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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 host−guest 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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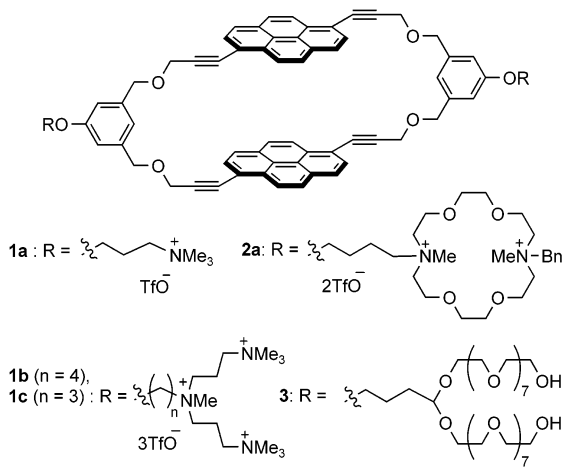

FIGURE 1. Macrocyclic pyrenophanes with cationic and amphiphilic side chains.

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 one[16] or more[17] 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 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 plate-shaped 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 **1a** was soluble in the mixture of water and ethylene glycol (3:1), in which complexations with guest molecules were studied.[14]

(20) Winnik, F. M. *Chem. Rev.* **1993**, *93*, 587−614.

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

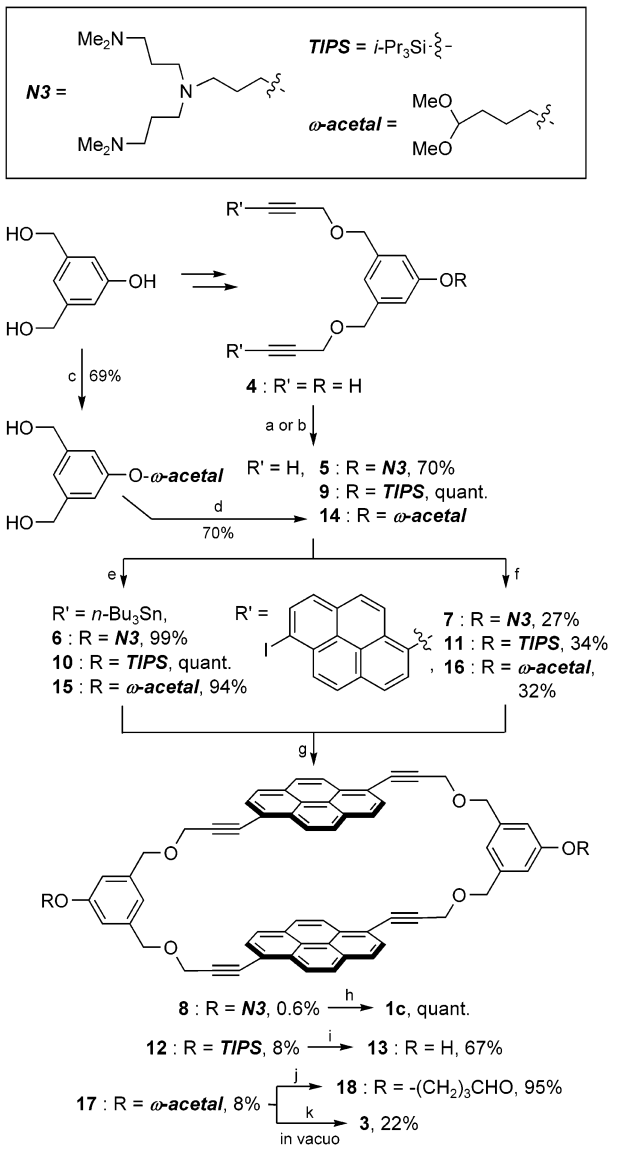
Synthesis of Water-Soluble Pyrenophanes. Polyammonium pyrenophane was the first target toward pure-water-soluble compounds. The major issues in their synthesis were how to construct the macrocyclic pyrenophane ring, when to introduce hydrophilic functionalities, and how to handle highly polar intermediates. One route (Scheme 1; **4** → **5** → (**6** and **7**) → **8** → **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 reaction[21] 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** → **9** → (**10** and **11**) → **12** → **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** → (**15** and **16**) → **17** → (**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

(21) Hughes, D. L. *Org. React.* **1992**, *42*, 335−656.

