A cucurbit[7]uril-based supra-amphiphile: Photo-responsive self-assembly and application in controlled release

Li Shao, Bin Hua *, Jifu Sun, Qing Li, Jie Yang *, Guocan Yu

Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China

ABSTRACT

A photo-responsive host–guest molecular recognition between a cucurbit[7]uril host and an azobenzene-containing guest was investigated. Based on this recognition motif, a photo-responsive supra-amphiphile was constructed. This supra-amphiphile can self-assemble into vesicles in water, which can be destroyed by UV irradiation. Depending on this photo-responsive assembly, its application in controlled release was further performed.

© 2017 Elsevier Ltd. All rights reserved.

Stimuli-responsive host–guest systems, exhibiting controlled host–guest association/dissociation properties triggered by external stimuli, are one of the major research focuses of supramolecular chemistry.[1] Well-established stimuli-responsive host–guest recognition motifs can be utilized to fabricate supramolecular systems with applications in various fields, such as molecular electronics, compound separation, molecular muscles, biosensors and smart surfaces.[2] External stimuli include, but is not limited to, light, pH-change, temperature-change, enzyme, redox, and a combination of these.[3] Among these stimuli, light is one of the most appealing stimuli-responsive species due to its easy operation, low cost, few by-products and high sensitivity.[4] Azobenzene is a widely used chromophore for the preparation of light-responsive host–guest systems on account of its excellent photoisomerization features including fast response, widely applicable performance and photochemical stability.[5]

Cucurbit[*n*]urils (CB[*n*]s) are an interesting class of macrocyclic receptor molecules consisting of a hydrophobic cavity and two identical carbonyl laced portals.[6] The CB rings have been employed to fabricate robust light-responsive host–guest systems because of their ability to bind a wide array of light-responsive guests with high affinity in water, such as azobenzene and stilbene derivatives.[7] The most relevant to the work described herein is that of Scherman and coworkers who have exploited the ability of CB[8] to promote the formation of heteroternary complexes to construct a supramolecular container system exhibiting light-controlled

encapsulation properties in water.[8] Zhang and the coworkers also utilized CB[8]-mediated heteroternary complexes to construct light responsive supramolecular systems for controlled drug release.[9] To date, a variety of examples have demonstrated CB [8]-mediated heteroternary complexes with a light-driven association/dissociation process. However, the related light-controlled system based on CB[7] has been rarely reported.[10] Maybe because the cavity size of CB[7] is relatively small, it's hard to find suitable guests to construct a photo-responsive recognition motif. It is extremely valuable to explore the potential of CB[7] in the fabrication of photo-controlled reversible self-assembly systems.

Herein, we investigate the complexation of an azobenzene-containing guest **M** (Scheme 1) with CB[6] and CB[7]. Because of the different cavity sizes of CB[6] and CB[7], *trans*-**M** cannot complex with CB[6], while it can locate in the cavity of the CB[7]. The photo-responsive threading–dethreading switch between CB[7] and **M** can be reversibly achieved upon UV and visible light irradiation due to the *trans–cis* photo-isomerization of **M**. Moreover, based on this novel host–guest recognition motif, a photo-responsive supra-amphiphile was constructed. The disassembly and assembly of the corresponding aggregates could be regulated by UV and visible light irradiation (Scheme 1).

The host–guest complexation between CB[6], CB[7] and **M** was firstly investigated by ¹H NMR spectroscopy. As shown in Fig. 1b, after the addition of 1 equiv. of CB[6] into a solution of **M**, the signals from protons on **M** and CB[6] did not show obvious chemical shift changes, indicating that **M** could not complex strongly with CB[6], because **M** was too large to be wrapped by CB[6] completely. In contrast, after the addition of 1 equiv. of CB[7] into the solution

