Molecular Recognition Abilities of a New Class of Water-Soluble Cyclophanes Capable of Encompassing a Neutral Cavity

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Received July 25, 1997

Abstract: We developed a new class of water-soluble cyclophanes, pyrenophanes, capable of encompassing a neutral cavity, in which the hydrophobic area is constructed by aligning two flat polynuclear aromatic rings parallel at an appropriate space that could interpose just one layer of aromatic plane. The height, depth, and width of the cavity in an open conformation of the pyrenophane are 0.46, 0.95, and 1.31 nm, respectively, i.e., the area of this cavity is so large that even porphirin compounds might be incorporated. In the fluorescence spectra, the pyrenophanes showed only excimer-emission, reflecting the existence of two proximal pyrene rings. Treatment of the pyrenophanes with anionic and cationic aromatic compounds revealed the formation of complexes in the UV and fluorescence spectra, suggesting that the binding affinities of the pyrenophanes for aromatic compounds were mainly governed by hydrophobic and/or π-stacking interactions. The macrocyclic structures of the pyrenophanes were found to be indispensable for the complexation.

Introduction

All of vital functions are based on molecular recognition in water at an initial process. To draw out chemical answers concerning the intermolecular interactions at a molecular level as seen in such processes, various artificial models have been developed.[1] Among them, cyclodextrins[2] and cyclophanes[3] are representative. Although naturally occurring cyclodextrins have been widely used as a building block of artificial models for enzymes and receptors because of their ready-made availability and well-defined cavity, the limitation for the synthetic versatilities of them may offset the advantages. On the other hand, a number of cyclophanes have been designed and synthesized in their own right, and most cyclophanes employ the recognition strategy of substrate-induced organization of the conformation, the so-called "induced-fit" mechanism.[4] Water solubility of the cyclophanes is often given by introducing positive charges near the cavity of the cyclophanes, so anionic substrates are preferentially accommodated into the cavity.[3,4] Thus, designing a new class of water-soluble cyclophanes possessing a well-defined neutral cavity may be a worthwhile subject for further construction of sophisticated artificial models.

In our successive model studies on molecular recognition,[5] our initial goal in this area described above is to create artificial receptors that recognize specific substrates via hydrogen bonds in water. With this in mind, we focused our attention on continuous stackings of nucleobase pairs seen in double-helical DNA, in which negatively charged phosphate is located on the periphery of the helix and the neutral hydrophobic areas are in the inside, so that specific hydrogen bondings between complementary nucleobases can be formed in water.[6] The hydrophobic areas of DNA are well-defined in shape and size but still have substantial flexibility, so plane aromatic compounds can intercalate into this area.[7] In this article, we present the synthesis and molecular recognition abilities of a new class of water-soluble cyclophanes, pyrenophanes, capable of encompassing a neutral cavity resembling the hydrophobic inside of DNA.

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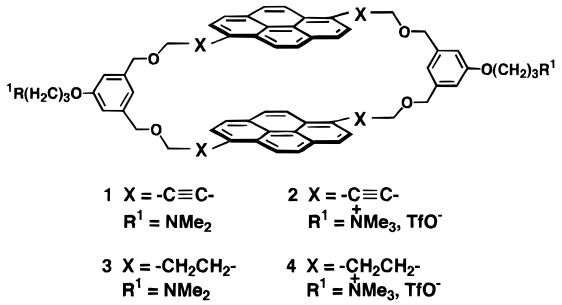

1 X = -C≡C- $R^1 = NMe_2$ **2** X = -C≡C- $R^1 = \overset{+}{N}Me_3, TfO^-$

3 X = $-CH_2CH_2-$ $R^1 = NMe_2$ **4** X = $-CH_2CH_2-$ $R^1 = \overset{+}{N}Me_3, TfO^-$

Figure 1. Candidates of water-soluble cyclophanes capable of encompassing a neutral cavity.

Molecular Design and Synthesis

As a starting point for the design of new cyclophanes, we thought that such DNA-like hydrophobic area would be constructed by aligning two flat polynuclear aromatic rings parallel at an appropriate space that could interpose just one layer of aromatic plane. Turning the idea into the water-soluble cyclophanes, accumulation of the following key-structural motifs is necessary: (i) moderately rigid three-dimensional hydrophobic frames, (ii) π-plane arrangement inducing changes of optical properties of the cyclophanes upon complexation with aromatic compounds for the detection, and (iii) hydrophilic parts making the pyrenophanes soluble in water.[8] Figure 1 showed candidates of such cyclophanes based on the considerations described above. The main characteristics of the candidates are the following: (1) sp and sp^2 carbons were mainly used for the basic skeleton to reduce the flexibility of the cyclophanes, (2) pyrenes were selected as a basic unit for hydrophobic walls, (3) the π-stacking force of pyrene rings which occupy the up and down faces of the cyclophane frame is expected to serve as a main intermolecular interaction, (4) *meta*-substituted benzenes perpendicular to the pyrenes regulate the height of the cavity exactly when planer aromatic guests are inserted, and (5) quaternary ammonium groups extending to the outside of the cyclophane frame will make the cyclophanes soluble in water and leave the cavity uncharged.

To realize the appropriateness of the molecular design of the new cyclophanes, pyrenophanes, CPK model examination and computer modeling were performed.[9] Geometry optimization of the pyrenophane **2** was carried with hydrophilic groups omitted from the pyrenophanes for simplification of the calculation. In an open conformation (Figure 2), the height of the cavity is ca. 0.46 nm (the distance between the π-plane centers of two pyrenes is 0.80 nm), so the pyrenophane can accommodate one layer of aromatic compounds (the thickness of a π-plane is 0.34 nm) in the cavity. The depth and width are 0.95 and 1.31 nm, respectively, i.e., the area of this cavity is so large that even porphirin compounds might be incorporated.[7,10] The pyrenophane, however, still has flexibility, so a number of closed (collapsed) conformations can exist, and some of the closed forms may be stable than the open form because hydrophobic forces will operate to keep the pyrene surfaces together.[11] This does not mean that the pyrenophane **2** cannot adopt a conformation capable of accepting an aromatic guest as illustrated in Figure 2. In the presence of an aromatic guest molecule, the loss in energy resulting from the parting of the pyrene surfaces may be compensated for by newly developed host−guest interactions.

