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Synthesis of water-soluble triazinophanes and evaluation of their molecular recognition properties

Shuhei Kusano,^{*[a]} Sae Konishi,^[a] Ryuta Ishikawa,^[a] Norihiro Sato,^[b] Satoshi Kawata,^[a] Fumi Nagatsugi,^[b] and Osamu Hayashida^{*[a]}

Abstract: Molecular recognition properties of water-soluble triazinophane **1a-c**, derivatized through the straightforward S_NAr reaction of common intermediate **5**, were explored in aqueous media. Fluorescence titration of **1a-c** using mono cationic aromatic hydrocarbon **G1** and **G2** as guests revealed that **1** prefers to form a host-guest complex with pyrene derivative **G2** rather than anthracene derivative **G1**. Complex formation between the derivatives of **1** and **G2** were in a 1:1 equimolar ratio with binding constants of $\sim 8 \times 10^3$ (M^{-1}), regardless of the substitution groups on the triazine rings. Additionally, we found that the molecular recognition of **1** was successfully fine-tuned through post-modification of the triazine rings. When dicationic anthracence **G3** was used as a guest, only **1b** formed a host-guest complex ($K_a = 5.5 \times 10^3$ M^{-1}).

Introduction

The molecular recognition properties of macrocyclic hosts provide an opportunity for their application in the fields of molecular delivery^[1] and separation,^[2] chemosensing of biologically related compounds,^[3] and construction of higher-ordered molecular architectures.^[4] In addition, molecular recognition contribute developing the field of “Molecular machine”, which won the Novel Prize in Chemistry 2016.^[5] Accordingly, the development of novel macrocyclic hosts in supramolecular chemistry is a fundamental task for creating advanced molecular systems. For this purpose, many kinds of macrocyclic hosts including cyclodextrin,^[6] calixarene,^[7] cucurbituril,^[8] pillararene,^[9] and cyclophane^[10] derivatives have been developed in past decades. Among them, water-soluble hosts are undoubtedly recognized as the most reliable and practical candidates for the above-mentioned applications.

Recently, much effort has been devoted for the development of triazine-based hosts such as heterocalix[2]arene[2]triazine^[11a] because of their unique host-functions.^[11] Triazine-based hosts are capable of capturing broad scope of guest molecules based on the nature of triazine ring. The electron deficient nature of the triazine ring is applicable for anion sensing, such as fluoride and chloride ions, through anion- π interactions.^[12] The coordinating and hydrogen bond forming properties of the nitrogen atom in the triazine ring are available

for metal ion (Cu^{2+})^[13] and carbohydrate recognition, respectively.^[14] As another characteristic feature of triazine-based hosts, they can be synthesized at low cost, in short synthetic steps, and in good yields from cyanuric chloride through the conventional S_NAr reaction with versatile diamines and diols.^[15] This advantage allows us to concisely design and construct various sizes and shapes of triazine-based hosts. Furthermore, triazine-based hosts can be easily post-functionalized through S_NAr or metal-catalyzed cross-coupling reactions on the triazine ring. Although diverse skeletal triazine-based hosts have been reported, almost all of them are insoluble in water due to their highly hydrophobic characteristics. Therefore, the guest-recognition properties of triazine-based hosts in aqueous media have been virtually unexplored.

Water-solubility of macrocyclic hosts is generally improved by introducing hydrophilic groups in a precise position on the macrocycle without disturbing the parent host-function. For example, a calixarene derivative was solubilized in water through the introduction of hydrophilic groups on the upper or lower rim of the macrocycle.^[16] Our group has developed water-soluble tetraaza[6.1.6.1]paracyclophanes where the bridged nitrogen atoms are functionalized with hydrophilic groups such as ammonium, carboxylates, and saccharides.^[17] These water-soluble tetraazacyclophanes maintain their parent host-function, and we have successfully evaluated their host-guest property in aqueous media.