SCHEME 1. Synthesis of Pyrenophanes[a]



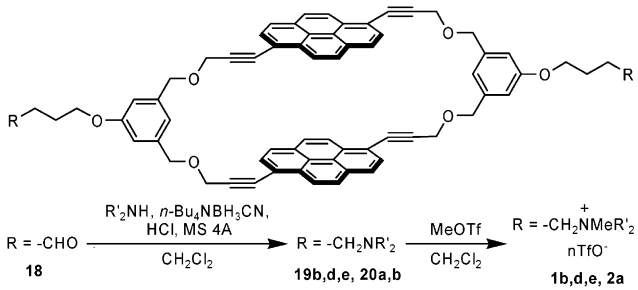
[a] Reagents: (a) $[Me_2N(CH_2)_3]_2N(CH_2)_3OH$, Ph_3P, DEAD, THF; (b) *i*-Pr_3SiCl, DMAP, Et_3N, CH_2Cl_2; (c) $Br(CH_2)_3CH(OMe)_2$, NaI, 18-crown-6, K_2CO_3, acetone; (d) propargyl bromide, NaH, THF, DMF; (e) *n*-BuLi, *n*-Bu_3SnCl, THF; (f) 1,6-diiodopyrene, $PdCl_2(PPh_3)_2$, CuI, morpholine; (g) $Pd(PPh_3)_4$, toluene; (h) MeOTf, CH_2Cl_2; (i) *n*-Bu_4NF, H_2O, THF; (j) CF_3CO_2H, H_2O, $CHCl_3$; (k) octa(ethylene glycol), 10-camphorsulfonic acid.

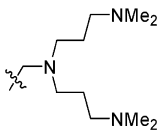
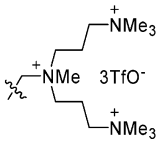
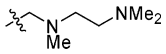
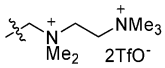
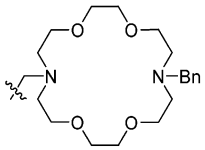
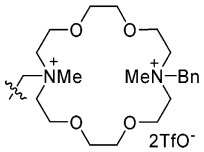
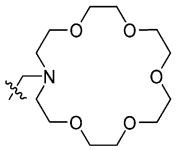
17, which was deprotected by trifluoroacetic acid to **18**. Aldehyde **18** was easily soluble in CH_2Cl_2 and was reductively aminated with 2 equiv of secondary amine by using tetra-*n*-butylammonium cyanoborohydride (*n*-Bu_4NBH_3CN)[22] to afford the corresponding hexa-, tetra-, and diaminated pyrenophanes **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-

(22) Hutchins, R. O.; Markowitz, M. *J. Org. Chem.* **1981**, *46*, 3571−3574.

(23) Hexaammonium **1b** could not be purified enough to permit complexation studies because of its too high polarity. See the Supporting Information.

TABLE 1. Synthesis of Pyrenophanes Possessing Amino or Ammonium Groups



aminopyrenophane			ammonium pyrenophane		
R		yield (%)	R		yield (%)
	**19b**	40		**1b**	•[a]
	**19d**	41		**1d**	88
	**19e**	63		**1e**	90
	**20a**	27		**2a**	99
	**20b**	57			

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

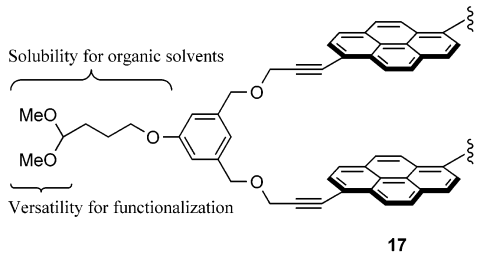


FIGURE 2. Virtues of ω-acetalic alkyl branches.

