ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2017, 53, 5326

Received 28th March 2017,
Accepted 11th April 2017

DOI: 10.1039/c7cc02364b

rsc.li/chemcomm

Pillar[5]arene-based [1]rotaxane: high-yield synthesis, characterization and application in Knoevenagel reaction†‡

Xu-Sheng Du, §[a] Chun-Yu Wang, §[b] Qiong Jia, [a] Rong Deng, [a] Hua-Sheng Tian, [a] Hou-Yu Zhang, *[b] Kamel Meguellati *[a] and Ying-Wei Yang *[a]

We report a quantitative synthetic strategy of a [1]rotaxane from a representative pseudo[1]rotaxane. The structure of the [1]rotaxane was characterized by ^{1}H NMR, ^{13}C NMR, 2D NMR, mass spectroscopy, and melting point, and its optimized geometry in $CHCl_3$ by theoretical calculation at the B3LYP/6-31G(D) level using the PCM model matched well with 2D NOESY. This [1]rotaxane proves to be a good catalyst for the Knoevenagel reaction in $CHCl_3$, which follows second order kinetics.

Topology in naturally occurring biological systems[1] has played a significant role in the expanding field of mechanically interlocked molecules (MIMs).[2] Rotaxane, a dumbbell-shaped molecule with a ring sliding along an axle, is widely used for artificial molecular machines.[3] Pseudo[1]rotaxanes that contain both the wheel and axle in one molecule, with a fast or slow exchange process between the threaded and open forms, are a special type of supramolecular self-assembly system. A [1]Rotaxane formed from stoppering of a pseudo[1]rotaxane (Fig. 1) deserves extensive and intensive investigation, but little attention has been paid due to the challenges in fabrication. To our best knowledge, synthetic macrocycle-based (pseudo)[1]rotaxanes are very limited in the literature. With the development of supramolecular and organic chemistry, many representative host molecules have been used for synthesis of pseudo[1]rotaxanes and [1]rotaxanes. For example, crown ethers and their analogues[4] were applied to the fabrication of functional [1]rotaxanes,[5] and cyclodextrins[6] were also employed.[7]

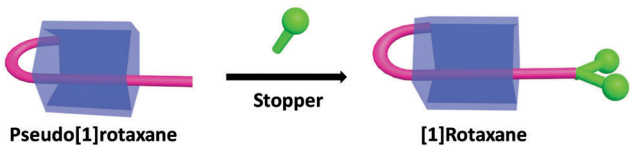


Fig. 1 Cartoon depicting the formation of a [1]rotaxane from a pseudo[1]-rotaxane *via* the stoppering method (pillar[5]arene is the representative macrocycle).

Pillar[*n*]arenes (pillararenes or pillarenes for short),[8] a very promising class of newly developed host compounds, have been extensively studied in recent years. Their pillar-shaped topology offers a promising platform for host–guest chemistry. Pillararene-based [2]rotaxanes have attracted much attention,[9] but pillararene-based [1]rotaxanes have rarely been studied. Some monofunctionalized pillar[5]arenes and their derivatives possess dynamic threading and dethreading properties, and they are endowed with inert moieties such as ammonium groups,[10] viologen side chains,[11] urea motifs,[12] and biotin moieties,[13] but they lack the reactivity to be further capped by potential stoppers. Even though, there are still a couple of examples related to the methodologies for fabricating pillararene-based [1]rotaxanes. For example, Yang *et al.* depicted a new monofunctionalized pillar[5]arene, bearing an imidazolium moiety, which formed a stable pseudo[1]rotaxane in chloroform, and subsequently formed a [1]rotaxane through the photo-initiated thiol–ene reaction.[14] The pre-organized pseudo[1]rotaxane between the primary amine group and carboxylic acid group attached on pillar[5]arene was also reported to form a [1]rotaxane.[15]

