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Well-defined aqueous nanoassemblies from amphiphilic *meta*-terphenyls and their guest incorporation[†]

Spherical molecular assemblies with diameters of \sim 2 nm were quantitatively formed in water from new amphiphilic *meta*-terphenyls with two hydrophilic pendants at the central benzene ring. Whereas intermolecular interactions between small aromatic rings are typically weak, the obtained

nanoassemblies are stable enough at wide-ranging concentrations and mostly remain intact even in the

presence of similar nanoassemblies with polyaromatic frameworks. The nanoassembly with

pentamethyl-substituted terminal benzene rings provides superior host capability for fluorescent dyes in

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Introduction

A benzene ring, the minimal unit of polyaromatic hydrocarbons, is widely utilized for the construction of various molecular architectures.^{1,2} However, intermolecular interactions between such small aromatic rings are relatively weak as compared with those between extended polyaromatic rings (e.g., anthracene and pyrene) therefore the certain formation of welldefined, benzene-based molecular assemblies requires core frameworks containing multiple benzene rings linked covalently.^{3,4} For instance, Lee et al. reported that linear amphiphilic compounds with a quaterphenyl framework (C₆H₅-C₆H₄-C₆H₄- C_6H_5) generate large micellar or vesicle-like assemblies (>~20 nm in diameter) in water.⁵ The bent oligophenyl $(C_6H_5-(C_6H_4)_7-$ C₆H₅) amphiphiles also form huge tubular assemblies.⁵ On the other hand, small frameworks composed of two or three benzene rings have not proven useful for the subunits of discrete molecular assemblies.6

water.

Here we employed a *meta*-terphenyl framework to explore new molecular assemblies with well-controlled size and shape distributions as well as guest incorporation ability. V-shaped amphiphilic compounds **1a** and **1b**, designed here (Fig. 1a), are composed of a *meta*-terphenyl skeleton with two hydrophilic pendants at the central benzene ring. To force the terminal benzene rings to adopt an orthogonal conformation with respect to the central ring, methyl groups were employed as substituents on the terminal rings (**1a**; Fig. 1b).⁷ In this context, we have recently revealed that a similar amphiphilic molecule **1c** with a bent *meta*-di(anthryl)benzene framework generates a spherical polyaromatic assembly **2c** in water through effective π -stacking interactions.⁸ Herein, we report the quantitative formation of well-defined, spherical assemblies **2a** and **2b** from \sim 5 molecules of **1a** and **1b** in aqueous media. The pentamethylbenzene-shelled assembly **2a** effectively incorporates well-known fluorescent dyes (*i.e.*, fluorescein and Eosin Y) in water at room temperature and the emissive colors of the encapsulated dyes are altered by the host–guest interactions.

Results and discussion

Quantitative formation of the spherical nanoassemblies

V-shaped amphiphilic compound **1a** was synthesized through four step reactions with \sim 35% overall yield.⁹ Once a white solid of **1a** (2.0 µmol) was dissolved in water (1.0 mL) at room temperature, spherical assembly **2a** was quantitatively formed



Fig. 1 (a) V-shaped amphiphilic compounds 1a-c. The optimized structures of (b) 1a and (c) 1b (side and front views) without the counterions, obtained by DFT calculations (B3LYP/6-31G(d,p) level).



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within 1 min (Fig. 2a). The ¹H NMR spectrum of 2a in D_2O is similar to that of **1a** in CD₃OD and contains two aromatic $(H_{a,b})$ and six aliphatic (H_{c-h}) signals (Fig. 2b and c). On the other hand, the observed diffusion coefficients (D) of 2a in D₂O and 1a in CD₃OD were evidently different. The diffusion-ordered spectroscopy (DOSY) NMR spectrum of 2a displayed a single band at a D of 4.3 \times 10 $^{-10}$ m² s $^{-1}$ (Fig. 2e), which is smaller than that of 1a (8.3 \times 10⁻¹⁰ m² s⁻¹; Fig. 2d). On the basis of the D value and the Stokes-Einstein equation, the core diameter of 2a was calculated to be about 1 nm. Further structural evidence for 2a was obtained by atomic force microscopy (AFM). We observed uniform, spherical particles with an average height of 2.2 nm on the AFM image (Fig. 2f), prepared by drop casting from an aqueous solution of 2a (1.0 mM based on 1a) on a mica surface. The diameter of the spherical assembly of pentamer (1a)₅ including the outer sulfonate groups (2.5 nm)¹⁰ is comparable to that of 2a obtained by the AFM analysis (Fig. 2g).