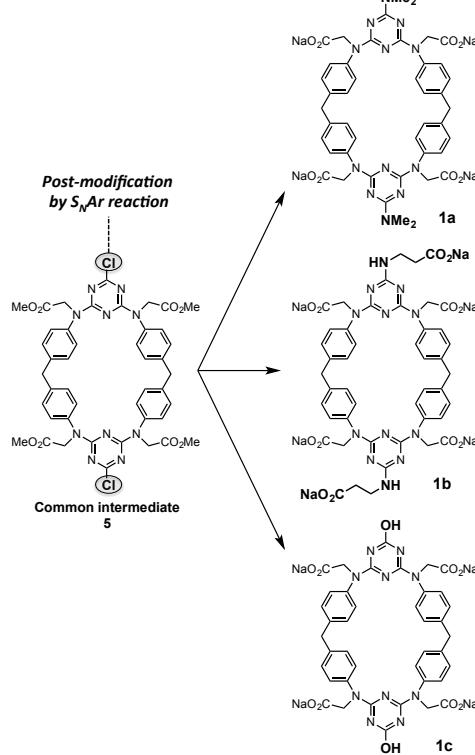


Fig 1 Molecular structure of novel water-soluble triazinophanes **1a-c**

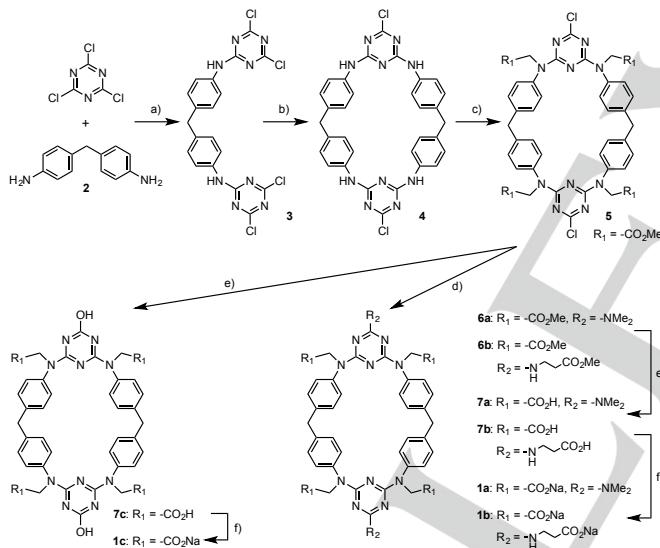
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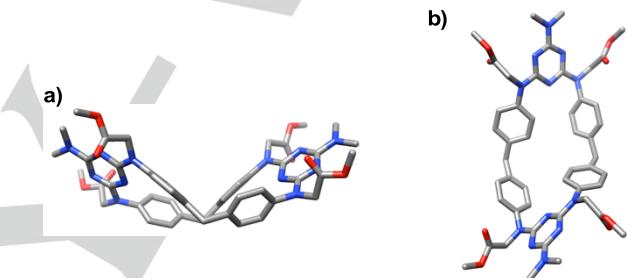
Based on our previous approach for solubilizing tetraazacyclophane in water, we designed the new water-soluble triazinophane **1a-c** (Fig 1). Four anionic carboxylate side chains on the bridged-nitrogen of **1** improve its hydrophilicity thereby allowing evaluation of host-guest properties in aqueous media. The macrocyclic core constructed by triazine and 4,4'-diaminodiphenylmethane is anticipated to give a larger hydrophobic cavity compared to previous triazine-based hosts.^[10] We thus hope that **1** is capable of accommodating relative large sized guest molecules in its internal hydrophobic cavity, expanding the scope of targetable guest molecules of triazine-based hosts. In addition, **1** can be conventionally derivatized through post-functionalization using a S_NAr reaction on the triazine ring of common intermediate **5**. This allows for investigation of the relationships between host-structure and guest-recognition properties. We herein report the synthesis of water-soluble triazinophane **1**, the structural analysis, and the evaluation of the molecular recognition properties in aqueous media using anthracene and pyrene cationic aromatic hydrocarbons derivatives as guest molecules.

Results and Discussion



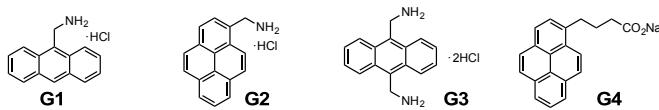
The macrocycle scaffold was constructed using a stepwise approach (**Scheme 1**).^{[15], [18]} The S_NAr reaction of 4,4'-diaminodiphenylmethane **2** with two equivalents of cyanuric chloride followed by cyclization between the resulting linear product **3** and diamine **2** provided a macrocycle **4** in 64% yield.