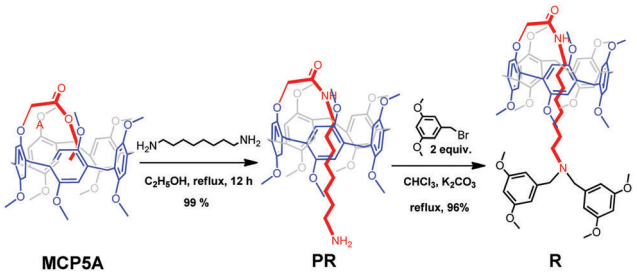
Inspired by the reports by Cao *et al.* that copillar[5]arenes bearing an acetate chain could form stable self-inclusion complexes in low and high concentration solutions,[16] and those by Hou *et al.* that aminolysis of ester-containing pillar[5]arenes displayed a self-inclusion property,[17] we directly synthesized a monoester-based copillar[5]arene (**MCP5A**) to form a self-included pseudo[1]rotaxane (**PR**), followed by direct capping *via* the S_N2 reaction with a stopper, *i.e.* 1-(bromomethyl)-3,5-dimethoxybenzene, to get a [1]rotaxane (**R**) (Scheme 1). Firstly, **MCP5A**[16]

[a] *International Joint Research Laboratory of Nano-Micro Architecture Chemistry (NMAC), College of Chemistry, Jilin University, 2699 Qianjin Street, Changchun 130012, P. R. China. E-mail: kamel@jlu.edu.cn, ywyang@jlu.edu.cn*
[b] *State Key Laboratory of Supramolecular Structure and Materials, Institute of Theoretical Chemistry, Jilin University, 2699 Qianjin Street, Changchun 130012, P. R. China. E-mail: houyuzhang@jlu.edu.cn*

† We dedicate this communication to Sir Fraser Stoddart on the occasion of his 75th birthday.

‡ Electronic supplementary information (ESI) available: experimental section, characterization data including ^{1}H NMR spectra, ^{13}C NMR spectra, 2D NMR spectra, mass spectra of related compounds, variable-concentration ^{1}H NMR spectra of **PR** in $CDCl_3$, calculated structures and data. See DOI: 10.1039/c7cc02364b

§ These authors contributed equally to this work.



Scheme 1 A synthetic route to **PR** and **R**.

was synthesized by a direct one-step cyclization of ethyl-4-methoxy phenoxy acetate and 1,4-dimethoxybenzene (Fig. S12–S14, ESI‡).

Subsequently, **PR** was synthesized from aminolysis of **MCP5A** by 1,8-diaminooctane and the exact mass was verified by HR-ESI-MS and MALDI-TOF-MS. (Fig. S15–S18, ESI‡). The ^{1}H NMR spectrum of **PR** was then taken into consideration. For comparison, ethyl-4-methoxy phenoxy acetate was also subjected to aminolysis by 1,8-diaminooctane (Fig. S3–S5, ESI‡). As in Fig. 2, several groups of peaks with chemical shift values below zero ppm demonstrated that the alkyl chain attaching onto the pillararene ring was in a shielding environment, which might result from either self-inclusion to form a pseudo[1]rotaxane, intermolecular threading to form a [c2]daisy chain, or self-assembly to give supramolecular polymers (Fig. S27, ESI‡). The signals in the ^{1}H NMR spectra were assigned with the assistance of 2D NMR analysis including ^{1}H–^{1}H COSY and ^{1}H–^{13}C HSQC (Fig. S19 and S20, ESI‡).