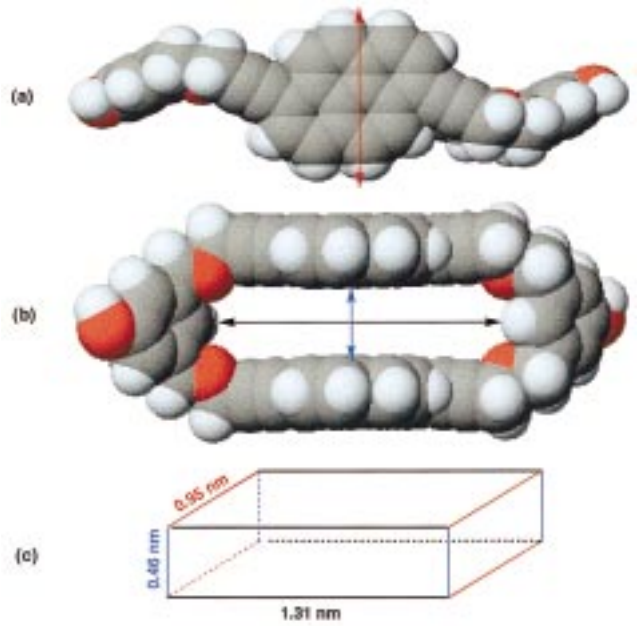

Figure 2. An open conformation for the pyrenophane **2**: (a) top view, (b) side view, and (c) the cavity size of the pyrenophanes.

The pyrenophane **1** was prepared from two components, the bis(alkynylstannane) derivative **13** and the bis(bromopyrene) derivative **14**, by macrocyclization of Stille-type coupling in the final step (Scheme 1).[12] Quaternarization at the external nitrogen of **1** produced the water-soluble pyrenophane **2**. Reduction of the acetylenic bonds of **1** followed by quaternarization yielded the saturated counterpart **4**. Both **13** and **14** were derived from **12** by stannylation and Sonogashira reaction[13] with 1,6-dibromopyrene, respectively. The key intermediate **12** was prepared from di-*n*-butyl 5-hydroxyisophthalate (**15**) in five steps by standard synthetic methods (Scheme 2). Other compounds were commercially available or easily synthesized. Pyrene derivatives **5**−**7** for comparison, aromatic guest compounds **8**−**10**, and nucleotides (**11**) were shown in Scheme 3.

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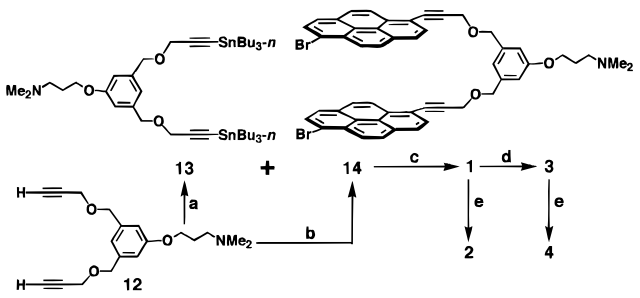
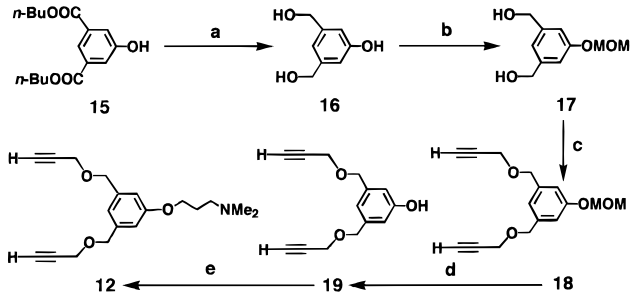
Scheme 1[a]



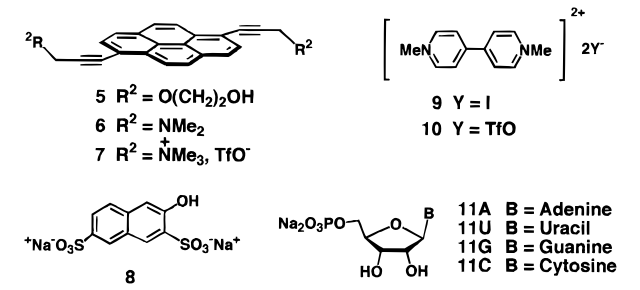
[a] (a) Tributyltin(IV) chloride, *n*-BuLi, THF; (b) 1,6-dibromopyrene, $PdCl_2(PPh_3)_2$, CuI, morpholine; (c) $PdCl_2(PPh_3)_2$, toluene; (d) H_2 (1 atm), PtO_2, THF; (e) methyl trifluoromethanesulfonate, CH_2Cl_2.

Scheme 2[a]



[a] (a) $LiAlH_4$, THF; (b) $ClCH_2OCH_3$, NaH, DMF; (c) propargyl bromide, NaH, DMF, THF; (d) concentrated HCl, MeOH; (e) MsO-$(CH_2)_3NMe_2$·HCl (**20**), NaH, DMF.