Larger sized macrocycles were not observed in this cyclization. We then attempted to introduce carboxymethyl groups on the bridged nitrogen of **4**. Alkylation with reactive methyl bromoacetate smoothly proceeded and gave corresponding N-alkylated product **5** in good yield. In contrast, any other functionalization of the bridged nitrogen such as condensation with an activated ester or alkylation with a non-activated alkyl halide failed and resulted in the recovery of **5** (data not shown). The derivatization of **5** by a S_NAr reaction using dimethylamine and methyl 3-aminopropanoate as a nucleophile was successful and gave corresponding products **6a** and **6b** in moderate to good yield. Subsequently, the methyl ester groups of **5**, **6a**, and **6b** were hydrolyzed to afford carboxylic acids **7a-c** using KOH as a base. To improve the water-solubility of **7a-c**, they were transformed to the corresponding sodium carboxylates **1a-c** and used for subsequent evaluation of their host-guest property. These novel compounds were characterized by 1H and ^{13}C NMR, IR, and HRMS spectroscopy.



The detailed molecular structure of the novel host was determined by X-ray crystallography and NMR spectroscopy. We successfully prepared the single crystal of **6a**. X-ray molecular structure revealed that **6a** in the solid state adopted a twisted V-shaped conformation and the triazine rings are oriented in a cis-configuration (**Fig 2**). The distance between the triazine rings in the hydrophobic cavity is appropriately 9.80 Å (N1-N1', see **Fig S1**). The average C-N bond distance between bridged-nitrogen atoms and triazine rings (1.38 Å) is shorter than that to phenyl rings (1.43 Å), which is close to the standard sp^3 C-N bond length, indicating that the bridged nitrogen atoms tend to conjugate with the electron deficient triazine ring rather than the adjacent phenyl ring.^[19]

The molecular structures of **1a-c** in solution were analyzed by NMR spectroscopy in D_2O (**Fig S3**). The 1H NMR spectra of **1a-c** showed a single set of resonances that were well resolved up to 5 mM at ambient temperatures suggesting that the interconversion between conformational isomers of **1** is rapid relative to NMR time scale. On the contrary, 1H NMR line broadening and peak shift of **1**, especially **1a** and **1b**, were observed with increasing the concentration over 10 mM (**Fig S3**). The hydrophobically-driven intermolecular aggregation of **1** probably occurs at high concentration.

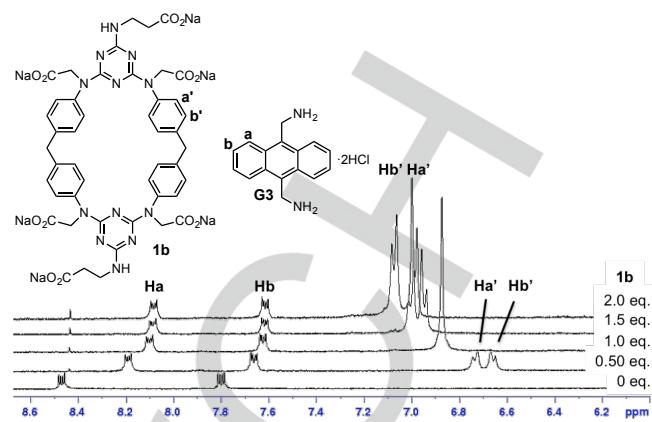
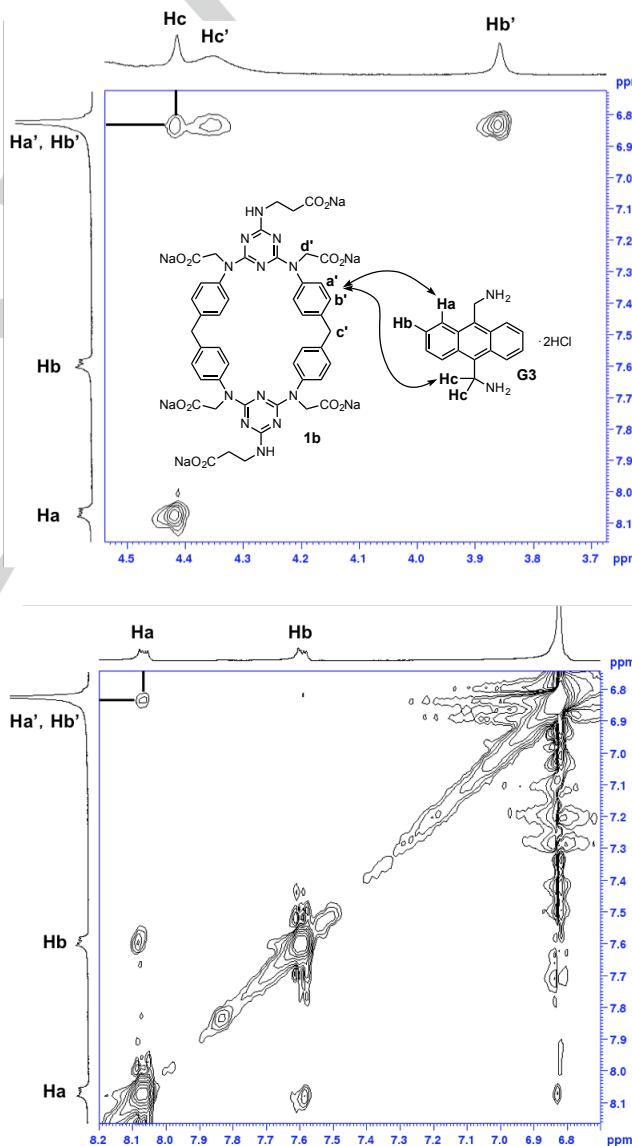
**Fig 3** Structures of cationic aromatic hydrocarbons **G1-G4****Table 1** Association constants K_a (M^{-1}) for 1:1 complexation between host **1** and guest^{a)}