To further confirm the conformation of the pseudo[1]rotaxane, the relationship of the concentration and chemical shift values of hydrogens belonging to the side chain of **PR** was investigated, which shows concentration-independence. This is a sign of the formation of a stable self-included compound (Fig. S28 and Table S2, ESI‡).[11,16] Nuclear Overhauser Effect Spectroscopy (NOESY) also gave strong evidence because the cross-peaks on 2D NOESY indicate the proximity of protons (within 5 Å) that are not necessarily chemically bonded.[18] Indeed, from the partial NOESY spectra (Fig. 3), it was shown that the hydrogens of the side chain of **PR** were close to

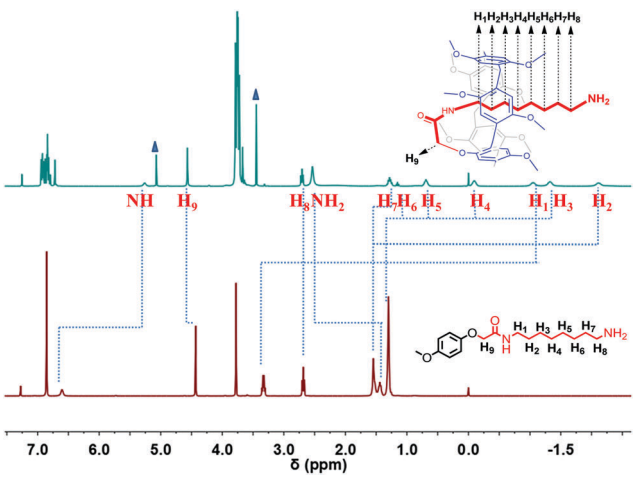


Fig. 2 ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of the monomer and **PR**. ▲ unassigned signal.

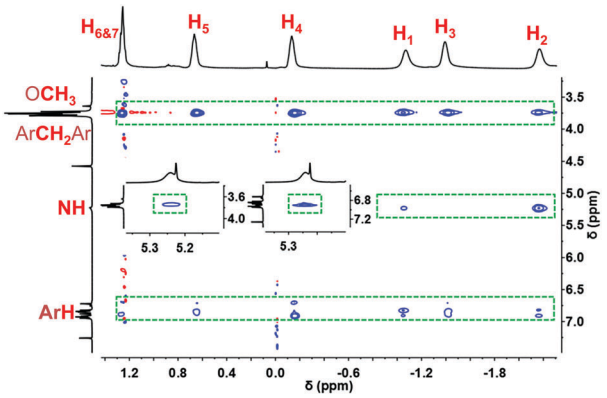


Fig. 3 Partial NOESY spectrum of **PR**.

pillararene itself because H_{1-7} displayed strong correlations with $-OCH_3$ and ArH indicating their presence in close proximity to the cavity. The –NH– group of the amide function is close to H_{1-2} and $-OCH_3$ and ArH. The calculated structure in the solvent is provided in Fig. S34–S36 (ESI‡), which is in accordance with the results from the NOESY spectra. Therefore, we conclude that **PR** is in a pseudo[1]rotaxane conformation. The driving force of **PR** in a stable self-included conformation is the bending of the pending chain induced by the flexibility of the methylene-containing side chain and amide group. This allows self-inclusion of the side chain within the pillar[5]arene cavity, which is thermodynamically favourable in $CHCl_3$.

Since **PR** in $CHCl_3$ can be described as a pseudo[1]rotaxane conformation, we decide to fabricate **R** *via* the S_N2 reaction between **PR** and 1-(bromomethyl)-3,5-dimethoxybenzene. This methodology is different from the one reported in the literature,[19] where imination of the amino group and aldehyde was accomplished to stop the pending chain moving out of the cavity. Initially, we proposed that the bulky space effect of the macrocyclic ring might favour the secondary amine. However, it is the tertiary amine that quantitatively formed **R** in $CHCl_3$. Significantly, the targeted **R** was quite easy to separate. Its exact mass was given by HR-ESI-MS and MALDI-TOF-MS (Fig. S21–S24, ESI‡).