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,

(24) (a) Uozumi, Y.; Nakai, Y. *Org. Lett.* **2002**, *4*, 2997−3000. (b) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919−2920. (c) Grassert, I.; Schmidt, U.; Ziegler, S.; Fischer, C.; Oehme, G. *Tetrahedron*: *Asymmetry* **1998**, *9*, 4193−4202. (d) Aida, T.; Takemura, A.; Inoue, S. *Tetrahedron Lett.* **1989**, *30*, 6883−6886. (e) Aida, T.; Takemura, A.; Fuse, M.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1988**, 391−393.

(25) Nakatsuji, Y.; Kameda, N.; Okahara, M. *Synthesis* **1987**, 280−281.

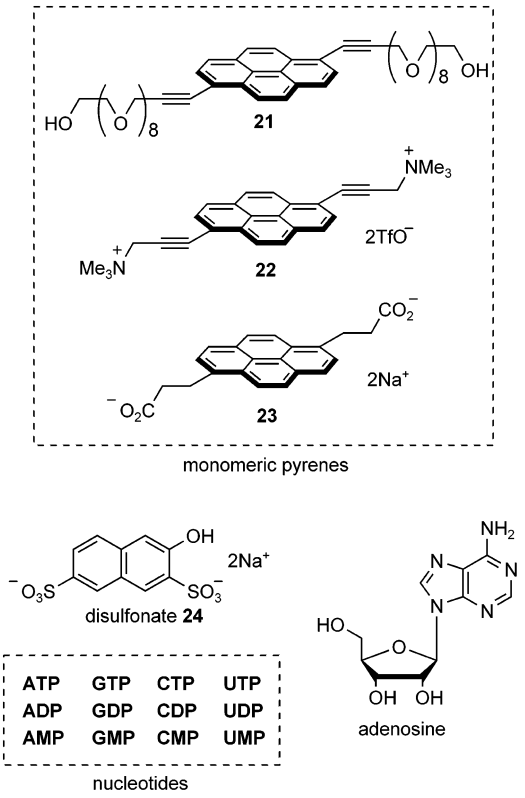


FIGURE 3. Guest molecules.

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 **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 (λ_{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 (λ_{max} = 395, 416 nm) and excimer (λ_{max} = 520 nm) emissions at the concentration of 2×10^{-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