	G1	G2	G3
1a	n.d. ^{b)}	$(8.1 \pm 0.98) \times 10^3$	n.d. ^{b)}
1b	n.d. ^{b)}	$(7.2 \pm 0.62) \times 10^3$	$(5.5 \pm 0.54) \times 10^3$
1c	n.d. ^{b)}	$(7.2 \pm 0.72) \times 10^3$	n.d. ^{b)}

a) These values are the average of three separate experiments b) No spectral change or too small a change to calculate the association constant

The molecular recognition properties of **1a-c** were explored to study host-guest complex formation between **1** and monocationic anthracene (**G1**) and pyrene (**G2**) by means of fluorescence titration in aqueous media (Fig 3, Fig S4-S6).^[20] Fluorescence quenching of **G2** was observed upon the addition of **1a-c** and showed saturation behavior, whereas that of **G1** was quite small and not saturated even in the presence of 100 equivalents of **1a-c** (Fig S4-S6). Job-plot analysis indicates that **1a-c** forms a host-guest complex with **G2** in a 1:1 equimolar ratio (Fig S4-S6). Based on these outcomes, the binding constants of **1a-c** for **G2** were calculated using the Benesi-Hildebrand method^[21] as summarized in Table 1. The binding constants for **G2** were appropriately $\sim 8 \times 10^3$ and comparable, regardless of the substitution group on the triazine ring. In contrast, the binding affinity of **1** for **G1** was too weak to calculate in our experimental system due to the limited solubility of **1a-c**. In the control experiment that used anionic **G4** as a guest, no interaction was observed, likely due to the electrostatic repulsion between the carboxylate groups of **1** and **G4** (Fig S7). Given the significance of electrostatic interactions for guest-recognition of **1**, we subsequently performed the fluorescence titration for **G3**, as a dicationic analogue of **G1**. Interestingly, **1b** formed a host-guest complex with **G3** in a 1:1 equimolar ratio with an association constant 5.5×10^3 (M^{-1}) in contrast to the quite low binding affinity for monocationic anthracene **G1**. Of note, the binding affinity of **1b** for **G3** was much higher than that of **1a** and **1c**. Regarding to this point, we presume that increasing number of carboxylate groups on **1b** relative to **1a** and **1c** effectively works for the complexation between **1b** and **G3** through electrostatic interaction (the detail is discussed in SI S15). Thus, we show the intrinsic potential that the molecular recognition properties of **1** are tunable through the post-modification of triazine rings.