Based on the analysis of **PR**, **R** was subjected to 2D NMR analysis for assignment of the corresponding signals in the ^{1}H NMR spectrum. The exact assignment of H_{1-8} was based on the COSY spectrum. It is worth noticing that, in the HSQC spectrum, H_7 is partially overlapped with H_8 and the signals of H_1 and H_7 split into two, due to chemical shift nonequivalence (Fig. S25 and S26 and Table S1, ESI‡). The NOE signals shown in Fig. 4a reveal that the [1]rotaxane **R** is formed in $CHCl_3$ because the NOE signals inside the dashed line demonstrate the correlation of the axial and aromatic hydrogen ArH of pillar[5]arene. H_{14} from the stopper has space correlation to the hydrogens H_{5-8} from **R** and H_{14} has an NOE signal with $-OCH_3$ of pillararene shown inside the full line, which might be ascribed to the dynamic motion of the stopper. To better understand the phenomenon, theoretical calculation using DFT theory for the conformation of **R** was also performed, which matched well with the results of the NOESY spectrum. The smallest distances are labelled in Fig. 4b (Fig. S37, ESI‡).

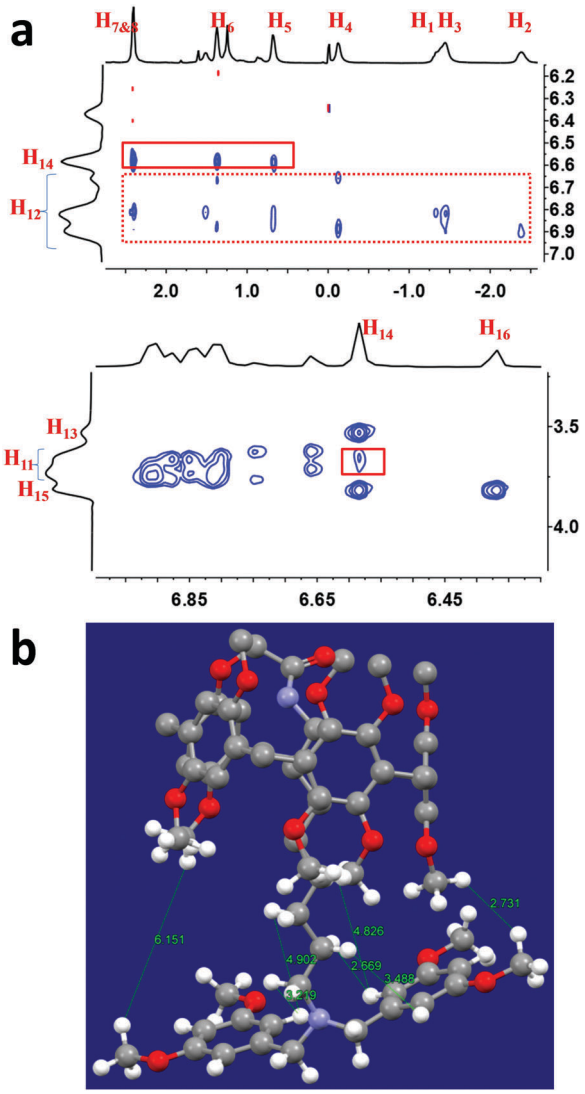
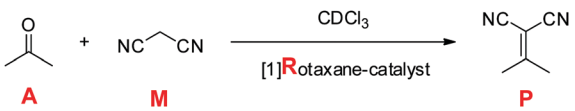


Fig. 4 (a) Partial NOESY spectra of **R**; (b) the optimized geometry of **R** at the B3LYP/6-31G(D) level using the PCM model in $CHCl_3$, where only the hydrogens in question are given for clarity.

The structural features of **R** include a tertiary amine, which is a weak organic base used for catalysis of some organic reactions. We applied this functionalized pillar[5]arene-based [1]rotaxane to Knoevenagel condensation as a model reaction. We selected, as a model, the reaction of malononitrile (**M**) and acetone (**A**) catalysed by **R** in $CHCl_3$ to generate the product (**P**), as is shown in Scheme 2. The results showed that **M** and **A** did not react in the absence of **R** at room temperature even after one month (Fig. S29, ESI‡). But when **R** was added in a catalytic amount, the condensation proceeded smoothly (Fig. S32, ESI‡). The malononitrile bearing active hydrogens were proposed to react with **R** to form the zwitterion, $[\mathbf{RH}]^+\cdot[\mathbf{M}]^-$, in $CHCl_3$ and initiate the reaction. For a



Scheme 2 Knovenagel condensation catalysed by **R**.

better understanding of the role pillar[5]arene played in the reaction, the corresponding monomer of the [1]rotaxane (**RM**) was put into use and the amide monomer (**AM**) was also used to eliminate the effect that the amide group may have on the catalysis of the model reaction (Fig. S33, ESI‡).