* Corresponding authors.
  E-mail addresses: huabin@zju.edu.cn (B. Hua), jieyang@zju.edu.cn (J. Yang).
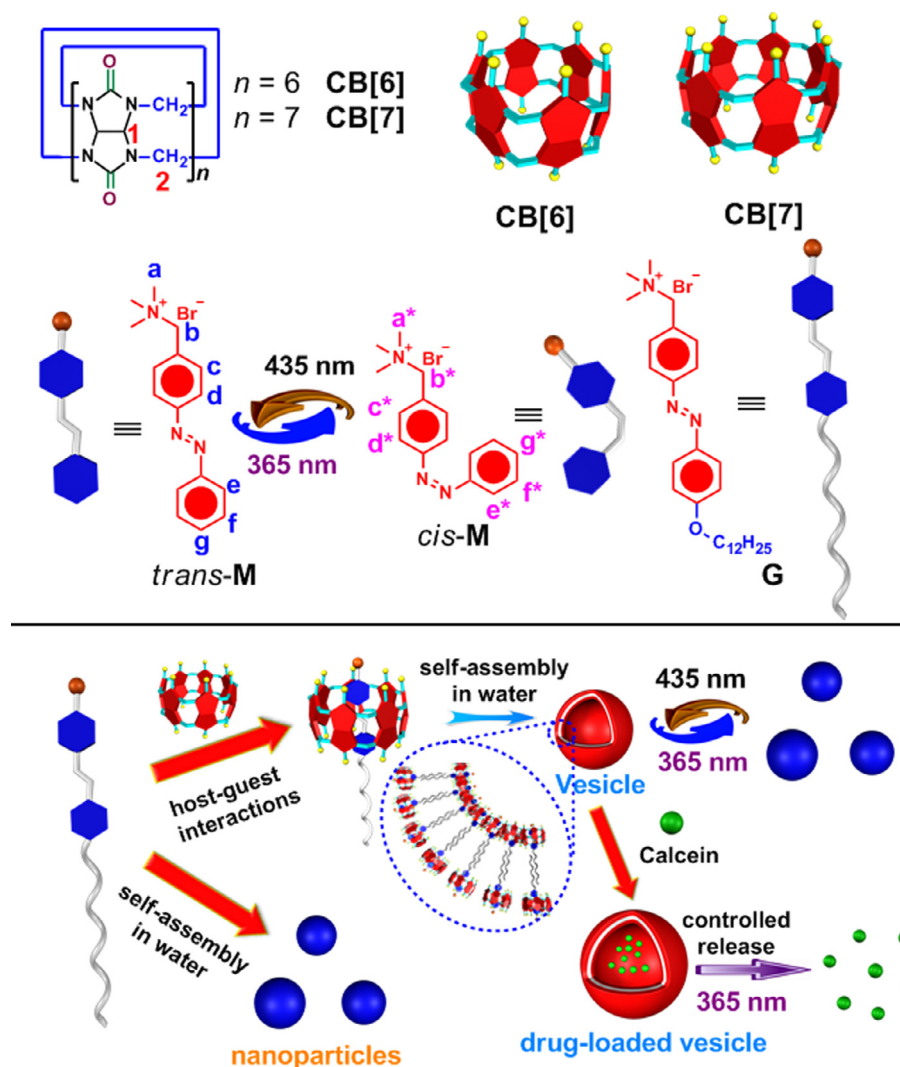
Scheme 1. Chemical structures of CB[*n*]s, **G** and **M**, and cartoon representation of the photo-responsive self-assembly between them in water.

of **M**, the chemical shift changes of signals related to the protons on **M** and CB[7] appeared (Fig. 1d). The signals related to protons H_{a-g} of **M** shifted upfield slightly ($\Delta\delta$ = −0.054, −0.124, −0.097, −0.015, −0.036, −0.049 and −0.049 ppm, respectively) and all the peaks corresponding to the protons on CB[7] shifted downfield slightly, which was ascribed to the ion-dipole interactions between **M** and CB[7].[7c] Moreover, the peaks corresponding to the protons on **M** and CB[7] all exhibited broadening effect, owing to the interactions between **M** and CB[7]. A 2D NOESY NMR experiment was conducted to investigate the relative positions of the components in the host–guest inclusion complex (Fig. 2a). NOE correlation signals were observed between protons $H_{1,2}$ on CB[7] and $H_{c,d,e,f,g}$ on **M**, which indicated that the azobenzene part of **M** located in the cavity of CB[7] upon forming a [2]pseudorotaxane.