Scheme 3



Results and Discussion

^{1}H NMR Chemical Shifts of the Pyrenophanes. The resonances were observed at 7.51−8.21 ppm for the pyrene protons of **1** in $CDCl_3$ and at 8.09−8.55 ppm for the nonmacrocyclic analogue **5** (Figure 3). The upfield shifts for the pyrene protons of **1** were due to the proximity of the two pyrene rings. The shifts were lower than that predicted in the case where the complete stacking of the two pyrene rings occurred such as in **21** and **22** developed by Misumi (7.20−7.47 and 7.22−7.51 ppm in $CDCl_3$, respectively).[14] These results indicated that the pyrene rings of **1** are close to each other but do not come into contact, so there will be some cavity between the two pyrene walls, and/or that in structures of **1** and **2** the opposite pyrene moiety is tilted.

Solvent polarity affected the ^{1}H NMR chemical shifts for pyrene protons of the pyrenophanes (Figure 3). Thus, the pyrene protons of **2** appeared at 7.53−8.03 and 7.28−7.85 ppm in CD_3OD and CD_3OD-D_2O−ethylene glycol-d_6 (4:3:1) mixed solvent, respectively. The increasing upfield shifts of the pyrene protons as a function of solvent polarity reflect that the hydrophobic interaction between the two pyrene rings became stronger, so that the pyrene−pyrene distance shortened.

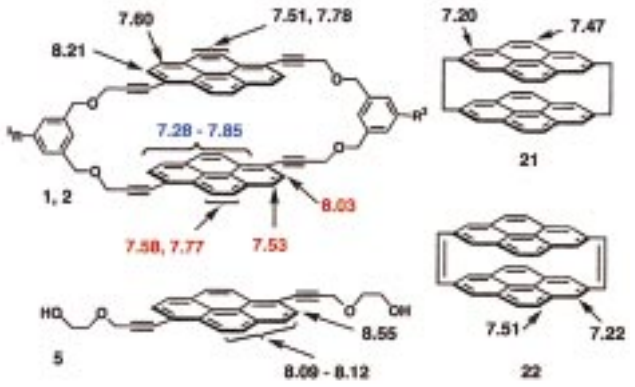


Figure 3. ^{1}H NMR chemical shifts (ppm) for pyrene protons in $CDCl_3$ (**1**, **5**, **21**, and **22**; black number), CD_3OD (**2**; red number), and CD_3OD-D_2O−ethylene glycol-d_6 (4:3:1) (**2**; blue number).

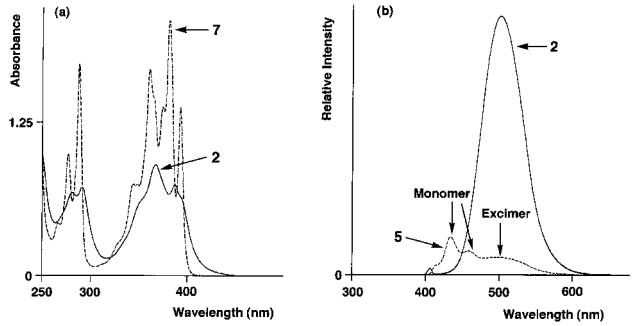


Figure 4. (a) Electronic absorption spectra of **2** (2.0×10^{-5} M) and **7** (4.0×10^{-5} M) in water−ethylene glycol (3:1). (b) Fluorescence emission spectra of **2** (8.2×10^{-5} M) and **5** (4.3×10^{-3} M) in MeOH. The excitation wavelength was 403 nm.

UV and Fluorescence Spectra of the Pyrenophanes. The optical properties of the pyrenophanes are expected to be different from those of the parent pyrene, because of the presence of two proximal pyrene rings.[14,15] The electronic absorption spectrum of pyrenophane **2** showed a small red shift of the longest wavelength bands and significant hypochromism, compared with that of the referential monomer **7** in H_2O−ethylene glycol (3:1) (Figure 4a). These phenomena resemble the absorbance decrease of nucleobases during the change from single-stranded to double-helical DNA that results from the stacking of the aromatic bases.

Fluorescence spectra were much affected by their structures (Figure 4b). Thus, the fluorescence emission spectrum of the pyrenophane **2** in CH_3OH ($\lambda_{max} = 500$ nm) showed a red shift compared with that of the reference monomer **5** ($\lambda_{max} = 433$, 460 nm). The wavelength of the emission maximum of **2** was independent of its concentration, while that of **5** revealed dependence on the concentration: at $\geq 4.0 \times 10^{-4}$ M, a new emission ($\lambda_{max} = 500$ nm) that was thought to be for an excimer appeared. These results indicated that the pyrenophane **2** showed only excimer emission, owing to the proximity of the two pyrene rings.

Fluorescence lifetimes for **1** and **5** were measured to reinforce the above conclusions. The fluorescence decay curve of **1** was

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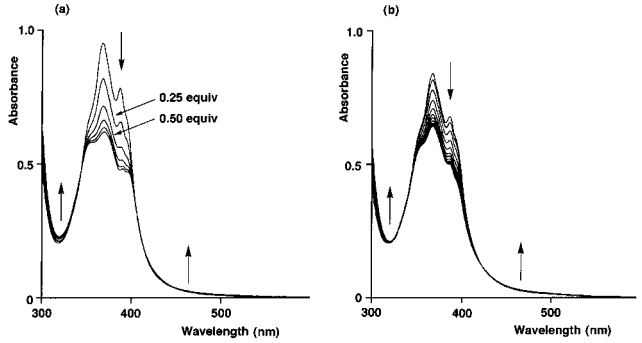

Figure 5. Electronic absorption spectra of **2** (2.0×10^{-5} M) in water−ethylene glycol mixed solvent (3:1) in the presence of (a) **8** (0.25−1.25 equiv) and (b) **9** (2.0 equiv). In part b, the spectra were recorded at 10 min intervals.