We can conclude that the tertiary amine is the main player in catalyzing the Knoevenagel reaction and the amide has no effect on the reaction. Comparing the rate of the model reaction catalysed by **R** and **RM**, the latter is two times faster than the former. This is ascribed to the space effect of pillar[5]arene that more or less hinders the rate determining step of the Knoevenagel reaction because of the slide of protonated **R** driven by the host–guest interaction, thus making the activated **M** on pillar[5]arene become less reactive.

To know more about the Knoevenagel reaction catalysed by **R**, the kinetics of the selected model were investigated. ^{1}H NMR spectroscopy was used to monitor the process of condensation, where a catalytic amount of **R** (10 mmol%) was used. With the reaction going, all of the reactants, **M** and **A**, were consumed and the corresponding condensation product **P** was formed. The ^{1}H NMR and ^{13}C NMR spectra of **P** were analysed and were in accordance with the literature[20] (Fig. S30 and S31, ESI‡). The integral values of **M**, **A** and **P** were recorded using **R** as a reference, and then were subjected to non-linear fitting, and the function adopted was an exponential function (Fig. 5a). The black line and the red one represent the decay of the reactants and the blue one the formation of the product. We estimated the half-time of the reactants experimentally as $t_{1/2}$ (**M**) to be 510 h and $t_{1/2}$ (**A**) to be 280 h, which came from the exponential function:

$$\mathbf{M}: y = 147.76e^{-\frac{x}{424}} + 55.62$$

$$\mathbf{A}: y = 122.82e^{-\frac{x}{278}} + 34.62$$

The reported kinetic study about Knoevenagel condensation obeyed second order kinetics.[21] We wondered if the model reaction fits to the same result. We theoretically used the secondary kinetic function that implied $1/[C] \propto t$ to plot the slope as is shown in Fig. 5b. The slopes represent the second order rate constant K(**M**) of 0.0099 L mol^{-1} h^{-1} and K(**A**) of 0.0232 L mol^{-1} h^{-1}, and the corresponding $t_{1/2}$(**M**) of 503 h and $t_{1/2}$(**A**) of 270 h. The half-time function of the second order kinetics is described as (K is the second order rate constant and $[C_i]$ is the initial concentration of reactant):

$$t_{1/2} = \frac{1}{K[C_i]}$$

Comparison of the theoretical and experimental half-times of the model Knoevenagel condensation catalysed by **R** showed that the values are the same and in accordance to second order kinetics. In short, the half-time found in this paper was reasonable in comparison with previously reported results, in which the half-time was estimated to be 70 days.[22]

In conclusion, we reported a new strategy to fabricate a functionalized [1]rotaxane *via* a "self-threading-stoppering" approach, and applied the [1]rotaxane successfully to catalysis of the Knoevenagel reaction in $CHCl_3$ with second order