After irradiation with UV light at 365 nm (8 W medium-pressure Hg lamp using a UV filter) for 30 min, the new peaks of the protons on *cis*-**M** appeared (Fig. 1f). As shown in Fig. 1g, the signals related to the protons on *cis*-**M** did not exhibit obvious upfield chemical shift changes, neither did the protons on CB[7]. These phenomena indicated that the photo-induced *E/Z* isomerization of azobenzene group of **M** occurred upon UV irradiation, resulting in the azobenzene part threading out of the cavity of CB[7], as shown in the cartoon representation of Fig. 1g. Upon further irradiation with visible light at 435 nm for 30 min, *cis*-**M** transformed

into the *trans* form. The proton signals related to the mixed solution of CB[7] and *trans*-**M** went back to the original state (Fig. 1h), indicating the azobenzene unit threading into the cavity of CB[7] again. The 2D NOESY NMR experiment was conducted again to demonstrate the complex model after the UV irradiation. As shown in Fig. 2b, no NOE correlation signals was observed between the protons on CB[7] and the benzene part of *cis*-**M**, confirming that the azobenzene part of *cis*-**M** was out of the cavity of CB[7].

Moreover, isothermal titration calorimetry (ITC) experiments were conducted to measure the association constant between CB[7] and **M**. As shown in Fig. S1, the association constant between CB[7] and *trans*-**M** was measured to be $(1.87 \pm 0.14) \times 10^6$ M^{-1}, while the association constant between CB[7] and *trans*-**M** after UV irradiation at 365 nm for 30 min decreased to $(1.21 \pm 0.07) \times 10^5$ M^{-1} (Fig. S2). It is notable that even though the azobenzene group threaded out of the cavity of CB[7], the association constant was still very high. The reason was that the main driving force of this host–guest complexation was ion-dipole interactions. After UV irradiation, the ion-dipole interactions were still very strong, thus the trimethylammonium group on the *cis*-**M** was bound by a rim of CB[7].

After the establishment of this photo-responsive host–guest complex model, we further applied it to construct a photo-responsive supra-amphiphile between CB[7] and **G**. From the work
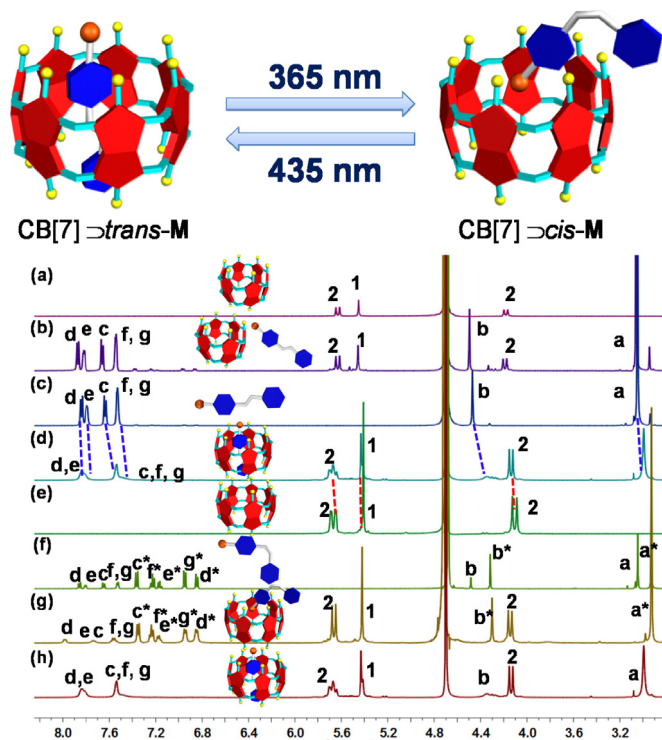
Fig. 1. Partial ^1H NMR spectra (400 MHz, D_2O, room temperature): (a) CB[6] (2.00 mM); (b) CB[6] (2.00 mM) and *trans*-**M** (2.00 mM); (c) *trans*-**M** (2.00 mM); (d) CB[7] (2.00 mM) and *trans*-**M** (2.00 mM); (e) CB[7] (2.00 mM); (f) *trans*-**M** (2.00 mM) after irradiation at 365 nm for 30 min; (g) CB[7] (2.00 mM) and *trans*-**M** (2.00 mM) after irradiation at 365 nm for 30 min; (h) (g) after irradiation at 435 nm for 30 min.