due to a one-component system, and that of **5** to a binary system. In CH_2Cl_2, the lifetime for **1** (τ_1) was 19.3 ns and those for **5** (τ_1 and τ_2) were 3.77 and 24.5 ns, respectively, i.e., the pyrenophane **1** showed only one emission that is attributed to pyrene-excimer fluorescence.[16] This behavior is irresponsible for the presence of the acetylene linkages. Indeed, in the case of the reduced pyrenophane **3**, similar results ($\lambda_{max} = 480$ nm, $\tau_1 = 35.3$ ns) were obtained in CH_2Cl_2. According to the above points, two pyrene rings in **1**−**4** were located in the positions giving only excimer emissions. These results will be receiving attention from not only molecular recognition but also investigation of transannular π-electron interaction between spatially arranged chromophores.[14,17,18]

Spectroscopic Detection of the Complexation. Under the conditions for detecting the complexation between the pyrenophanes and various aromatic compounds, the solubility of **2** and **4** is poor in pure water, so that the water−ethylene glycol (3:1) mixed solvent was used.[8] Aromatic compounds of **8**−**11** were chosen as a guest molecule. The aromatic guests thus selected showed no absorption bands above 350 nm in the mixed solvent, so the changes for absorption or fluorescence spectra of the pyrenophanes in such a region can be used directly to obtain the information for the guest binding. Intermolecular stacking (aggregation) of **2** can be ruled out since **2** obeyed the Lambert−Beer law at $\leq 8.2 \times 10^{-5}$ M, so that all binding assays were carried out below that concentration.

The absorption spectra of **2** changed upon the addition of various aromatic guests in the solvent. When the anionic guest **8** was added incrementally to the solution of **2**, the decrease of the absorbance at 370 and 390 nm of **2** was observed with several isosbestic points (Figure 5a). From these changes, 1:1 stoichiometry was confirmed, and the association constant (K_a) was estimated to be at least 1.0×10^6 M^{-1}.[19] It is noteworthy that the even cationic aromatic guest **9** displayed $K_a \geq 5.0 \times 10^5$ M^{-1} for the cationic pyrenophane **2**, suggesting that the binding affinities of the pyrenophanes for aromatic compounds were mainly governed by hydrophobic and/or π-stacking not by electrostatic interactions because of the neutral cavity. Unique and time-dependent complexation behavior was observed for **2** and **9**. When a solution of **9** (4.0×10^{-5} M) was added into a solution of **2** (2.0×10^{-5} M), the decrease of the absorbance of **2** was observed. Further decrease of the absorbance then gradually occurred over the course of time, and after about 2 h, equilibrium was reached (Figure 5b). Such a slow interaction might result from the absence of the long-reaching electrostatic interaction that will be initially important for the approach of an anionic guest molecule to the cationic pyrenophane **2**, and from the difficulty of insertion of nonplaner **9** into the narrow hydrophobic cavity of **2**. The counteranion of **9** is not important. Indeed, similar slow changes for spectra of **2** were obtained in the case of **10**, but never with **8** and **11**. The absorption spectra of **7** and the corresponding acyclic analogue of **2** showed only negligible changes upon addition of any of the aromatic compounds under identical experimental conditions. As expected, the change for the absorption spectra of **2** in CH_3OH was too small to obtain any information for the complexation.

Table 1. Association Constants Determined for the Binding of **2** to the Guests in Water−Ethylene Glycol (3:1) at 25 °C

guest	K_a (M^{-1})	guest	K_a (M^{-1})
8	$\geq 1.0 \times 10^6$	**11U**	$(1.8 \pm 0.1) \times 10^4$
9	$\geq 5.0 \times 10^5$	**11G**	$(3.5 \pm 0.5) \times 10^4$
10	$\geq 5.0 \times 10^5$	**11C**	$(9.0 \pm 0.5) \times 10^3$
11A	$(1.2 \pm 0.1) \times 10^4$		

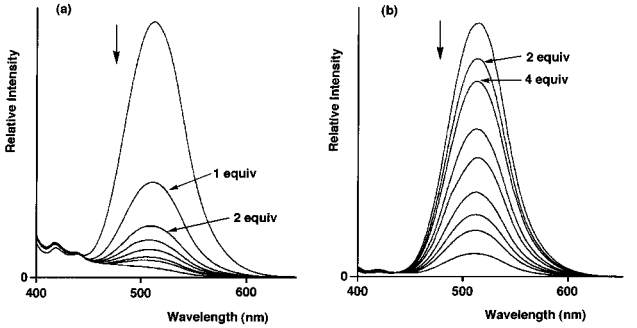

Figure 6. Fluorescence quenching of **2** in the presence of (a) **8** and (b) **9** in water−ethylene glycol mixed solvent (3:1): (a) [**2**] = 1.0×10^{-6} M, (b) [**2**] = 1.0×10^{-5} M. The excitation wavelength was 380 nm.

The complexation for nucleobases is particularly interesting, because the further introduction of nucleobase recognition motif in the cavity of the pyrenophane might be expected to produce artificial nucleobase receptors in water. The decrease of the absorbance **2** was observed by the addition of various nucleotides, AMP (**11A**), UMP (**11U**), GMP (**11G**), and CMP (**11C**). The association constants were summarized in Table 1, in which different values for each nucleotide were obtained, and selective binding of GMP was shown. These results also indicated the importance of the π-stacking interactions.

Fluorescence spectra of the pyrenophane **2** were influenced by the presence of aromatic compounds (Figure 6). In the mixed solvent, additions of 1 and 2 equiv of **8** induced a 60% and an 80% quenching of the fluorescence emission of **2** (1.0×10^{-6} M).[20] This type of quenching was also observed for **9**. Similar

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phenomena were obtained for nucleotides. In these cases, only negligible or no changes of the fluorescence emission of the acyclic analogue **7** were observed under identical conditions in agreement with the UV spectra. The UV and fluorescence experiments revealed the importance of the macrocyclic structure of the pyrenophane for the binding to aromatic compounds.