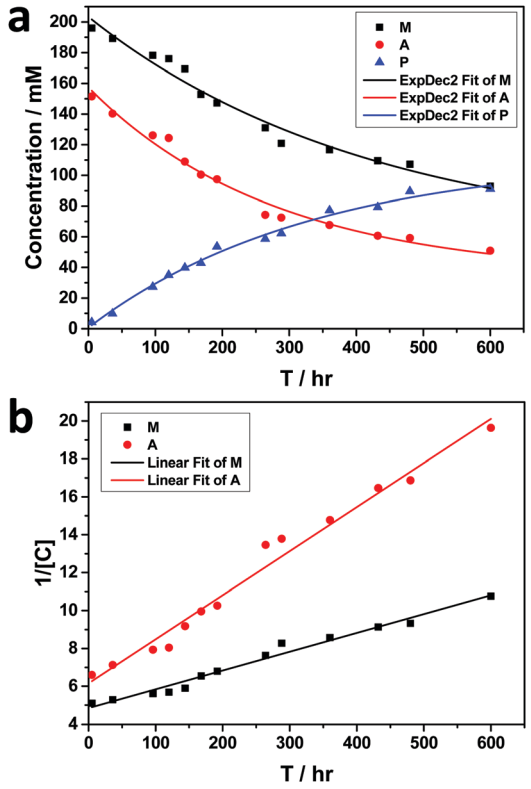


Fig. 5 (a) Non-linear fitting of the concentration change of constituents with the reaction going. The experimental $t_{1/2}$(**M**) was 510 h and $t_{1/2}$(**A**) was 280 h. (b) The theoretical second order rate constant function illustrated the linear correlation. The slopes represent the K(**M**) of 0.0099 L mol^{-1} and K(**A**) of 0.0232 L mol^{-1}, and the corresponding $t_{1/2}$(**M**) of 503 h and $t_{1/2}$(**A**) of 270 h.

kinetics. On the NMR time scale, we studied and assigned the position of the different methylene groups by 2D NMR analysis and theoretical calculation. This is to date the first example of a pillar[5]arene-based [1]rotaxane for catalysis. Based on the aforementioned results, several perspectives are on-going in our laboratory such as the construction of molecular machines with multiple stations for catalysis and biological purposes.

We thank the National Natural Science Foundation of China (51673084, 51473061) for financial support.