Fig. 2. Partial NOESY NMR spectra (500 MHz, D_2O, room temperature): (a) CB[7] (5.00 mM) and *trans*-**M** (5.00 mM); (b) CB[7] (5.00 mM) and *trans*-**M** (5.00 mM) after irradiation at 365 nm for 30 min.

reported before, the critical aggregation concentration (CAC) value of *trans*-**G** was measured to be 2.19×10^{-5} M.[4e] After the addition of CB[7], the CAC value of *trans*-**G** decreased to be 2.21×10^{-6} M (Fig. S3), which was ascribed to the host–guest complexation between CB[7] and **G**.[11] Transmission electron microscopy (TEM) experiments were conducted above the CAC value to investigate the microscopic morphologies of **G** and CB[7]⊃**G**. As shown in Fig. 3a, *trans*-**G** self-assembled into nanoparticles with an average diameter about 20 nm. Interestingly, after the addition of 1 equiv. of CB[7], the nanoparticles transformed to vesicle-like aggregates, with an average diameter about 150 nm (Fig. 3b). The wall thickness of the vesicles was measured to be 5 nm, in line with the length of two CB[7]⊃*trans*-**G** complexes with antiparallel packing, where the alkyl chains were overlapped (Fig. 3c). The vesicles can be destroyed by UV light irradiation. As shown in Fig. 3d, after irradiation at 365 nm for 30 min, the self-assembled vesicles transformed to nanoparticles with an average diameter about 50 nm. Moreover, upon further irradiation with visible light at 425 nm for 30 min, the nanoparticles transformed to vesicles again (Fig. 3e), indicating the reversibility of this photo-responsive self-assembly. Dynamic light scattering (DLS) experiments were utilized to measure the size of the self-assemblies. As shown in Figs. 3c and S4, the average sizes of the vesicles and the nanoparticles self-assembled from *trans*-**G** and CB[7] before and after UV irradiation were measured to be 142 and 51 nm, respectively, in good accordance with the TEM images.

A possible mechanism was proposed to explain the change in the morphology of the photo-responsive assemblies. *Trans*-**G** self-assembled into nanoparticles because of its amphiphilic property. After the addition of CB[7], the azobenzene part threaded into the cavity of CB[7] to form an inclusion complex-type supra-amphiphile, resulting in the formation of the vesicles with lower
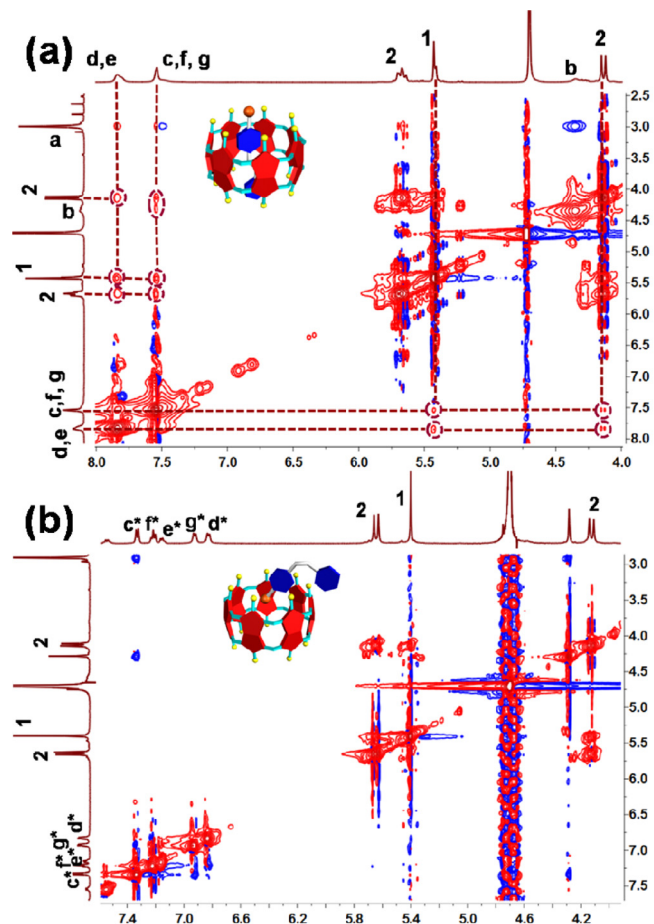
curvature because of the steric hindrance and the electrostatic repulsion. After UV irradiation, the azobenzene part of *cis*-**G** threaded out of CB[7], causing the destruction of the bilayer, and the re-formation of nanoparticles. Notably, the re-formed nanoparticles were larger than those from *trans*-**G**. The reason was that after UV irradiation, *cis*-**G** still complexed with CB[7], thus CB[7] could adhere to the nanoparticles self-assembled by *cis*-**G**, resulting in the increase of the size. Further irradiation with visible light, *cis*-**G** turn back to *trans*-**G** and its azobenzene part rethread into the cavity of CB[7], leading to the formation of vesicles again.