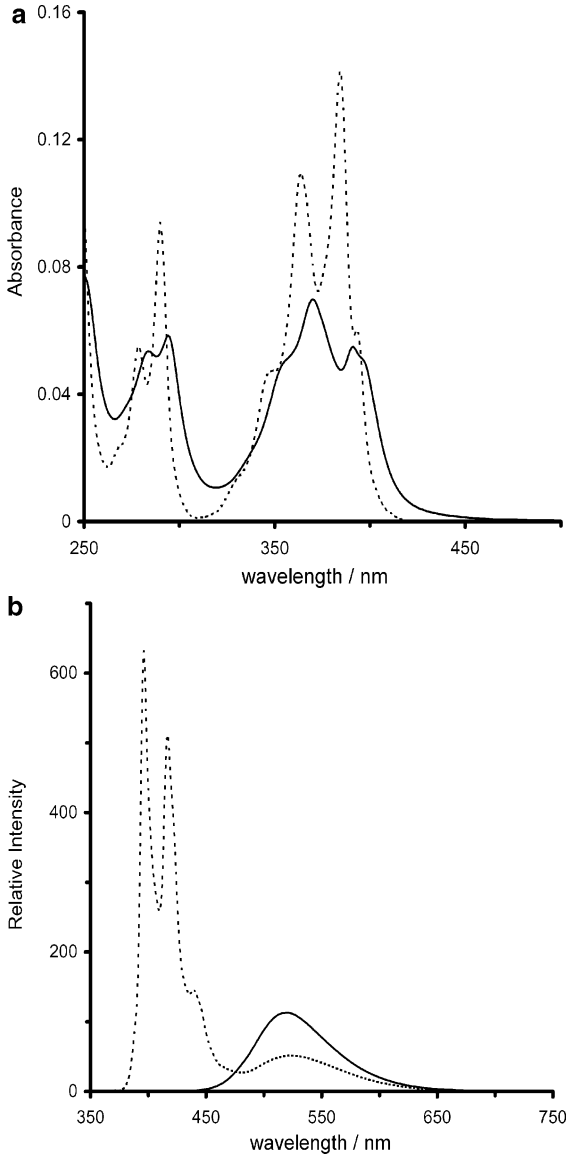


FIGURE 4. (a) The absorption spectra of **3** (1.5×10^{-5} M, —) and **21** (3×10^{-5} M, ···) in water. (b) The fluorescent spectra of **3** (1×10^{-5} M, —) and **21** (2×10^{-5} M, ···) in water. The excitation wavelength was 370 nm.

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 self-association of each substrate is negligible under the conditions of the following measurements. Therefore, self-association 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	$<2.5 \times 10^{-4}$	520	$<1.0 \times 10^{-5}$
21	370	$<3.0 \times 10^{-5}$	395	$<3.0 \times 10^{-6}$
22	383	$<2.5 \times 10^{-4}$	400	$<6.4 \times 10^{-6}$
23	350	$<2.5 \times 10^{-4}$	380	$<3.1 \times 10^{-5}$

linearity over a certain concentration, it means self-interaction 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** (1×10^5 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 fluorescent 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.

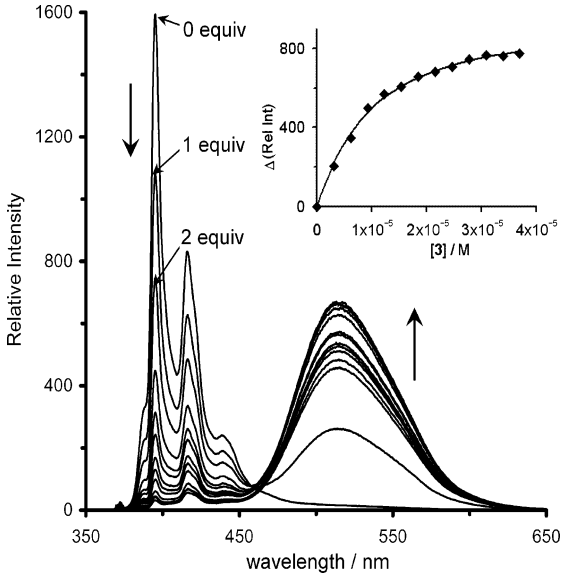


FIGURE 5. Fluorimetric titration of **21** (3.1×10^{-6} M) with **3** (0−12 equiv) in water. The excitation wavelength was 370 nm. Inset: The relationship between [**3**] and the decrease in intensity of the emission of **21** at 416 nm. The solid line shows the fitted curve.

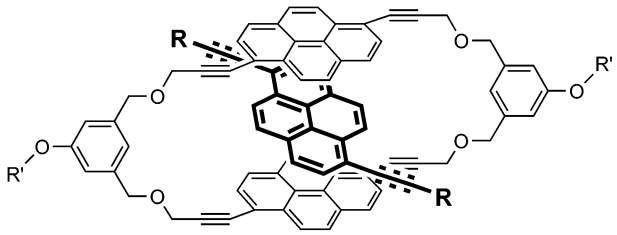


FIGURE 6. The postulated triply π,π,π-stacking coordination between a pyrenophane host and a monopyrenyl guest.