Notes and references

1 K. J. Rosengren, R. J. Clark, N. L. Daly, U. Göransson, A. Jones and D. J. Craik, *J. Am. Chem. Soc.*, 2003, **125**, 12464–12474.
2 (*a*) R. S. Forgan, J.-P. Sauvage and J. F. Stoddart, *Chem. Rev.*, 2011, **111**, 5434–5464; (*b*) D. B. Amabilino and L. Perez-Garcia, *Chem. Soc. Rev.*, 2009, **38**, 1562–1571; (*c*) C. J. Bruns and J. F. Stoddart, *The Nature of the Mechanical Bond: From Molecules to Machines*, John Wiley & Sons, Inc., Hoboken, NJ, USA, 2016.
3 S. Erbas-Cakmak, D. A. Leigh, C. T. McTernan and A. L. Nussbaumer, *Chem. Rev.*, 2015, **115**, 10081–10206.
4 G. W. Gokel, W. M. Leevy and M. E. Weber, *Chem. Rev.*, 2004, **104**, 2723–2750.
5 (*a*) H. Li, X. Li, Z.-Q. Cao, D.-H. Qu, H. Ågren and H. Tian, *ACS Appl. Mater. Interfaces*, 2014, **6**, 18921–18929; (*b*) G. Yu, Y. Suzaki and K. Osakada, *RSC Adv.*, 2016, **6**, 41369–41375; (*c*) T. Ogawa, K. Nakazono, D. Aoki, S. Uchida and T. Takata, *ACS Macro Lett.*, 2015, **4**, 343–347; (*d*) P. Waeles, C. Clavel, K. Fournel-Marotte and F. Coutrot, *Chem. Sci.*, 2015, **6**, 4828–4836; (*e*) H. Li, J.-N. Zhang, W. Zhou, H. Zhang, Q. Zhang, D.-H. Qu and H. Tian, *Org. Lett.*, 2013, **15**, 3070–3073; (*f*) T. Ogawa, N. Usuki, K. Nakazono, Y. Koyama and T. Takata, *Chem. Commun.*, 2015, **51**, 5606–5609; (*g*) H. Li, H. Zhang, Q. Zhang, Q.-W. Zhang and D.-H. Qu, *Org. Lett.*, 2012, **14**, 5900–5903; (*h*) Q. Zhou, P. Wei, Y. Zhang, Y. Yu and X. Yan, *Org. Lett.*, 2013, **15**, 5350–5353; (*i*) Z. Xue and M. F. Mayer, *J. Am. Chem. Soc.*, 2010, **132**, 3274–3276; (*j*) K. Hiratani, M. Kaneyama, Y. Nagawa, E. Koyama and M. Kanesato, *J. Am. Chem. Soc.*, 2004, **126**, 13568–13569.
6 (*a*) G. Wenz, B.-H. Han and A. Müller, *Chem. Rev.*, 2006, **106**, 782–817; (*b*) J. Szejtli, *Chem. Rev.*, 1998, **98**, 1743–1754; (*c*) S. A. Nepogodiev and J. F. Stoddart, *Chem. Rev.*, 1998, **98**, 1959–1976.
7 (*a*) J. Cao, X. Ma, M. Min, T. Cao, S. Wu and H. Tian, *Chem. Commun.*, 2014, **50**, 3224–3226; (*b*) L. Zhu, H. Yan and Y. Zhao, *Int. J. Mol. Sci.*, 2012, **13**, 10132; (*c*) X. Ma, D. Qu, F. Ji, Q. Wang, L. Zhu, Y. Xu and H. Tian, *Chem. Commun.*, 2007, 1409–1411.
8 (*a*) T. Ogoshi, S. Kanai, S. Fujinami, T.-A. Yamagishi and Y. Nakamoto, *J. Am. Chem. Soc.*, 2008, **130**, 5022–5023; (*b*) M. Xue, Y. Yang, X. Chi, Z. Zhang and F. Huang, *Acc. Chem. Res.*, 2012, **45**, 1294–1308; (*c*) P. J. Cragg and K. Sharma, *Chem. Soc. Rev.*, 2012, **41**, 597–607; (*d*) T. Ogoshi, T.-A. Yamagishi and Y. Nakamoto, *Chem. Rev.*, 2016, **116**, 7937–8002; (*e*) C. Sathiyajith, R. R. Shaikh, Q. Han, Y. Zhang, K. Meguellati and Y.-W. Yang, *Chem. Commun.*, 2017, **53**, 677–696; (*f*) Y. Wang, G. Ping and C. Li, *Chem. Commun.*, 2016, **52**, 9858–9872; (*g*) N. L. Strutt, H. Zhang, S. T. Schneebeli and J. F. Stoddart, *Acc. Chem. Res.*, 2014, **47**, 2631–2642; (*h*) Y.-W. Yang, Y.-L. Sun and N. Song, *Acc. Chem. Res.*, 2014, **47**, 1950–1960; (*i*) N. Song and Y.