hz, 4 H), 2.71 (t, J = 7.0 Hz, 4 H), 2.21–2.14 (m, 4 H); ¹³C NMR (75 MHz, $CDCl_3$) δ 201.8, 159.6, 139.0, 131.6, 130.5, 129.5, 127.6, 125.5, 124.8, 123.0, 121.8, 117.1, 114.2, 90.5, 85.8, 71.0, 66.9, 57.5, 40.7, 22.1; IR (KBr) 2210, 1718 cm⁻¹; FABMS (2-nitrophenyl octyl ether) m/z 996 (M⁺, 100); ESI-HRMS m/z calcd for $C_{68}H_{52}^{-}$ - NaO_8 (M + Na⁺) 1019.3560, found 1019.3560.

7-Benzyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane.³⁶ NaH (60% oil dispersion; 26 mg, 0.64 mmol) was washed thoroughly with hexane and suspended in THF (2 mL). At 0 °C a THF (9 mL) solution of 1,4,10,13-tetraoxa-7,16diazacyclooctadecane (500 mg, 1.91 mmol) was added to the suspension dropwise, and the mixture was stirred for 30 min. To the resulting mixture was added benzyl bromide (120 mg, 0.70 mmol), and the reaction mixture was further stirred for 24 h, being allowed to reach room temperature. The concentrated residue was subjected to reverse-phase HPLC (ODS

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column (Shinwa Chemical Industries, Ltd.); MeOH) to give 7-benzyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane as a light yellow oil (121 mg, 49%).

Diazacrown Pyrenophane 20a. Reductive Amination. To a CH₂Cl₂ (2 mL) solution of **18** (11 mg, 0.011 mmol) were successively added 7-benzyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (49 mg, 0.14 mmol), 1 N HCl in Et₂O (0.044 mL, 0.044 mmol), finely ground molecular sieves 4A (5 mg), and *n*-Bu₄NBH₃CN (6.2 mg, 0.022 mmol). The mixture was stirred at room temperature for 30 h and filtered. To the filtrate was added additional CH₂Cl₂, and the combined CH₂Cl₂ layer was washed with water, concentrated, and subjected to column chromatography (silica gel; CH₂Cl₂:MeOH:Et₃N 50:1:1) to give **19e** (5 mg, 27%). Mp 71-73 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.21 (d, J = 9.0 Hz, 4 H), 7.78 (d, J = 7.7 Hz, 4 H), 7.59 (d, J= 9.0 Hz, 4 H), 7.51 (d, J = 7.7 Hz, 4 H), 7.44 (s, 2 H), 7.34-7.23 (m, 10 H), 7.04 (s, 4 H), 4.94 (s, 8 H), 4.63 (s, 8 H), 4.07 (t, J = 6.0 Hz, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 2.83 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (s, 4 H), 3.68 - 3.61 (m, 32 H), 3.49 (m, 32 H), 3.49 (m, 32 H), 3.68 - 3.61 (m, 32 H), 3.68 - 3.612.81 (m, 16 H), 2.61 (t, J = 7.1 Hz, 4 H), 1.84-1.68 (m, 8 H); ¹³C NMR (75 MHz, CDCl₃) δ 160.0, 139.5, 138.9, 131.6, 130.5, 129.5, 128.9, 128.2, 127.6, 126.9, 125.5, 124.8, 123.0, 121.6, 117.1, 114.3, 90.5, 85.8, 76.8, 71.0, 70.7, 70.0, 68.0, 59.9, 57.4, 55.6, 54.0, 53.8, 27.2, 23.5; IR (KBr) 3434, 2924, 2863, 1097 cm^-1; ESI-HRMS $\mathit{m/z}$ calcd for $C_{106}H_{117}N_4O_{14}$ (M + H^+) 1669.8566, found 1669.8571.

Diazoniacrown Pyrenophane 2a. Quarternarization to Ammonium Salt. To a CH₂Cl₂ (1 mL) solution of **20a** (5 mg, 0.003 mmol) was added MeOTf (10 mg, 0.06 mmol) dropwise at 0 °C. The resulting precipitate was filtered and washed sequentially with hexane and ether to afford **1e** (7 mg, 99%) as a solid. Mp >230 °C dec; ¹H NMR (300 MHz, CD₃OD) δ 7.93 (d, J = 8.5 Hz, 4 H), 7.70 (d, J = 7.7 Hz, 4 H), 7.55– 7.46 (m, 20 H), 7.11 (s, 4 H), 4.95 (s, 8 H), 4.66 (s, 8 H), 4.59 (d, J = 6.8 Hz, 4 H), 4.17–4.15 (m, 4 H), 4.09–3.44 (m, 52 H), 3.11 (s, 6 H), 3.00 (s, 6 H), 1.95–1.89 (m, 8 H); IR (KBr) 3477, 2870, 1262, 1160, 1031 cm⁻¹; ESI-HRMS m/z calcd for $C_{112}H_{128}F_6N_4O_{20}S_2$ ((M - 2TfO $^{-})^{2+}$) 1013.4234, found 1013.4210.

Poly(oxyethylene) Pyrenophane 3. Transacetalization. To octa(ethylene glycol)25 (200 mg, 0.53 mmol) were successively added 17 (14 mg, 0.013 mmol) and 10-camphorsulfonic acid (21 mg, 0.093 mmol), and the mixture was stirred at 80 °C under reduced pressure for 20 min. After the mixture had cooled to room temperature, finely ground K₂CO₃ was added. The resulting mixture was stirred for an additional 10 min and filtered. The filtrate was concentrated and subjected to column chromatography (silica gel; CH₂Cl₂:MeOH:Et₃N 50: 1:1), followed by reverse-phase HPLC (ODS column (Shinwa Chemical Industries, Ltd.); MeOH:Et₃N 100:0.3) to give 3 as a yellowish viscous oil (7.1 mg, 22%). ¹H NMR (300 MHz, \dot{CDCl}_3) δ 8.20 (d, J = 9.0 Hz, 4 H), 7.78 (d, J = 8.1 Hz, 4 H), 7.59 (d, J = 9.0 Hz, 4 H), 7.50 (d, J = 8.1 Hz, 4 H), 7.44 (s, 2 H), 7.02 (s, 4 H), 4.93 (s, 8 H), 4.70 (t, J = 5.6 Hz, 4 H), 4.62 (s, 8 H), 4.07 (t, J = 6.0 Hz, 4 H), 3.80–3.76 (m, 4 H), 3.75– 3.69 (m, 12 H), 3.68-3.59 (m, 112 H), 2.98 (br, 4 H), 1.95-1.84 (m, 8 H); ¹³C NMR (75 MHz, CDCl₃) δ 160.1, 139.0, 131.8, 130.6, 129.7, 127.8, 125.7, 125.0, 123.2, 121.8, 117.3, 114.5, 90.7, 86.0, 72.8, 71.1, 70.8, 70.74, 70.73, 70.70, 70.67, 70.4, 67.9, 64.7, 61.9, 57.6, 30.0, 24.8; IR (KBr) 3380, 2218 cm⁻¹; ESI-HRMS m/z calcd for $C_{132}H_{184}NaO_{42}$ (M + Na⁺) 2464.2160, found 2464.2099.

Supporting Information Available: Preparation of **1b**–**e**, **5**–**13**, **19b**, **19d**, **19e**, **20b**, **21**, and **23**, and ¹H NMR spectra of **1d**, **1e**, **2a**, **3**, **5–18**, **19b**, **19d**, **19e**, **20a**, and **20b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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