To elucidate the host-guest complex structure, we subsequently attempted NMR analysis of the complexes. We obtained NMR spectra only for the **1b-G3** complex due to the limited solubility of the **1-G2** complex in D_2O (Fig S10). The host-guest complex of **1b-G3** afforded a simple and single set of 1H NMR spectrum signals (Fig 4 and Fig S8). This result indicates a rapid exchange processes between the complexed and uncomplexed form. Additionally, the global up-field shifts of

**Fig 4** Partial 1H NMR spectra of the mixture of **G3** and **1b** in D_2O at 298 K. $[G3] = 0.50$ mM, $[1b] = 0, 0.25, 0.50, 0.75, 1.0$ mM from bottom to top

the proton signals of **G3** were observed upon the addition of **1b**.

Fig 5 Partial ROESY spectra of 1:1 complex of **1b-G3** in D_2O , $[1b] = [G3] = 2.0$ mM at 298 K

Specifically, the signal represented as Ha and Hc in **Fig 4** and **Fig S8** shifted to a much larger extent compared to Hb. In the ROESY spectrum of the 1:1 complex of **1b-G3**, intermolecular through-space spin couplings between Ha'-Ha and Ha'-Hc were observed (**Fig 5**). The above-mentioned shielding effect of **1b** toward **G3** along with the result of ROESY correlations strongly suggests that **G3** bind into or onto the macrocyclic cavity of **1b** (SI S15).

DFT-based molecular modeling for **1b-G1** and **1b-G2** complexes was performed to further disclose the detail-binding mode of the host-guest complexes and the binding preference of **1** (**Fig S11**). Pyrene moiety of **G2** is partially incorporated into the macrocyclic cavity, while **G1** binds onto the cavity likely due to large molecular size of **G1** not fitting to the cavity. This difference might lead to the binding preference of **1b** for **G2** over **G1** in spite of both **G1** and **G2** possessing the same charge.

Conclusions

We have synthesized novel triazine-based water-soluble triazinophanes **1a-c** and successfully evaluated their host-guest properties in aqueous media. Compounds **1a-c** showed much higher binding affinity for pyrene derivative guest **G2** than that for antracene derivative guest **G1**. The binding constants of **1a-c** for **G2** were comparable, regardless of the substitution group on triazine rings ($K_a = \sim 8 \times 10^3 \text{ M}^{-1}$). Furthermore, we have demonstrated that the molecular recognition of host **1** is fine-tuned by proper post-modification of the triazine rings. Among **1a-c**, only **1b** showed binding affinity for **G3** ($K_a = 5.5 \times 10^3 \text{ M}^{-1}$). NMR analysis indicates inclusion complex formation between **1b** and **G3**. Thus, this study contributed to understanding the molecular recognition behavior of triazinophane **1** toward cationic aromatic hydrocarbons in aqueous media. As the binding constants of **1** for **G2** and **G3** are not so high, we are currently exploring another guest molecules to best fit the internal cavity of **1**. In addition, based on the results obtained in this study, we are developing a novel water-soluble triazine-based host with improved functionality.

Experimental Section

• General information

The ^1H and ^{13}C NMR were recorded on a Bruker 400 (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer. Chemical shifts were reported in ppm (δ), and coupling constants were reported in Hz. ^1H and ^{13}C -resonances were referenced to solvent residual peaks for CDCl_3 (^1H , 7.26 ppm), $\text{DMSO}-d_6$ (^1H , 2.50 ppm), CDCl_3 (^{13}C , 77.2 ppm) and $\text{DMSO}-d_6$ (^{13}C , 39.5 ppm). High resolution mass analyses (HRMS) were recorded using a Bruker MicroTOFQII mass spectrometer. MALDI-TOF mass spectra were measured by using Bruker autoflex speed mass spectrometer. Fluorescence spectra were recorded on JASCO FP-8200. Infrared spectra were recorded on Perkin Elmer Spectrum Two ATR/FT-IR spectrometer, and ν_{max} are partially reported in cm^{-1} .