-W. Yang, in *Pillararenes*, ed. T. Ogoshi, Royal Society of Chemistry, Thomas Graham House, United Kingdoms, 2016, ch. 10, pp. 229–262; (*j*) N. Song and Y.-W. Yang, *Sci. China: Chem.*, 2014, **57**, 1185–1198; (*k*) M.-C. Xia and Y.-W. Yang, *Prog. Chem.*, 2015, **27**, 655–665; (*l*) N. Song and Y.-W. Yang, *Chem. Soc. Rev.*, 2015, **44**, 3474–3504; (*m*) H. Zhang, X. Ma, K. T. Nguyen and Y. Zhao, *ACS Nano*, 2013, **7**, 7853–7863; (*n*) W. Si, P. Xin, Z.-T. Li and J.-L. Hou, *Acc. Chem. Res.*, 2015, **48**, 1612–1619.
9 (*a*) W.-B. Hu, W.-J. Hu, X.-L. Zhao, Y. A. Liu, J.-S. Li, B. Jiang and K. Wen, *Chem. Commun.*, 2015, **51**, 13882–13885; (*b*) C. Ke, N. L. Strutt, H. Li, X. Hou, K. J. Hartlieb, P. R. McGonigal, Z. Ma, J. Iehl, C. L. Stern, C. Cheng, Z. Zhu, N. A. Vermeulen, T. J. Meade, Y. Y. Botros and J. F. Stoddart, *J. Am. Chem. Soc.*, 2013, **135**, 17019–17030; (*c*) X. Hou, C. Ke, C. Cheng, N. Song, A. K. Blackburn, A. A. Sarjeant, Y. Y. Botros, Y.-W. Yang and J. F. Stoddart, *Chem. Commun.*, 2014, **50**, 6196–6199.
10 T. Ogoshi, K. Demachi, K. Kitajima and T.-A. Yamagishi, *Chem. Commun.*, 2011, **47**, 7164–7166.
11 N. L. Strutt, H. Zhang, M. A. Giesener, J. Lei and J. F. Stoddart, *Chem. Commun.*, 2012, **48**, 1647–1649.
12 (*a*) Y. Guan, P. Liu, C. Deng, M. Ni, S. Xiong, C. Lin, X.-Y. Hu, J. Ma and L. Wang, *Org. Biomol. Chem.*, 2014, **12**, 1079–1089; (*b*) M. Ni, X.-Y. Hu, J. Jiang and L. Wang, *Chem. Commun.*, 2014, **50**, 1317–1319.
13 X. Wu, M. Ni, W. Xia, X.-Y. Hu and L. Wang, *Org. Chem. Front.*, 2015, **2**, 1013–1017.
14 C.-L. Sun, J.-F. Xu, Y.-Z. Chen, L.-Y. Niu, L.-Z. Wu, C.-H. Tung and Q.-Z. Yang, *Chin. Chem. Lett.*, 2015, **26**, 843–846.
15 (*a*) B. Xia and M. Xue, *Chem. Commun.*, 2014, **50**, 1021–1023; (*b*) M. Cheng, Q. Wang, Y. Cao, Y. Pan, Z. Yang, J. Jiang and L. Wang, *Tetrahedron Lett.*, 2016, **57**, 4133–4137.
16 Y. Chen, D. Cao, L. Wang, M. He, L. Zhou, D. Schollmeyer and H. Meier, *Chem. – Eur. J.*, 2013, **19**, 7064–7070.
17 L. Chen, Z. Li, Z. Chen and J.-L. Hou, *Org. Biomol. Chem.*, 2013, **11**, 248–251.
18 (*a*) W. Nerdal, D. R. Hare and B. R. Reid, *Biochemistry*, 1989, **28**, 10008–10021; (*b*) M. I. Gjerde, W. Nerdal and H. Høiland, *J. Colloid Interface Sci.*, 1996, **183**, 285–288; (*c*) Y. Y. Chien and W. F. Bleam, *Environ. Sci. Technol.*, 1998, **32**, 3653–3658; (*d*) D. Leitz, B. Vögeli, J. Greenwald and R. Riek, *J. Phys. Chem. B*, 2011, **115**, 7648–7660; (*e*) J. T. Lo, H. T. Yen, C. C. Tsai, B. H. Chen and S. S. Hou, *J. Phys. Chem. B*, 2014, **118**, 6922–6930.
19 Y. Han, G.-F. Huo, J. Sun, J. Xie, C.-G. Yan, Y. Zhao, X. Wu, C. Lin and L. Wang, *Sci. Rep.*, 2016, **6**, 28748.
20 A. R. Longstreet, B. S. Campbell, B. F. Gupton and D. T. McQuade, *Org. Lett.*, 2013, **15**, 5298–5301.
21 F. S. Prout, V. D. Beaucaire, G. R. Dyrkacz, W. M. Koppes, R. E. Kuznicki, T. A. Marlewski, J. J. Pienkowski and J. M. Puda, *J. Org. Chem.*, 1973, **38**, 1512–1517.
22 E. V. Dalessandro, H. P. Collin, M. S. Valle and J. R. Pliego, *RSC Adv.*, 2016, **6**, 57803–57810.