^{1}H NMR spectroscopy was used to try to detect the complexation. Unfortunately, in the D_2O−ethylene glycol-d_6 (3:1) mixed solvent, ^{1}H NMR signals of **2** (2.5×10^{-3} M) were considerably broadened up to 70 °C, indicating that **2** exists as an aggregate at such high concentration in contrast to the UV experiments (vide supra). Furthermore, precipitation occurred upon addition of the aromatic compounds. The precipitate was analyzed to be 1:1 complex by ^{1}H NMR after dissolving it in DMSO-d_6.

Conclusion

We developed novel water-soluble cyclophanes, pyrenophanes. The well-defined neutral hydrophobic area of the pyrenophanes was constructed by mimicking the π-plane arrangement seen in double-helical DNA. The fluorescence emission spectra of the pyrenophanes gave only excimer-emission in any concentration. The two pyrenes of the pyrenophanes were found to be situated in positions where electronic perturbations could occur. Complexation of the pyrenophanes was observed with cationic aromatic guests as well as anionic ones. The driving force for the binding was found to be governed by hydrophobic and/or aromatic π-stacking interactions. We are currently modifying the hydrophilic site of the pyrenophanes in order to dissolve it in pure water. In the future, the introduction of the nucleobase recognition site in the cavity of the pyrenophane might be expected to produce artificial nucleobese receptors in water.

Experimental Section

Instrumentation. ^{1}H and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz, respectively, unless otherwise noted. EI mass spectra were measured at 70 eV. For FAB mass experiments, Xe was used as the atom beam accelerated to 8 keV. Melting points are uncorrected.

Materials. The starting materials were all commercially available, and 1,6-dibromopyrene[21] and the cationic guest **9**[22] were prepared according to literature procedures.

Computational Method. Molecular modeling was performed with Chem 3D. Geometry optimization for the pyrenophane was carried out by using the PM3 level approximation on MOPAC 93 with EF PRECISE key words.[9] Molecular dynamics calculation was performed on Chem 3D by using the MM2 force field with a time step of 2×10^{-15} and a target temperature of 300 K.

Fluorescence Spectra. The fluorescence spectra of the pyrenophanes were obtained below the concentration without quenching of the emission: [**2**] $\leq 8.2 \times 10^{-5}$ M and [**5**] $= 4.3 \times 10^{-3}$ M.

Measurement of Fluorescence Lifetime. Fluorescence lifetimes were measured by time correlation, a single-photon counting methodology using a nanosecond fluorometer. The excitation wavelengths were excitation maximum of the pyrenophanes and the acyclic analogues (370−400 nm). Emissions were detected in the range 460−520 nm. These measurements were performed at concentrations of ca. 10^{-5}−10^{-6} M in open air. Fluorescence decay profiles were analyzed on the basis of the following equation: $I_f(t) = A_1\exp(-t/\tau_1) + A_2\exp(-t/\tau_2)$.

Methods for the Evaluation of Stoichiometry and Association Constants. These measurements were performed by UV titration at 25 °C. The absorbances of pyrenophane **2** (370 nm) were measured as a function of the concentration of aromatic compounds (0.25−2.0 equiv). The concentration of **2** was 2.0×10^{-5} M. The stoichiometry and association constants were estimated by using an iterative least-squares curve-fitting to the absorbance changes at 370−390 nm with weighting of data points according to the error analysis of Deranleau.[19]

Di-*n*-butyl 5-Hydroxyisophthalate (15). An *n*-BuOH (250 mL) suspension of 5-hydroxyisophthalic acid (25.0 g, 137 mmol) and concentrated H_2SO_4 (a few drops) was refluxed with a Dean−Stark apparatus for 24 h. To the reaction mixture was added a saturated $NaHCO_3$ aqueous solution until no more CO_2 evolved. After removal of the solvent, the residue was recrystallized from hexane to give **15**: yield 99% (40.0 g); mp 58−59 °C; IR (KBr) 3438, 2956, 1722, 1612, 1463, 1396, 1295, 1236, 1106 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 6.3 Hz, 6 H), 1.47 (m, 4H), 1.76 (m, 4H), 4.35 (t, J = 6.7 Hz, 4 H), 7.32 (br s, 1 H), 7.84 (d, J = 1.2 Hz, 2 H), 8.22 (t, J = 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.66, 19.19, 30.58, 65.57, 121.00, 122.43, 131.89, 156.76, 166.40; MS *m*/*e* (rel intensity) 294 (M^+, 5.4%).

3,5-Bis(hydroxymethyl)phenol (16). To a THF (300 mL) suspension of $LiAlH_4$ (6.85 g, 180 mmol) was added a THF (100 mL) solution of **15** (12.5 g, 42.5 mmol) dropwise at 0 °C. The reaction mixture was refluxed for 12 h. H_2SO_4 aqueous solution (10%) was carefully added dropwise at 0 °C to the mixture until no more hydrogen evolved. The reaction mixture was filtered, and the filtrate was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2:MeOH = 10:1) to give **16**: yield 85% (5.58 g); mp 71−73 °C; IR (KBr) 3110, 2947, 1601, 1529, 1456, 1309, 1225, 1159, 1039 cm^{-1}; ^{1}H NMR (CD_3OD) δ 4.57 (s, 4 H), 6.75 (s, 2 H), 6.85 (s, 1H); ^{13}C NMR (CD_3OD) δ 65.11, 113.65, 117.59, 144.31, 158.68; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 154 (M^+, 66%). Anal. Calcd for $C_8H_{10}O_3 \cdot {}^1/_8H_2O$: C, 61.43; H, 6.61. Found: C, 61.46; H, 6.61.