It is worth noting that the methyl groups on the terminal benzene rings of **1a** are not essential for the formation of welldefined, small nanoassemblies. Thus, in a manner similar to **2a**, simple V-shaped amphiphile **1b** without the methyl groups⁷ quantitatively formed spherical assembly **2b** in water at room temperature. The size of the product is slightly smaller than that of **2a** but the shape is quite similar to that of **2a**, as confirmed by DOSY NMR, DLS, and AFM analyses (Fig. S38– **41**†).⁹ In agreement with our previous study of amphiphile **1c** with a bent polyaromatic framework,⁸ the *meta*-terphenyl



Fig. 2 (a) Schematic representation of the formation of spherical nanoassembly 2a from V-shaped amphiphilic compound 1a in water. ¹H NMR and DOSY spectra (400 MHz, 25 °C) of (b and d) 1a in CD₃OD and (c and e) 2a in D₂O (2.0 mM based on 1a). (f) AFM image of 2a on mica and the size and number (*N*) distribution. (g) Molecular modeling of 2a, composed of five molecules of 1a.

moiety was therefore proved to be one of the key skeletons in this supramolecular system.

Photophysical properties and stability of the spherical nanoassemblies

Assemblies 2a and 2b turned out to be stable enough in water under ambient conditions. Dynamic light scattering (DLS) analysis of 2a indicated the exclusive existence of small particles $(d_{av.} = 1.6 \text{ nm})$ with a sharp size distribution $(\pm 1 \text{ nm})$ at the monomer concentration of 1.0 mM. Concentration-dependent DLS studies revealed that the particles of 2a and 2b remained intact at up to 10 mM in water at room temperature for more than one week (Fig. S39 and 40†). The water-solubility of 2a and 2b is higher than that of 2c (up to ~2 mM based on 1c). Concentration-dependent fluorescence studies (in the range of 0.001–1.0 mM based on 1a) elucidated that the critical micelle concentration (CMC) value of 2a is ~0.005 mM.

The UV-visible spectra of monomer **1a** in methanol and assembly **2a** in water exhibited similar absorption bands at $\lambda_{max} = \sim 290$ nm (Fig. 3a). The absorption bands are blue-shifted ($\Delta \lambda = \sim 10$ nm) as compared with those of **1b** and **2b**. Similarly, the emission bands of **1a** and **2a** are also blue-shifted ($\Delta \lambda_{max} = \sim 30$ nm) with respect to those of **1b** and **2b** (Fig. 3b). These photophysical properties can be explained by the conformational difference between the two amphiphiles. Sterically hindered **1a** adopts a rigidly bent structure for the methyl-substituted *meta*-terphenyl moiety but **1b** adopts a slightly twisted, planar structure for the *meta*-terphenyl framework with an extended π -conjugated system, as also suggested by the optimized structures of **1a** and **1b** (Fig. 1b and c).

Mixing two linear amphiphilic compounds with different hydrophobic alkyl chains usually generates a complex mixture of spherical aggregates with a statistical distribution of the amphiphiles in water.¹¹ In contrast, the combination of V-shaped amphiphiles **1a** and **1c** led to an equilibrium mixture of nanoassemblies, mainly including **2a** and **2c** (Fig. 4a). When **1a** and **1c** (in a 1 : 1 ratio) were agitated in H₂O (1.0 mM) at room temperature for 1 min, the resultant solution was analyzed by UV-visible and fluorescence spectroscopies. The observed absorption and emission bands nearly overlapped with the sum of the bands of assemblies **2a** and **2c** (Fig. 4b and c). No



Fig. 3 (a) Normalized UV-visible and (b) fluorescence spectra (r.t.) of nanoassemblies 2a and 2b in H₂O (1.0 mM based on 1a and 1b) and monomers 1a and 1b in CH₃OH. Excitation wavelengths: $\lambda_{ex} = 286$ nm for 1a and 2a, $\lambda_{ex} = 299$ nm for 1b and 2b.