Depending on the photo-responsive assembly, controlled release experiments were then performed. A hydrophilic fluorescent indicator, calcein, was suitable to be encapsulated into the interior of the vesicles drugs. Calcein-loaded vesicles were prepared by mixing calcein, *trans*-**G**, and CB[7] together, and free calcein molecules were removed by dialyzing. As shown in Fig. 4, upon irradiation with UV light at 365 nm, the release percentage of calcein molecules from the vesicles was obtained by checking the fluorescence change in the solution. The release amount reached 100% at about 30 min, indicating the total collapse of the vesicles then.

In conclusion, a photo-responsive host–guest recognition motif based on CB[7] and an azobenzene-containing guest (**M**) was constructed successfully. Due to the size-selective effect, the guest can thread into the cavity of CB[7] rather than CB[6]. After UV irradiation, the azobenzene part of the guest would thread out of the cavity of CB[7] owing to the increased steric hindrance. Further irradiation with visible light, the guest can thread into the cavity
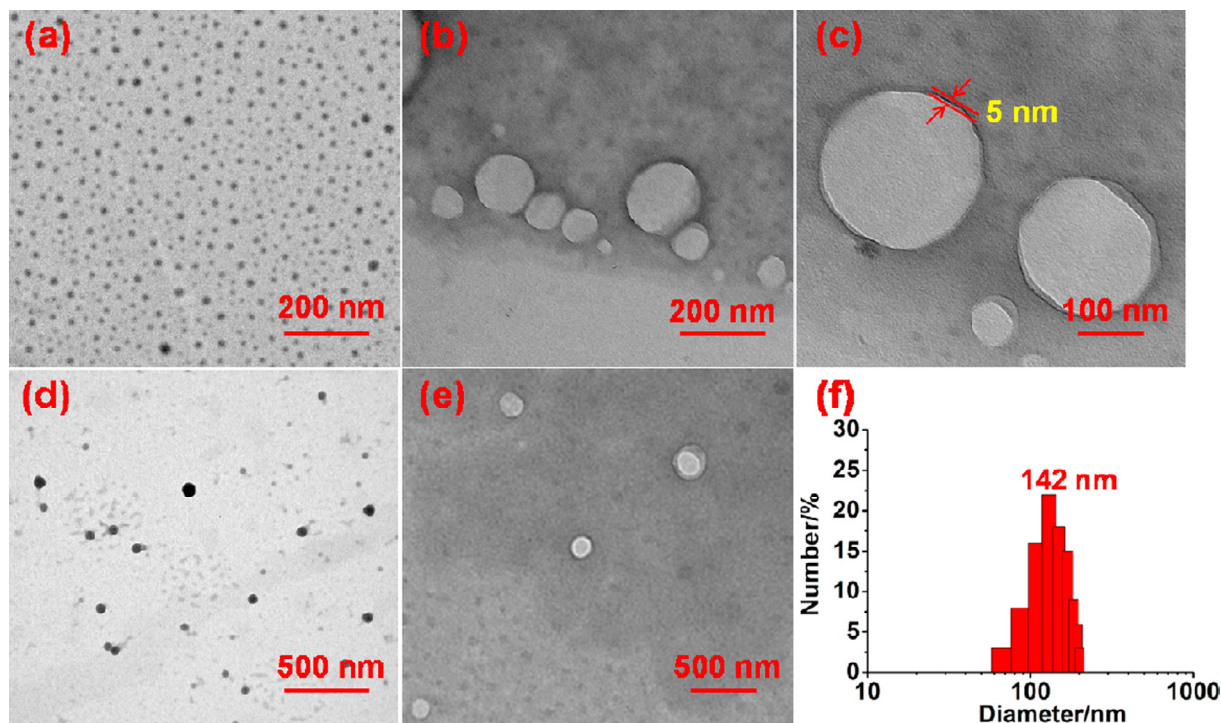