1,3-Bis(hydroxymethyl)-5-(methoxymethoxy)benzene (17). To a DMF (75 mL) suspension of NaH (1.40 g, 35.0 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was added a DMF (100 mL) solution of **16** (5.22 g, 34.0 mmol) dropwise at 0 °C. After the solution was stirred 1 h at that temperature, $ClCH_2OCH_3$ (2.86 g, 35.5 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for an additional 12 h. After removal of the solvent, CH_2Cl_2 was added to the residue. The mixture was stirred for 1 h and filtered. The filtrate was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2:MeOH = 25:1) to give **17**: yield 85% (5.70 g); mp 76−77 °C; IR (KBr) 3257, 3184, 2929, 1599, 1456, 1290, 1155, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.39 (s, 3 H), 4.29 (br s, 2 H), 4.45 (d, J = 3.1 Hz, 4 H), 5.07 (s, 2 H), 6.82 (s, 2 H), 6.85 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 55.80, 64.19, 94.07, 113.42, 118.63, 142.75, 157.04; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 198 (M^+, 44%). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.97; H, 7.33.

1,3-Bis(propargyloxymethyl)-5-(methoxymethoxy)benzene (18). To a THF (15 mL) suspension of NaH (1.10 g, 27.5 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was added a DMF (50 mL) solution of **17** (2.28 g, 11.5 mmol) dropwise at 0 °C. After the solution was stirred 1 h at that temperature, propargyl bromide (5.47 g, 46.0 mmol) was added dropwise at −78 °C. The reaction mixture was warmed to room temperature gradually and stirred at that temperature for an additional 12 h. After removal of the solvent, the residue was dissolved in water and extracted with Et_2O. The Et_2O extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2) to give **18**: yield 79% (2.49 g); oil; IR (KBr) 3290, 2902, 2360, 1599, 1458, 1352, 1149, 1084 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.48 (t, J = 2.4 Hz, 2 H), 3.47 (s, 3 H), 4.18 (d, J = 2.4 Hz, 4 H), 4.57 (s, 4 H), 5.18 (s, 2 H), 6.98 (s, 2 H), 7.00 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 56.01, 57.24, 71.21, 74.75, 79.54, 94.35, 115.18, 120.90, 139.13, 157.52; MS *m*/*e* (rel intensity) 274 (M^+, 4%).

3,5-Bis(propargyloxymethyl)phenol (19). A MeOH (12 mL) solution of **18** (2.22 g, 8.12 mmol) containing a small amount of concentrated HCl aqueous solution (a few drops) was stirred at room temperature for 1 day. After removal of the solvent, the residue was dissolved in water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2:AcOEt = 20:1) to give **19**: yield 95% (1.80 g); oil; IR (KBr) 3290, 2858, 2117, 1603, 1458, 1302, 1157, 1082 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.50 (t, J = 2.4 Hz, 2 H), 4.16 (d, J = 2.4 Hz, 4 H), 4.54 (s, 2 H), 6.76 (br s, 2 H),

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6.87 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 57.00, 71.05, 75.03, 79.31, 114.65, 119.60, 138.79, 156.23; MS *m*/*e* (rel intensity) 230 (M^+, 7%).

3-(*N*,*N*′-Dimethylamino)propyl Methanesulfonate Hydrochloride (20). To a CH_2Cl_2 (100 mL) solution of 3-(*N*,*N*′-dimethylamino)-1-propanol (5.00 g, 48.5 mmol) was added methanesulfonyl chloride (13.9 g, 120 mmol) dropwise at 0 °C. After the solution was stirred 6 h at room temperature, the resulting precipitate was filtered to afford **20**: yield 100% (10.6 g); IR (KBr) 3585, 2921, 2670, 2474, 2360, 1481, 1336, 1267, 1174, 1014 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.12 (m, 2 H), 2.73 (d, J = 4.9 Hz, 6 H), 3.10 (m, 2 H), 3.22 (s, 3 H), 4.30 (t, J = 6.1 Hz, 2 H), 10.92 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 23.89, 36.87, 42.15, 53.26, 67.82; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 182 (M^+ − Cl, 100%).

1,3-Bis(propargyloxymethyl)-5-[3-(*N*,*N*′-dimethylamino)propoxy]-benzene (12). To a DMF (25 mL) suspension of NaH (0.63 g, 15.7 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was added a DMF (10 mL) solution of **19** (1.76 g, 7.50 mmol) dropwise at 0 °C. After the solution was stirred 1 h at that temperature, **20** (1.71 g, 7.85 mmol) was added by portions at 0 °C. The reaction mixture was warmed to room temperature gradually and stirred at that temperature for an additional 12 h. After removal of the solvent, the residue was dissolved in water and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2:MeOH = 8:1) to give **12**: yield 90% (2.13 g); oil; IR (KBr) 3291, 2945, 2860, 2767, 1599, 1458, 1167, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.95 (m, 2H), 2.26 (s, 6 H), 2.46 (t, J = 7.9 Hz, 2 H), 2.50 (t, J = 2.4 Hz, 2 H), 4.04 (t, J = 8.5 Hz, 2 H), 4.17 (d, J = 2.4 Hz, 4 H), 4.56 (s, 4 H), 6.85 (s, 2 H), 6.91 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.26, 45.25, 56.21, 57.00, 66.03, 71.13, 74.06, 79.44, 113.34, 119.56, 138.83, 159.20; MS *m*/*e* (rel intensity) 316 (MH^+, 100%).