• Synthesis and characterization

Compound 3: To a solution of cyanuric chloride (1.98 g, 10.0 mmol) in acetone (120 mL) was added dropwise 4,4'-diaminodiphenylmethane **2** (3.69 g, 10.0 mmol) in acetone (80 mL) over 1 h at 0 °C. After stirring for 1 h at 0 °C, K_2CO_3 (2.76 g, 20.0 mmol) was added to this mixture. The mixture was additionally stirred for 1 h at 0 °C. H_2O (100 mL) was then added to the reaction mixture, and the resulting mixture was filtered. The residue was washed with water and acetone to afford linear bistriazine product **3** (3.87 g, 78%) as a white solid. This product was used without further purification. ^1H NMR spectrum of this product was well agreed with previous reported one.^{17c}

Compound 4: A solution of **2** (1.10 g, 5.52 mmol) in acetone (168 mL) and linear bistriazine product **3** (2.73 g, 5.52 mmol) in acetone (168 mL) in separate dropping funnel were simultaneously added dropwise to a solution of DIPEA (2.4 mL, 13.8 mmol) in acetone (106 mL) at almost same rate over 4 hours at room temperature. During the reaction, a white solid was gradually precipitated. After stirring for 18 hours, the resulting precipitation was filtered and collected to afford **4** (2.19 g, 64%) as a white solid. This product was enough pure to use in next reaction without any purification; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.87 (s, 4H), 7.21 (d, $J = 8.4 \text{ Hz}$, 8H), 7.52 (d, $J = 8.4 \text{ Hz}$, 8H), 10.2 (s, 4H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 121.4, 128.6, 136.1, 137.1, 163.8, 168.1; IR (FT-ATR, cm^{-1}) 1704, 1571, 1501, 1413, 1230, 988; MS-MALDI: calculated for $[\text{C}_{32}\text{H}_{24}\text{Cl}_2\text{N}_{10} + \text{H}]^+$ requires $m/z = 619.16$, found 619.01.

Compound 5: The mixture of **3** (1.50 g, 2.42 mmol), K_2CO_3 (2.01 g, 14.5 mmol), methylbromoacetate (1.1 mL, 12.1 mmol) was reacted in DMF (48 mL) for 16 h at room temperature. The mixture was then diluted with CHCl_3 and washed with H_2O and brine. The organic phase was dried with MgSO_4 , filtered and concentrated. The resulting crude product was applied for chromatography (silicagel, CHCl_3 , EtOAc, 1:0 to 25:1) to afford **5** (1.68 g, 69%) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 3.56 (s, 12H), 4.01 (s, 4H), 4.62 (s, 8H), 6.92 (d, $J = 8.4 \text{ Hz}$, 8H), 7.10 (d, $J = 8.4 \text{ Hz}$, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ 40.8, 51.7, 52.5, 126.7, 129.2, 138.4, 140.4, 165.2, 169.4, 170.1; IR (FT-ATR, cm^{-1}) 2960, 1731, 1565, 1499, 1459, 1393, 1337, 1256, 1224, 1008; HRMS-ESI: calculated for $[\text{C}_{44}\text{H}_{40}\text{Cl}_2\text{N}_{10}\text{O}_8 + \text{H}]^+$ requires $m/z = 907.2480$, found 907.2484.

General procedure for $S_N\text{Ar}$ reaction of 5: K_2CO_3 (124 mg, 0.900 mmol) and each amine hydrochlorides (0.375 mmol) were added to a solution of **5** (136 mg, 0.150 mmol) in DMF (1.5 mL). The mixture was reacted 18 h at 70 °C. After cooling to room temperature, the mixture was diluted with CHCl_3 and washed with H_2O and brine. The organic phase was dried with MgSO_4 , filtered and concentrated. The resulting crude product was applied for chromatography to afford **6**

Compound 6a: Silicagel chromatography condition was performed with Hexane, EtOAc, 2:1 to afford **6a** (83.4 mg, 60%) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 3.06 (s, 12H), 3.73 (s, 12H), 3.99 (s, 4H), 4.53 (s, 8H), 6.97 (d, $J = 8.4 \text{ Hz}$, 8H), 7.25 (d, $J = 8.4 \text{ Hz}$, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ 35.8, 40.5, 51.8, 52.5, 126.16, 128.6, 137.1, 141.5, 164.8, 165.1, 171.3; IR (FT-ATR, cm^{-1}) 1748, 1729, 1538, 1455, 1395, 1199; HRMS-ESI: calculated for $[\text{C}_{46}\text{H}_{52}\text{N}_{12}\text{O}_8 + \text{H}]^+$ requires $m/z = 925.4104$, found 925.4107.