Fig. 3. TEM images: (a) the aggregates of **G** (1.00 × 10⁻⁴ M); (b) the aggregates of CB[7] (1 × 10⁻⁴ M) and *trans*-**G** (1.00 × 10⁻⁴ M); (c) enlarged TEM image of (b); (d) (b) after irradiation with UV light at 365 nm for 30 min; (e) (d) after irradiation with visible light at 435 nm for 30 min, (f) DLS result of (b).
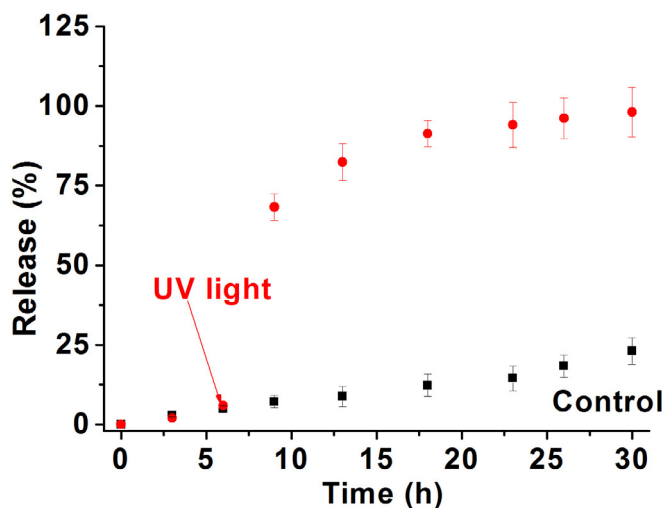
Fig. 4. Controlled release of calcein from the supramolecular vesicles upon UV stimulus and the free release of calcein from the vesicles without stimuli.

of CB[7] again. Based on this recognition motif, a photo-responsive supra-amphiphile was constructed by using an azobenzene-containing amphiphile (**G**) as the guest and CB[7] as the host. The nanoparticles formed by *trans*-**G** and the vesicles self-assembled from CB[7]⊃*trans*-**G** could be reversibly adjusted by UV and visible light irradiation on account of the photo-controlled association and disassociation between CB[7] and **G**, which resulted from the *trans*- and *cis*-photo-isomerization process of **G**. Furthermore, the present smart supramolecular vesicles based on this novel host–guest recognition motif can be applied in controlled release, which exemplify potential applications in drug delivery, sensors and some other smart nanomaterials.

Acknowledgments

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.03.091.