Bis(alkynylstannane) Derivative 13. To a THF (25 mL) solution of **12** (1.13 g, 3.58 mmol) was added a *n*-hexane solution of *n*-BuLi (7.15 mmol) dropwise at 0 °C. After the solution was stirred 1 h at that temperature, tributyltin(IV) chloride (2.46 g, 7.54 mmol) was added. The reaction mixture was warmed to room temperature gradually and stirred at that temperature for an additional 12 h. After removal of the solvent, the residue was dissolved in saturated potassium fluoride aqueous solution and extracted with Et_2O. The Et_2O extract was filtered and evaporated to give crude **13**. This compound was used in the next reaction without further purification: yield 100% (3.20 g); oil; IR (KBr) 2956, 2927, 2854, 1598, 1521, 1457, 1375, 1294, 1164, 1082 cm^{-1};^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.3 Hz 18 H), 1.01 (m, 12 H), 1.34 (m, 12 H), 1.94 (m, 2 H), 2.25 (s, 6 H), 2.44 (t, J = 6.7 Hz 2 H), 4.01 (t, J = 6.7 Hz 2 H), 4.18 (t, J = 4.3 Hz 4 H), 4.57 (s, 4 H), 6.85 (s, 2 H), 6.90 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.93, 13.55, 26.86, 27.54, 28.76, 45.41, 56.33, 58.05, 66.04, 70.79, 89.87, 105.59, 113.29, 119.60, 139.23, 159.24; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 892 (MH^+, 100%).

Bis(bromopyrene) Derivative 14. A morpholine (270 mL) suspension of 1,6-dibromopyrene[21] (4.39 g, 12.1 mmol), $(PPh_3)_2PdCl_2$ (143 mg, 0.20 mmol), and CuI (18.9 mg, 0.10 mmol) was stirred at 80 °C until the reaction mixture became homogeneous. To the solution was added **12** (0.96 g, 3.06 mmol). The reaction mixture was stirred at that temperature for an additional 12 h. After removal of the solvent, the residue was dissolved in water and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and chromatographed (silica gel; eluent, $CHCl_3$: EtOH = 8:1) to give **14**: yield 40% (1.07 g); IR (KBr) 3291, 2945, 2860, 2767, 1599, 1458, 1167, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.98 (m, 2 H), 2.25 (s, 6 H), 2.46 (t, J = 6.7 Hz, 2 H), 4.08 (t, J = 6.1 Hz, 2 H), 4.64 (s, 4 H), 4.83 (s, 4 H), 7.01 (s, 2 H), 7.22 (s, 1 H), 7.77 (d, J = 8.5 Hz, 2 H), 7.84 (d, J = 9.2 Hz, 2 H), 7.87 (d, J = 8.5 Hz, 2 H), 7.90 (d, J = 7.9 Hz, 2 H), 8.00 (d, J = 7.9 Hz, 2 H), 8.06 (d, J = 7.9 Hz, 2 H), 8.22 (d, J = 9.2 Hz, 2 H), 8.36 (d, J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.42, 45.35, 56.35, 58.25, 66.27, 71.61, 85.50, 91.06, 113.82, 117.70, 120.31, 120.45, 123.40, 124.72, 125.04, 125.42, 125.87, 126.52, 127.83, 128.44, 129.41, 130.15, 130.21, 130.86, 131.83, 139.31, 159.61; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 877 (M^+ + 2, 42%).

Pyrenophane 1. To a toluene (450 mL) solution of **14** (938 mg, 1.07 mmol) and $(PPh_3)_2PdCl_2$ (50 mg, 0.0712 mmol) was added a toluene (50 mL) solution of **13** (1054 mg, 1.18 mmol) at 50 °C. The reaction mixture was stirred at that temperature for 2 days. After removal of the solvent, the residue was dissolved in water and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2:Et_3N = 40:1). The eluent was corrected and evaporated. The residue was washed with MeOH to give **1**: yield 8% (88 mg); IR (KBr) 3170, 2854, 2684, 1743, 1596, 1456, 1351, 1297, 1166, 1062 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (m, 4 H), 2.30 (s, 12 H), 4.12 (t, J = 6.7 Hz, 4 H), 4.62 (s, 8 H), 4.93 (s, 8 H), 7.05 (s, 4 H), 7.44 (s, 2 H), 7.51 (d, J = 7.9 Hz, 4 H), 7.60 (d, J = 9.2 Hz, 4 H), 7.78 (d, J = 7.9 Hz, 4 H), 8.21 (d, J = 9.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 45.58, 56.47, 57.48, 66.44, 71.03, 85.82, 90.61, 114.35, 117.16, 124.78, 125.54, 127.61, 129.55, 130.13, 130.50, 131.65, 134.64, 138.95, 157.14; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 1028 (MH^+, 54%).

Pyrenophane 2. To a CH_2Cl_2 (2 mL) solution of **1** (41 mg, 0.040 mmol) was added methyl trifluoromethanesulfonate (66 mg, 0.40 mmol) dropwise at 0 °C. The reaction mixture was stirred at that temperature for 1 h. After removal of the solvent at 0 °C, the residue was washed sequentially with hexane, Et_2O, and CH_2Cl_2 to afford **2**: yield 92% (50 mg); IR (KBr) 2854, 1601, 1487, 1259, 1165, 1029 cm^{-1}; ^{1}H NMR (CD_3OD) δ 2.35 (br m, 4 H), 3.23 (s, 18 H), 3.65 (m, 4 H), 4.27 (t, J = 5.5 Hz, 4 H), 4.69 (s, 8 H), 5.01 (s, 8 H), 7.16 (s, 4 H), 7.53 (d, J = 9.2 Hz, 4 H), 7.58 (d, J = 7.9 Hz, 4 H), 7.62 (s, 2 H), 7.77 (d, J = 7.9 Hz, 2 H), 8.03 (d, J = 9.2 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 26.34, 30.02, 53.49, 53.71, 58.42, 72.06, 77.91, 86.58, 91.96, 115.25, 118.28, 123.92, 125.96, 126.22, 128.59, 130.47, 131.66, 132.53, 140.88, 144.60, 151.31; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 1205 (M^+ − OTf, 100%).