Compound 6b: Silicagel chromatography condition was performed with Hexane, EtOAc, 1:1 to afford **6b** (133 mg, 85%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 2.61 (t, $J = 6.4 \text{ Hz}$, 4H), 3.61 (dt, $J = 6.0, 6.4 \text{ Hz}$, 4H), 3.64 (s, 6H), 3.73 (s, 12H), 3.98 (s, 4H), 4.53 (s, 8H), 5.30 (t, $J = 6.0 \text{ Hz}$, 2H), 6.93 (d, $J = 8.4 \text{ Hz}$, 8H), 7.17 (d, $J = 8.4 \text{ Hz}$, 8H); ^{13}C NMR (100

MHz, CDCl₃) δ 34.1, 36.3, 40.6, 51.6, 52.0, 126.5, 128.7, 137.2, 141.3, 165.0, 165.6, 171.1, 172.9; IR (FT-ATR, cm⁻¹) 2953, 1733, 1539, 1512, 1435, 1393, 1362, 1201, 1016; HRMS-ESI: calculated for [C₅₂H₅₆N₁₂O₁₂ + H]⁺ requires m/z = 1041.4213, found 1041.4241

General procedure for basic hydrolysis of 6a, 6b, and 5

Methyl ester 5 or 6 (0.100 mmol) was reacted in THF (1.5 mL), MeOH (1.5 mL), and 10 M KOH aq. (1 mL) for 18 h at 60 °C. Upon cooling, the mixture was acidified with 1 M HCl aq. The resulting white solid was filtered and washed with methanol and acetone to afford corresponding carboxylic acid 7a (80%), 7b (66%), and 7c (65%)

Compound 7a: ¹H NMR (400 MHz, DMSO-d₆) δ 3.04 (s, 12H), 3.96 (s, 4H), 4.47 (s, 8H), 6.98 (d, J = 8.4 Hz, 8H), 7.23 (d, J = 8.4 Hz, 8H); ¹³C NMR (100 MHz, DMSO-d₆) δ 35.5, 52.2, 125.6, 128.5, 136.8, 141.2, 164.0, 164.5, 171.6; IR (FT-ATR, cm⁻¹) 1738, 1587, 1511, 1404, 1224, 1006; HRMS-ESI: calculated for [C₄₄H₄₄N₁₂O₈ + H]⁺ requires m/z = 869.3478, found 869.3484.

Compound 7b: ¹H NMR (400 MHz, DMSO-d₆) δ 3.97 (s, 4H), 4.52 (s, 8H), 6.98 (d, J = 6.8 Hz, 8H), 7.04 (t, J = 5.6 Hz, 2H), 7.20–7.25 (m, 8H); ¹³C NMR (100 MHz, DMSO-d₆) δ 34.0, 36.5, 51.1, 51.8, 125.6, 128.4, 136.7, 141.1, 154.5, 165.0, 171.4, 171.6, 173.3; IR (FT-ATR, cm⁻¹) 3355, 2903, 1704, 1667, 1622, 1595, 1514, 1398, 1350, 1245, 1016; HRMS-ESI: calculated for [C₄₆H₄₄N₁₂O₁₂ + 2H]²⁺ requires m/z = 479.1674, found 479.1714.

Compound 7c: ¹H NMR (400 MHz, DMSO-d₆) δ 4.01 (s, 4H), 4.51 (s, 8H), 6.91 (d, J = 7.2 Hz, 8H), 7.08 (d, J = 7.2 Hz, 8H); ¹³C NMR (100 MHz, DMSO-d₆) δ 51.5, 126.3, 128.6, 137.5, 140.6, 162.5, 170.7; IR (FT-ATR, cm⁻¹) 3039, 1564, 1489, 1448, 1378, 1203, 1000; HRMS-ESI: calculated for [C₄₀H₃₄N₁₀O₁₀ + H]⁺ requires m/z = 815.2532, found 815.2538

General procedure for the transformation of carboxylic acid 7 to sodium carboxylate 1

Carboxylic acid 7 (0.100 mmol) was treated with 1 M NaOH aq. (4 eq. for 7a and 7c, 6 eq. for 7b) for 30 minutes at room temperature. The mixture was then concentrated and used without any purification for subsequent evaluation of host-guest property.