References

1. (a) Xue M, Yang Y, Chi X, Yan X, Huang F. *Chem Rev*. 2015;115:7398;
   (b) Karimi M, Ghasemi A, Zangabad PS, et al. *Chem Soc Rev*. 2016;45:1457;
   (c) Palivan CG, Goers R, Najer A, Zhang X, Car A, Meier W. *Chem Soc Rev*. 2016;45:377;
   (d) Wang W, Wang Y-X, Yang H-B. *Chem Soc Rev*. 2016;45:2656;
   (e) Heinzmann C, Weder C, Espinosa de LM. *Chem Soc Rev*. 2016;45:342.
2. (a) Wang F, Zhang J, Ding X, et al. *Angew Chem Int Ed*. 2010;49:1090;
   (b) Si W, Chen L, Hu X-B, et al. *Angew Chem Int Ed*. 2011;50:12564;
   (c) Niu L-Y, Guan Y-S, Chen Y-Z, Wu L-Z, Tung C-H, Yang Q-Z. *J Am Chem Soc*. 2012;134:18928;
   (d) Hu X-B, Chen Z, Tang G, Hou J-L, Li Z-T. *J Am Chem Soc*. 2012;134:8384;
   (e) Zhu K, Vukotic VN, Noujeim N, Loeb S. *J Chem Sci*. 2012;3:3265;
   (f) Duan Q, Cao Y, Li Y, et al. *J Am Chem Soc*. 2013;135:10542;
   (g) Wang X, Deng H, Li J, Zheng K, Jia X, Li C. *Macromol Rapid Commun*. 2013;34:1856;
   (h) Sun Y-L, Yang Y-W, Chen D-X, et al. *Small*. 2013;9:3224;
   (i) Ji X, Yao Y, Li J, Yan X, Huang F. *J Am Chem Soc*. 2013;135:74;
   (j) Li C. *Chem Commun*. 2014;50:12420;
   (k) Zhang Y, Shi B, Li H, et al. *Polym Chem*. 2014;5:4722;
   (l) Song N, Yang Y-W. *Chem Soc Rev*. 2015;44:3474;
   (m) Cao Y, Li Y, Hu X-Y, et al. *Chem Mater*. 2015;27:1110;
   (n) Yu G, Jie K, Huang F. *Chem Rev*. 2015;115:7240;
   (o) Luo L, Nie G, Tian D, Deng H, Jiang L, Li H. *Angew Chem Int Ed*. 2016;55:12713;
   (p) Wang P, Gao Z, Yuan M, Zhu J, Wang F. *Polym Chem*. 2016;7:3664.
3. (a) Piepenbrock M-OM, Clarke N, Steed JW. *Soft Matter*. 2010;6:3541;
   (b) Dong S, Luo Y, Yan X, et al. *Angew Chem Int Ed*. 2011;51:1905;
   (c) Hu J, Zhang G, Liu S. *Chem Soc Rev*. 2012;41:5933;
   (d) Zhang H, Ma X, Guo J, et al. *RSC Adv*. 2013;3:368;

(e) Cao Y, Hu X-Y, Li Y, et al. *J Am Chem Soc*. 2014;136:10762;
(f) Zhu B, Chen H, Lin W, Ye Y, Wu J, Li S. *J Am Chem Soc*. 2014;136:15126;
(g) Wang Q, Cheng M, Zhao Y, et al. *Chem Commun*. 2014;50:15585;
(h) Wu N-W, Chen L-J, Wang C, et al. *Chem Commun*. 2014;50:4231;
(i) Zhang M, Yan X, Huang F, Niu Z, Gibson HW. *Acc Chem Res*. 2014;47:1995;
(j) Li S, Weng G-H, Lin W, et al. *Polym Chem*. 2014;5:3994;
(k) Meng Z, Chen C-F. *Org Biomol Chem*. 2014;12:6937;
(l) Yang Z, Shi Y, Chen W, Wang F. *Polym Chem*. 2015;6:5540;
(m) Jie K, Zhou Y, Yao Y, Shi B, Huang F. *J Am Chem Soc*. 2015;137:10472;
(n) Jones CD, Steed JW. *Chem Soc Rev*. 2016;45:6546;
(o) Chi X, Zhang H, Vargas-Zúñiga GI, Petersand GM, Sessler JL. *J Am Chem Soc*. 2016;138:5829;
(p) Han Y, Meng Z, Chen C-F. *Chem Commun*. 2016;52:590;
(q) Li C, Wu L, Chen L, et al. *Dalton Trans*. 2016;45:19299.
4. (a) Sessler JL, Wang B, Harriman A. *J Am Chem Soc*. 1993;115:10418;
(b) Yu G, Han C, Zhang Z, et al. *J Am Chem Soc*. 2012;134:8711;
(c) Liu Y, Yu C, Jin H, et al. *J Am Chem Soc*. 2013;135:4765;
(d) Yang J, Yu G, Xia D, Huang F. *Chem Commun*. 2014;50:3993;
(e) Xia D, Yu G, Li J, Huang F. *Chem Commun*. 2014;50:3606;
(f) Barnes JC, Frasconi M, Young RM, et al. *J Am Chem Soc*. 2014;136:10569;
(g) Wang Y, Xu J-F, Chen Y-Z, et al. *Chem Commun*. 2014;50:7001;
(h) Sun H-L, Chen Y, Zhao J, Liu Y. *Angew Chem Int Ed*. 2015;54:9376;
(i) Chi X, Ji X, Xia D, Huang F. *J Am Chem Soc*. 2015;137:1440;
(j) Xia D, Wei P, Shi B, Huang F. *Chem Commun*. 2016;52:513;
(k) Shao L, Hua B, Yang J, Yu G. *Chem Commun*. 2016;52:6573;
(l) Schwarz FB, Heinrich T, Lippitz A, Unger WES, Schalley CA. *Chem Commun*. 2016;52:14458.
5. (a) Natansohn A, Rochon P. *Chem Rev*. 2002;102:4139;
(b) Dhammika BHM, Burdette SC. *Chem Soc Rev*. 2012;41:1809;