(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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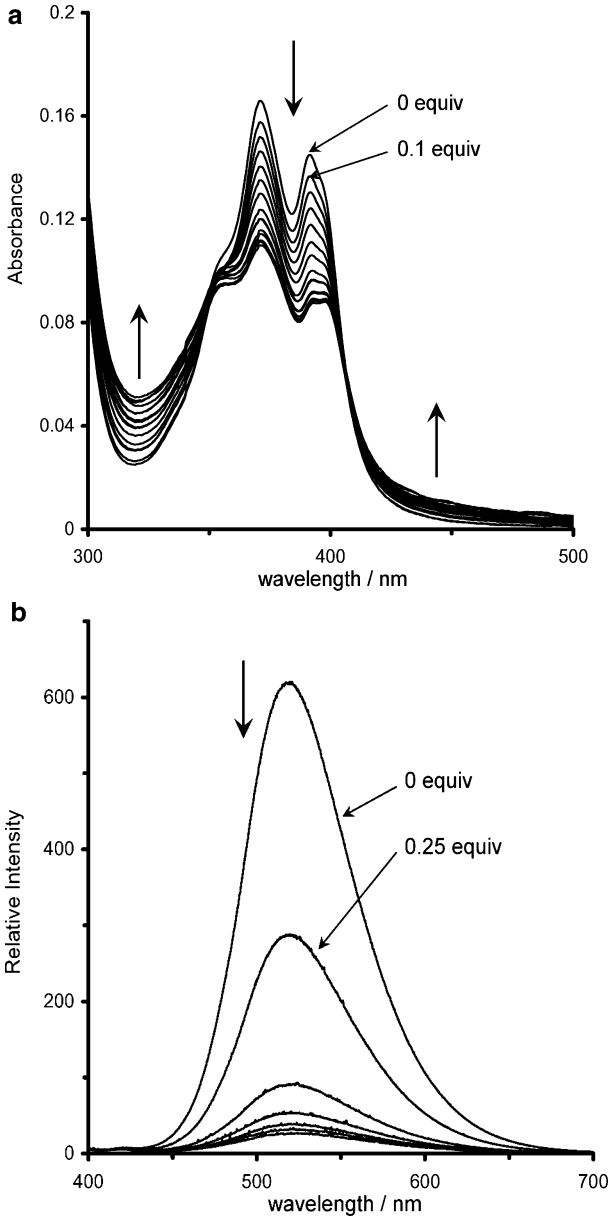

FIGURE 7. (a) UV−vis titration of **2a** (1.1×10^{-5} M) with **24** (0−1.5 equiv) in water. (b) Fluorimetric titration of **2a** (1.6×10^{-5} M) with **24** (0−1.5 equiv) in water. The excitation wavelength was 370 nm.

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

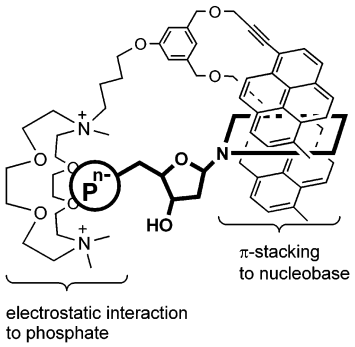

FIGURE 8. Multipoint recognition of **2a** for nucleotide.

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, acridine-armed 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

(27) Teulade-Fichou, M.-P.; Vigneron, J.-P. In *DNA and RNA Binders*; Demeunynck, M., Bailly, C., Wilson, W. D., Eds.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, pp 278−314. Hosseini, M. W. In *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., García-España, E., Eds.; Wiley-VCH: New York, 1997; pp 421−448. For intercalating agents for DNA, see: Johnson, D. S.; Boger, D. L. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Murakami, Y., Eds.; Pergamon: Oxford, UK, 1996; Vol. 4, pp 73−176. Aoki, S.; Kimura, E. *Rev. Mol. Biotechnol.* **2002**, *90*, 129−155.