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coalesced emission bands were observed, in contrast to similar polyaromatic assemblies (Fig. S47 and 48†).⁹ In addition, the mixed solution of **2a** and **2c** in H₂O at room temperature (even after heating at 80 °C for 10 min) exhibited the same spectrum. These behaviors are most probably caused by the difference of the major intermolecular interactions between the two amphiphiles: **2a** forms through hydrophobic effects but **2c** forms through π -stacking interactions in aqueous solutions.

Effective incorporation of fluorescent dyes

Surprisingly, the guest incorporation ability of 2a and 2b is strikingly different in water. Nanoassembly 2a with its bent bispentamethylbenzene frameworks promoted guest incorporation. For example, an excess amount of fluorescein (3; 1.0 µmol) with slightly hydrophilic properties was suspended in a D₂O solution (2.0 mL) of 2a (2.0 µmol based on 1a) and the resultant mixture was stirred at room temperature for 1 h (Fig. 5a). The filtration of the suspended mixture yielded $2\mathbf{a} \cdot (3)_n$ as a clear pale-yellow solution. In the ¹H NMR spectrum, new signals derived from encapsulated 3 were clearly observed in the range of 6.6-7.9 ppm (Fig. 5b), whereas the proton signals of free 3 were hardly detectable in water (Fig. S50[†]). The UV-visible spectrum showed a new prominent absorption band at $\lambda_{max} =$ 487 nm assignable to the incorporated guest molecules (Fig. 5c). In stark contrast, similar assemblies 2b and 2c exhibited weak binding abilities for 3 under the same conditions, as revealed by the UV-visible analysis (Fig. 5c).

Eosin Y (4) was also effectively incorporated into 2a in water at room temperature to give a red solution due to the formation of $2a \cdot (4)_n$ (Fig. 5d).^{9,12} Assemblies 2b and 2c showed lower binding abilities for 4. On the basis of the absorption intensities, the concentrations of 3 and 4 in the obtained aqueous solutions of $2a \cdot (3)_n$ and $2a \cdot (4)_n$ were estimated to be 0.32 and 0.30 mM, respectively.¹³ The values are >20-times larger than



Fig. 4 (a) Schematic representation of the selective formation of nanoassemblies 2a and 2c from a mixture of 1a and 1c in water. (b) Normalized UV-visible and (c) fluorescence spectra (H₂O, r.t., λ_{ex} = 286 nm) of 2a, 2c, and 2a + 2c (1.0 mM based on 1a and 1c each).



Fig. 5 (a) Schematic representation of the incorporation of fluorescein (3) or Eosin Y (4) by nanoassembly 2a in water. (b) ¹H NMR spectrum (400 MHz, r.t.) of $2a \cdot (3)_n$ in D_2O . UV-visible spectra (r.t. H_2O) of (c) nanoassemblies $2a - c \cdot (3)_n$ and (d) $2a - c \cdot (4)_n$ (1.0 mM based on 1a - c). (e) Normalized fluorescence spectra (r.t. H_2O , $\lambda_{ex} = 487$ nm) and (f) CIE coordinate diagram and quantum yields of 3 and $2a - c \cdot (3)_n$.

those of the saturated solutions of 3 and 4 in water without 2ac. Furthermore, the intense fluorescence band ($\Phi_{\rm F} = 72\%$) of the incorporated 3 within 2a was found at $\lambda_{\rm max} = 532$ nm, which is slightly red-shifted ($\Delta\lambda_{\rm max} = 13$ nm) as compared with that of free 3 due to being enclosed in the pentamethylbenzene frameworks (Fig. 5e). The difference in the total emission colors of 3 and 2a-c·(3)_n is clearly revealed in the CIE chromaticity diagram (Fig. 5f). Thus, it is revealed that the bent conformation of the pentamethyl-substituted *meta*-terphenyl framework is of importance for the formation of a nanoassembly with an inner space capable of binding guest molecules.