Compound 1a: ¹H NMR (400 MHz, D₂O) δ 3.06 (s, 12H), 3.97 (s, 4H), 4.25 (s, 8H), 7.02 (d, J = 8.4 Hz, 8H), 7.11 (d, J = 8.4 Hz, 8H); ¹³C NMR (100 MHz, D₂O) δ 35.5, 52.2, 125.6, 128.5, 136.8, 141.2, 164.0, 164.5, 171.6; IR (FT-ATR, cm⁻¹) 3363, 1539, 1505, 1445, 1380, 1296, 1002; HRMS-ESI: calculated for [C₄₄H₄₀N₁₂Na₄O₈ – 4Na + 5H]⁺ requires m/z = 869.3478, found 869.3485.

Compound 1b: ¹H NMR (400 MHz, D₂O) δ 2.38 (brs, 4H), 3.50 (t, J = 6.4 Hz, 4H), 4.00 (s, 4H), 4.29 (brs, 8H), 7.03 (d, J = 8.0 Hz, 8H), 7.12–7.13 (m, 8H); ¹³C NMR (100 MHz, D₂O) δ 37.4, 37.8, 39.4, 54.4, 125.9, 129.0, 141.6, 165.1, 165.8, 178.2, 181.4; IR (FT-ATR, cm⁻¹) 3349, 1531, 1511, 1479, 1446, 1381, 1288, 1224, 1080, 1035, 1017; HRMS-ESI: calculated for [C₄₆H₃₈N₁₂Na₆O₁₂ – 6Na + 7H]⁺ requires m/z = 957.3274, found 957.3260.

Compound 1c: ¹H NMR (400 MHz, D₂O) δ 4.04 (s, 4H), 4.42 (s, 8H), 7.06 (d, J = 8.4 Hz, 8H), 7.22 (d, J = 8.4 Hz, 8H); ¹³C NMR (100 MHz, D₂O) δ 39.4, 53.6, 126.1, 129.0, 137.2, 141.8, 166.5, 178.4; IR (FT-ATR, cm⁻¹) 3355, 1584, 1512, 1484, 1434, 1379, 1292, 1224, 1188, 1003; HRMS-ESI: calculated for [C₄₀H₃₀N₁₀Na₄O₁₀ – 3Na + 4H]⁺ requires m/z = 837.2352, found 837.2347.

• Fluorescence measurement

All fluorescence spectra were measured in following conditions; pH 7.4, 10 mM HEPES, 150 mM NaCl at 25 °C, bandwidth = 5 nm, scanning speed = 100 nm/min, 1 cm quartz cuvet.

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Keywords:

Host-guest chemistry • Triazinophane

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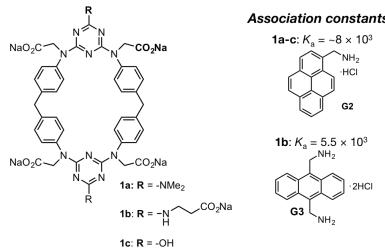
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- [20] **G1** and **G3** were synthesized by following reported procedure. ¹H NMR spectra of **G1** and **G3** were well matched with reported one. For **G1**: R. Moritoh, T. Morita, S. Kimura, *Biopolymers*, **2013**, *100*, 1; For **G3**: C. Ke, H. Destecroix, M. P. Crump, A. P. Davis, *Nat. Chem.* **2012**, *4*, 718. **G2** was obtained from Sigma Aldrich used without any purification.
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Novel water-soluble triazinophanes **1a-c** have been developed. The exploration of host-guest properties of **1a-c** in aqueous media revealed that the guest recognition properties could be modulated through the post-modification on the triazine rings of **1**.

**Key Topic*** Host-guest chemistry • Triazinophane*Shuhei Kusano,* Sae Konishi, Ryuta Ishikawa, Norihiro Sato, Satoshi Kawata, Fumi Nagatsugi, and Osamu Hayashida****Page No. – Page No.****Title****Synthesis of water-soluble triazinophanes and evaluation of their molecular recognition properties**

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