(c) Beharry AA, Woolley GA. *Chem Soc Rev*. 2011;40:4422;
(d) Ceroni P, Credi A, Venturi M. *Chem Soc Rev*. 2014;43:4068;
(e) Qu D-H, Wang Q-C, Zhang Q-W, Ma X, Tian H. *Chem Rev*. 2015;115:7543.
6. (a) Behrend R, Meyer E, Rusche F. *Justus Liebigs Ann Chem*. 1905;339:1;
(b) Freeman WA, Mock WL, Shih N-Y. *J Am Chem Soc*. 1981;103:7367;
(c) Kim J, Jung I-S, Kim S-Y, et al. *J Am Chem Soc*. 2000;122:540;
(d) Kim K, Selvapalam N, Ko YH, Park KM, Kim D, Kim J. *Chem Soc Rev*. 2007;36:267;
(e) Isaacs L. *Chem Commun*. 2009;619.
7. (a) Angelos S, Yang Y-W, Khashab NM, Stoddart JF, Zink JI. *J Am Chem Soc*. 2009;131:11344;
(b) Li C, Li J, Jia X. *Org Biomol Chem*. 2009;7:2699;
(c) Sun Y-L, Yang B-J, Zhang SX-A, Yang Y-W. *Chem Eur J*. 2012;18:9212;
(d) Barrow SJ, Kasera S, Rowland MJ, Barrio del J, Scherman OA. *Chem Rev*. 2015;115:12320;
(e) Nicolas H, Yuan B, Zhang X, Schönhoff M. *Langmuir*. 2016;32:2410;
(f) Chen R, Gu H, Qiu F, et al. *Tetrahedron*. 2016;72:5290.
8. (a) Barrio del J, Horton PN, Lairez D, Lloyd GO, Toprakcioglu C, Scherman OA. *J Am Chem Soc*. 2013;135:11760;
(b) Barrio del J, Ryan STJ, Jambrina PG, Rosta E, Scherman OA. *J Am Chem Soc*. 2016;138:5745.
9. Ma N, Wang W-J, Chen S, et al. *Chem Commun*. 2015;51:12970.
10. (a) Choi S, Park SH, Ziganshina AY, Ko YH, Lee JW, Kim K. *Chem Commun*. 2003;2176;
(b) Wu J, Isaacs L. *Chem Eur J*. 2009;15:11675;
(c) Baroncini M, Gao C, Carboni V, et al. *Chem Eur J*. 2014;20:10737;
(d) Xing P, Chen H, Ma M, Xu X, Hao A, Zhao Y. *Nanoscale*. 2016;8:1892.
11. Guo D-S, Wang K, Wang Y-X, Liu Y. *J Am Chem Soc*. 2012;134:10244.