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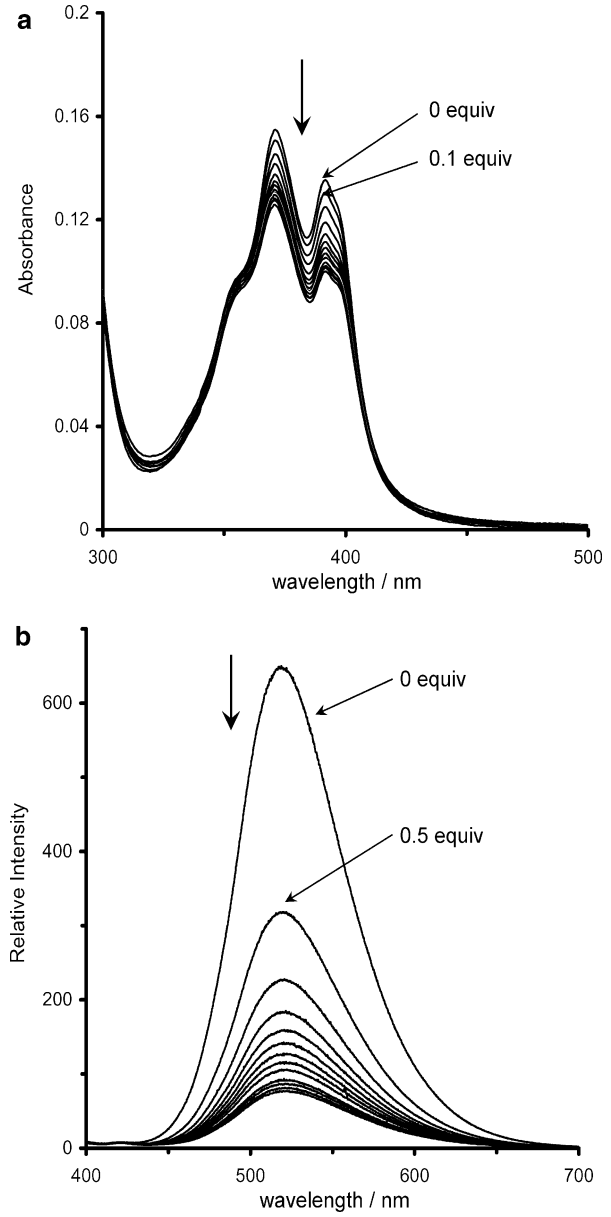

FIGURE 9. (a) UV−vis titration of **2a** (1.0×10^{-5} M) with ATP (0−1.4 equiv) in water. (b) Fluorimetric titration of **2a** (1×10^{-5} M) with ATP (0−6.0 equiv) in water. The excitation wavelength was 370 nm.

π-stacking coordination (Figure 9a), and the association constant was determined (1.0×10^6 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 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 (6.5×10^3 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.

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	1.0×10^6	34
ADP	5.3×10^3	21
AMP	1.9×10^3	18
GTP	1.3×10^6	34
GDP[b]	4.0×10^3	20
GMP	2.7×10^3	19
CTP	2.6×10^5	30
CDP	7.7×10^3	22
CMP[b]	4.0×10^3	20
UTP	7.7×10^5	33
UDP	2.2×10^4	24
UMP	3.0×10^3	20

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

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 Stille-type 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-4,4-dimethoxybutane[34] (16 g, 81 mmol), NaI (0.61 g, 4.1 mmol), 18-crown-6 (1.1 g, 4.1 mmol), and finely ground K_2CO_3 (28 g, 203 mmol) was added an acetone (70 mL) solution of 3,5-bis(hydroxymethyl)phenol[14] (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; CH_2Cl_2:MeOH 50:1) to give 1-(4,4-dimethoxybutyloxy)-3,5-bis(hydroxymethyl)benzene as a colorless oil (7.6 g, 69%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.81 (s, 1 H), 6.71 (s, 1 H), 5.13 (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); ^{13}C 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 (3-nitrobenzyl 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-(4,4-dimethoxybutyloxy)-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 $CHCl_3$. The $CHCl_3$ extract was concentrated and subjected to column chromatography (silica gel; CH_2Cl_2) to give **14** as a colorless oil (4.0 g, 70%). ^{1}H 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{20}H_{26}NaO_5$ (M + Na$^+$) 369.1678, found 369.1637.