Conclusions

In conclusion, we have revealed that *meta*-terphenyl, a small benzene oligomer, acts as a useful building block for the quantitative formation of well-defined, spherical assemblies (\sim 2 nm in diameter) in water by attaching hydrophilic groups to the central benzene ring. The nanoassemblies are stable enough in a wide range of concentrations and remain intact even when mixed with a similar nanoassembly with polyaromatic frameworks. Moreover, pentamethyl substitution on

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the terminal benzene rings of the amphiphile forces the *meta*terphenyl framework to adopt a bent conformation, which imparts the nanoassembly with a superior hosting capability for fluorescent dyes in water. The present study demonstrated the utility of a simple $C_6H_5-C_6H_4-C_6H_5$ skeleton for discrete supramolecular systems with designed structures and functions.

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Notes and references

- (a) K. N. Baker, A. V. Fratini, T. Resch, H. C. Knachel, W. W. Adams, E. P. Socci and B. L. Farmer, *Polymer*, 1993, 34, 1571–1587; (b) D. J. Williams, H. M. Colquhoun and C. A. O'Mahoneya, *Chem. Commun.*, 1994, 1643–1644; (c) M. Panda and J. Chandrasekhar, *J. Am. Chem. Soc.*, 1998, 120, 13517–13518; (d) N. Kobayashi, S. Sasaki, M. Abe, S. Watanabe, H. Fukumoto and T. Yamamoto, *Macromolecules*, 2004, 37, 7986–7991.
- 2 (a) H. A. Staab and F. Binnig, Tetrahedron Lett., 1964, 5, 319–321; (b) Y. Fujioka, Bull. Chem. Soc. Jpn., 1984, 57, 3494–3506; (c) C. Grave and A. D. Schlüter, Eur. J. Org. Chem., 2002, 3075–3098; (d) M. Iyoda, M. J. Rahman, A. Matsumoto, M. Wu, Y. Kuwatani, K. Nakao and Y. Miyake, Chem. Lett., 2005, 34, 1474–1475; (e) R. Jasti, J. Bhattacharjee, J. B. Neaton and C. R. Bertozzi, J. Am. Chem. Soc., 2008, 130, 17646–17647; (f) K. Matsui, Y. Segawa, T. Namikawa, K. Kamada and K. Itami, Chem. Sci., 2013, 4, 84–88; (g) A. Yagi, Y. Segawa and K. Itami, J. Am. Chem. Soc., 2012, 134, 2962–2965; (h) E. Kayahara, T. Iwamoto, H. Takaya, T. Suzuki, M. Fujitsuka, T. Majima, N. Yasuda, N. Matsuyama, S. Seki and S. Yamago, Nat. Commun., 2013, 4, 2694.
- 3 (a) M. Lee, C.-J. Jang and J.-H. Ryu, J. Am. Chem. Soc., 2004, 126, 8082–8083; (b) H.-J. Kim, T. Kim and M. Lee, Acc. Chem. Res., 2011, 44, 72–82.
- 4 (a) S. Hiraoka, K. Harano, M. Shiro and M. Shionoya, J. Am. Chem. Soc., 2008, 130, 14368–14369; (b) S. Hiraoka, T. Nakamura, M. Shiro and M. Shionoya, J. Am. Chem. Soc., 2010, 132, 13223–13225.
- 5 (a) B.-S. Kim, D.-J. Hong, J. Bae and M. Lee, *J. Am. Chem. Soc.*, 2005, 127, 16333–16337; (b) Z. Huang, S.-K. Kang, M. Banno, T. Yamaguchi, D. Lee, C. Seok, E. Yashima and M. Lee, *Science*, 2012, 337, 1521–1526.
- 6 (a) S. Leininger, B. Olenyuk and P. J. Stang, *Chem. Rev.*, 2000, 100, 853–908; (b) F. Hof, S. L. Craig, C. Nuckolls and J. Rebek Jr, *Angew. Chem., Int. Ed.*, 2002, 41, 1488–1508; (c)