Pyrenophane 3. A THF (5 mL) suspension of **1** (26 mg, 0.025 mmol) and PtO_2 (3 mg) was stirred at room temperature for 12 h under hydrogen at a pressure of 1 atm. The reaction mixture was filtered through Celite. The filtrate was evaporated and washed with MeOH to give **3:** yield 95% (25 mg); IR (KBr) 2940, 2864, 1597, 1456, 1362, 1294, 1103, 1063 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.09 (m, 12 H), 2.37 (s, 12 H), 2.61 (t, J = 7.3 Hz, 4 H), 3.36 (t, J = 7.9 Hz, 8 H), 3.59 (t, J = 6.1 Hz, 8 H), 4.08 (t, J = 6.1 Hz, 4 H), 4.56 (s, 8 H), 6.84 (s, 4 H), 7.29 (s, 2 H), 7.52−7.67 (m, 12 H), 8.01 (d, J = 9.2 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 27.42, 30.17, 31.87, 45.35, 53.86, 56.43, 69.61, 72.84, 112.87, 119.02, 122.25, 124.25, 125.04, 126.88, 127.06, 128.72, 129.28, 135.77, 140.58, 159.14; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 1043 (MH^+, 100%).

Pyrenophane 4. This compound was synthesized from **3** (35 mg, 0.034 mmol) in a manner similar to that described for **2**. **4**: yield 97% (45 mg); IR (KBr) 2939, 2862, 1601, 1487, 1259, 1163, 1032 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.08 (m, 8 H), 2.24 (m, 4 H), 2.84 (m, 4 H), 3.11(s, 18 H), 3.52 (m, 12 H), 4.12 (t, J = 6.1 Hz, 8 H), 4.55 (s, 8 H), 6.87 (s, 4 H), 7.26 (s, 2 H), 7.58 (d, J = 7.9 Hz, 12 H), 7.68 (d, J = 7.9 Hz, 12 H), 7.74 (d, J = 9.2 Hz, 4 H), 8.05 (d, J = 9.2 Hz, 4 H); ^{13}C NMR (DMSO-d_6) δ 22.81, 29.61, 31.80, 52.47, 63.23, 64.93, 69.14, 71.87, 112.61, 119.57, 122.14, 124.49, 127.13, 128.26, 128.88, 136.08, 140.77, 158.29; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 1221 (M^+ − OTf, 100%).

Acyclic Analogue 5. The THP-protected intermediate of **5** was derived from 1,6-dibromopyrene[21] (180 mg, 0.50 mmol) and 2-(1,4-dioxahept-6-ynyl)tetrahydropyran[23] (230 mg, 1.25 mmol) in a manner similar to that described for **14**. Deprotection of the intermediate was carried out in a manner similar to that described for **19** to give **5**: yield (from 1,6-dibromopyrene in two steps) 35% (70 mg); IR (KBr) 3750, 3290, 2888, 1706, 1598, 1436, 1351, 1261, 1112, 1074, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 8 H), 4.68 (s, 4 H), 8.11 (m, 6 H), 8.55 (d, J = 9.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 59.62, 61.95, 71.43, 85.44, 90.84, 117.70, 120.45, 125.12, 126.23, 128.23, 130.27, 131.27, 132.17; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 398 (M^+, 13%).

Acyclic Analogue 6. This compound was synthesized from 1,6-dibromopyrene[21] (500 mg, 1.39 mmol) and 1-(*N*,*N*′-dimethylamino)-2-propyne (289 mg, 3.47 mmol) in a manner similar to that described for **14**. **6**: yield 36% (183 mg); mp 152−153 °C; IR (KBr) 2939, 2863, 1603, 1462, 1321, 1157, 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 12

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H), 3.73 (s, 4 H), 8.10−8.13 (m, 6 H), 8.60 (d, $J = 9.2$ Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 44.48, 49.07, 84.23, 90.73, 118.43, 124.11, 124.94, 126.13, 129.09, 128.01, 131.09, 130.15, 130.92, 132.01; MS *m*/*e* (rel intensity) 365 (MH^+, 48%).

Acyclic Analogue 7. This compound was synthesized from **6** (94 mg, 0.26 mmol) in a manner similar to that described for **2**. **7**: yield 98% (174 mg); mp 263−265 °C; IR (KBr) 2976, 1502, 1431, 1201, 1140, 893, 600 cm^{-1}; ^{1}H NMR (D_2O) δ 3.45 (s, 18 H), 4.79 (s, 4 H), 8.06 (d, $J = 9.8$ Hz, 2 H), 8.15−8.17 (m, 4 H), 8.29 (d, $J = 9.2$ Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 52.54, 56.46, 84.18, 88.90, 115.95, 123.02, 126.02, 129.09, 131.09, 131.43, 131.76; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 543 ($M^+ - OTf$, 100%).

Methyl Viologen 10. To a CH_2Cl_2 (2 mL) solution of 4,4′-bipyridyl (100 mg, 0.64 mmol) was added methyl trifluoromethanesulfonate (630 mg, 3.84 mmol) dropwise at 0 °C. The reaction mixture was stirred at that temperature for 1 h. After removal of the solvent at 0 °C, the residue was washed sequentially with hexane, Et_2O, and CH_2Cl_2 to afford **10**: yield 97% (300 mg); IR (KBr) 3112, 3066, 1648, 1573, 1515, 1450, 1276, 1141, 1031 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.45 (s, 6 H), 8.75 (d, $J = 7.3$ Hz, 4 H), 9.26 (d, $J = 6.7$ Hz, 4 H); ^{13}C NMR (DMSO-d_6) δ 48.23, 118.48, 123.23, 126.32, 146.86, 148.54; FABMS (in 3-nitrobenzyl alcohol) *m*/*e* (rel intensity) 335 ($M^+ - OTf$, 100%).

Acknowledgment. We are grateful to Professor Kazuhiko Mizuno and Yohtaro Inoue (Osaka Prefecture University) for measurement of fluorescence lifetime. The preliminary work in this paper was supported by Sumitomo Foundation.

JA9725256