1-(4,4-Dimethoxybutyloxy)-3,5-bis(3-tributylstannyl-2-propynyloxymethyl)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*-Bu_3SnCl (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 Et_2O. The Et_2O 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. ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{44}H_{78}NaO_5{}^{118}Sn^{120}Sn$ (M + Na$^+$) 947.3785, found 947.3768.

1-(4,4-Dimethoxybutyloxy)-3,5-bis[3-(6-iodopyren-1-yl)-2-propynyloxymethyl]benzene (16). A morpholine (120 mL) suspension of **14** (1.1 g, 3.2 mmol), 1,6-diiodopyrene[35] (5.25 g, 11.6 mmol), $Pd(PPh_3)_4$ (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 $CHCl_3$. The $CHCl_3$ extract was concentrated and purified by repeated column chromatography (silica gel; CH_2Cl_2:MeOH 100:1) to give **16** as a solid (1.0 g, 32%). Mp 154−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (2-nitrophenyl octyl ether) m/z 998 (M$^+$, 100); ESI-HRMS m/z calcd for $C_{52}H_{40}I_2NaO_5$ (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 $Pd(PPh_3)_4$ (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 $CHCl_3$. The $CHCl_3$ extract was concentrated and subjected to column chromatography (silica gel; CH_2Cl_2:MeOH 50:1) to give **17** as a solid (0.23 g, 8%). Mp 169−171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 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 = 5.5 Hz, 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, $CDCl_3$) 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 $C_{72}H_{64}NaO_{10}$ (M + Na$^+$) 1111.4397, found 1111.4349.

Aldehydic Pyrenophane 18. To a $CHCl_3$ (5 mL) solution of **17** (50 mg, 0.046 mmol) was added aqueous 50% CF_3CO_2H (2.5 mL) dropwise at 0 °C, and the mixture was stirred at that temperature for 18 h. To the mixture was added aqueous K_2CO_3 at room temperature until no more CO_2 evolved. The reaction mixture was extracted with CH_2Cl_2, and the CH_2Cl_2 extract was concentrated and subjected to column chromatography (silica gel; CH_2Cl_2:MeOH 20:1) to give **18** (45 mg, 95%). Mp >240 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C 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-7,16-diazacyclooctadecane (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 CH_2Cl_2 (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 Et_2O (0.044 mL, 0.044 mmol), finely ground molecular sieves 4A (5 mg), and *n*-Bu_4NBH_3CN (6.2 mg, 0.022 mmol). The mixture was stirred at room temperature for 30 h and filtered. To the filtrate was added additional CH_2Cl_2, and the combined CH_2Cl_2 layer was washed with water, concentrated, and subjected to column chromatography (silica gel; CH_2Cl_2:MeOH:Et_3N 50:1:1) to give **19e** (5 mg, 27%). Mp 71−73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 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), 2.83−2.81 (m, 16 H), 2.61 (t, J = 7.1 Hz, 4 H), 1.84−1.68 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 *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 CH_2Cl_2 (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; ^{1}H NMR (300 MHz, CD_3OD) 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 K_2CO_3 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; CH_2Cl_2:MeOH:Et_3N 50:1:1), followed by reverse-phase HPLC (ODS column (Shinwa Chemical Industries, Ltd.); MeOH:Et_3N 100:0.3) to give **3** as a yellowish viscous oil (7.1 mg, 22%). ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 ^{1}H 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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