D. M. Vriezema, M. C. Aragonès, J. A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan and R. J. M. Nolte, Chem. Rev., 2005, 105, 1445-1489; (d) J. Rebek Jr, Angew. Chem., Int. Ed., 2005, 44, 2068-2078; (e) M. Fujita, M. Tominaga, A. Hori and B. Therrien, Acc. Chem. Res., 2005, 38, 371-380; (f) M. D. Pluth, R. G. Bergman and K. N. Raymond, Acc. Chem. Res., 2009, 42, 1650-1659; (g) M. Yoshizawa, J. K. Klosterman and M. Fujita, Angew. Chem., Int. Ed., 2009, 48, 3418-3438; (h) M. M. Safont-Sempere, G. Fernámdez and F. Würthner, Chem. Rev., 2011, 111, 5784–5814; (i) R. Chakrabarty, P. Sarath Mukherjee and P. J. Stang, Chem. Rev., 2011, 111, 6810-6918; (j) H. Amouri, C. Desmarets and J. Moussa, Chem. Rev., 2012, 112, 2015-2041; (k) M. M. J. Smulders, I. A. Riddell, C. Browne and J. R. Nitschke, Chem. Soc. Rev., 2013, 42, 1728-1754; (l) K. Harris, D. Fujita and M. Fujita, Chem. Commun., 2013, 49, 6703-6712; (m) G. Zhang and M. Mastalerz, Chem. Soc. Rev., 2014, 43, 1934-1947; (n) M. Han, D. M. Engelhard and G. H. Clever, Chem. Soc. Rev., 2014, 43, 1848-1860; (o) L. Xu, L.-J. Chen and H.-B. Yang, Chem. Commun., 2014, 50, 5156-5170; (p) A. M. Castilla, W. J. Ramsay and J. R. Nitschke, Acc. Chem. Res., 2014, 47, 2063-2073.

- 7 The dihedral angles between the adjacent aromatic rings of **1a** and **1b** are 72.7° and 40.5°, respectively (Fig. 1b and c).
- 8 (a) K. Kondo, A. Suzuki, M. Akita and M. Yoshizawa, Angew. Chem., Int. Ed., 2013, 52, 2308–2312; (b) A. Suzuki, K. Kondo, M. Akita and M. Yoshizawa, Angew. Chem., Int. Ed., 2013, 52, 8120–8123; (c) K. Kondo, A. Suzuki, M. Akita and M. Yoshizawa, Eur. J. Org. Chem., 2014, 33, 7389–7394; (d) Y. Okazawa, K. Kondo, M. Akita and M. Yoshizawa, J. Am. Chem. Soc., 2015, 137, 98–101; (e) K. Kondo, M. Akita, T. Nakagawa, Y. Matsuo and M. Yoshizawa, Chem.–Eur. J., 2015, 21, in press.
- 9 See the ESI.†
- 10 Molecular modeling study was carried out by using Materials Studio (version 5.0, Accelrys Software Inc., San Diego, CA). The outer diameters of the optimized structures of spherical assemblies (1a)₄ and (1a)₆ were estimated to be ~2.0 and ~3.0 nm, respectively (Fig. S49†).
- 11 (a) Y. Moroi, Micelles: Theoretical and applied aspects, Plenum, New York, 1992; (b) S. P. Moulik, M. E. Haque, P. K. Jana and A. R. Das, J. Phys. Chem., 1996, 100, 701– 708; (c) E. Lee, J.-K. Kim and M. Lee, J. Am. Chem. Soc., 2009, 131, 18242–18243; (d) S. Honda, T. Yamamoto and Y. Tezuka, J. Am. Chem. Soc., 2010, 132, 10251–10253.
- 12 The DLS analysis (H₂O, r.t.) of $2\mathbf{a} \cdot (3)_n$ and $2\mathbf{a} \cdot (4)_n$ indicated the formation of larger particles with average diameters of 10.2 and 12.7 nm, respectively (Fig. S46†). The host-guest ratio of $2\mathbf{a} \cdot (3)_n$ was estimated to be $1\mathbf{a} : 3 = 3 : 1$.
- 13 (a) N. O. Mchedlov-Petrossyan and V. N. Kleshchevnikova, J. Chem. Soc., Faraday Trans., 1994, 90, 629–640; (b)
 E. M. Arbeloa, G. V. Porcal, S. G. Bertolotti and C. M. Previtali, J. Photochem. Photobiol., A, 2013, 252, 31–36.