Chinese Chemical Letters 31 (2020) 1550–1553

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

Pillar[5]arene-based [3]rotaxanes: Convenient construction *via* multicomponent reaction and pH responsive self-assembly in water

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ARTICLE INFO

Article history:
Received 28 September 2019
Received in revised form 19 November 2019
Accepted 25 November 2019
Available online 25 November 2019

Keywords:
Pillar[5]arene
[3]Rotaxane
Multicomponent reaction
Molecular machine
Self-assembly

ABSTRACT

Four pillar[5]arene based [3]rotaxanes (**1-4**) involving two 1,4-diethoxypillar[5]arene (**DEP5**) rings and a dumbbell-shaped component were successfully synthesized. The dumbbell-shape molecules contain one longer bridge, two triazole sites and two multicomponent stoppers. After threading **DEP5** rings with linear guests (**G1**-**G4**) which contain two benzaldehyde units, the base catalyzed three-component reaction of dimedone, malononitrile and benzaldehyde was performed to construct the stoppers and connected the pseudorotaxanes with stoppers to generate **1–4**. The structures of [3]rotaxanes and their self-assembly behaviors were characterized by ^{1}H NMR, ^{13}C NMR, NOESY, HR-ESI-MS, DLS and TEM technologies. We hope that pillar[5]arene based [3]rotaxanes may have potential applications in drug delivery systems and molecular devices.

Rotaxane [1], usually constructed from macro-cyclic wheels and linear axles, have been attracted great interesting due to their unique interlocked structures and wide application in various areas such as molecular machines, stimuli-responsive materials, information storage and supramolecular catalysts [2]. The macrocyclic host and its noncovalent interaction are keys for the construction rotaxanes [3]. During the past decades, crown ethers, cyclodextrins, calix[*n*]arenes and cucurbiturils have been used as wheels to fabricate [*n*]rotaxanes successfully [4].

Pillar[5]arenes, which were first prepared by Ogoshi in 2008 [5], are a very “smart” type of newly supramolecular hosts and have been widely investigated in recent years [6,7]. The symmetrical pillar-like topology and π-electron rich cavity endow pillar[5]arenes as ideal platforms for host-guest chemistry [8]. Pillar[5]arene-based [1]rotaxanes and [2]rotaxanes have been attracted much attention and widely investigated [9]. For example, Prof. Yang and co-workers synthesized a pillar[5]arene-based [1]rotaxane from a self-included pseudo[1]rotaxane direct reacting with a stopper. What is more, this [1]rotaxane proved to be a good catalyst for Knoevenagel reaction in $CHCl_3$ [9a]. Prof. Huang and co-workers prepared a pillar[5]arene/imidazolium [2]rotaxane, and found this [2]rotaxane showed solvent- and thermo-driven molecular motions [9b].

However, higher-ordered [*n*]rotaxanes ($n \geq 3$) based on pillar[5]arene remain rarely studied limited by the poor synthetic yield, despite their fascinating structure and potential applications in molecular devices [10]. Herein, in this study, we designed and conveniently constructed four pillar[5]arene-based [3]rotaxanes (**1-4**) from two pillar[5]arene wheels and a linear guest in high yields with one-pot multicomponent reaction. As shown in Scheme 1, linear guests **G1-G4** containing two benzaldehyde groups were prepared in 3 steps from *p*-hydroxybenzaldehyde with yields about 80% firstly (Figs. S1-S12 in Supporting information). Then, 1,4-diethoxypillar[5]arene (**DEP5**) and aliphatic chain axel **G1-G4** were stirred in chloroform/ethanol mixture at room temperature overnight, which enable the axel threaded into the cavity of pillar[5]arene. At last, the base catalyzed three-component reaction of dimedone, malononitrile and benzaldehyde was used as the stopper reaction. The three-component reaction was carried out in refluxing ethanol in the presence of piperidine for 3 h. After workup, the expected pillar[5]arene-based [3]rotaxanes **1-4** were successfully obtained in moderate yields (Figs. S13-S24 in Supporting information). For comparison, “dumbbell” molecule **5** was also prepared in the absence of **DEP5** (Scheme 1).

Fig. 1 showed the typical ^{1}H NMR spectra of dumbbell **5**, wheel **DEP5** and [3]rotaxane **4**. The -CH_2- protons H_c, H_d, H_e, H_f, H_h and H_b in triazole of **4** showed clearly upfield shifts in comparison with

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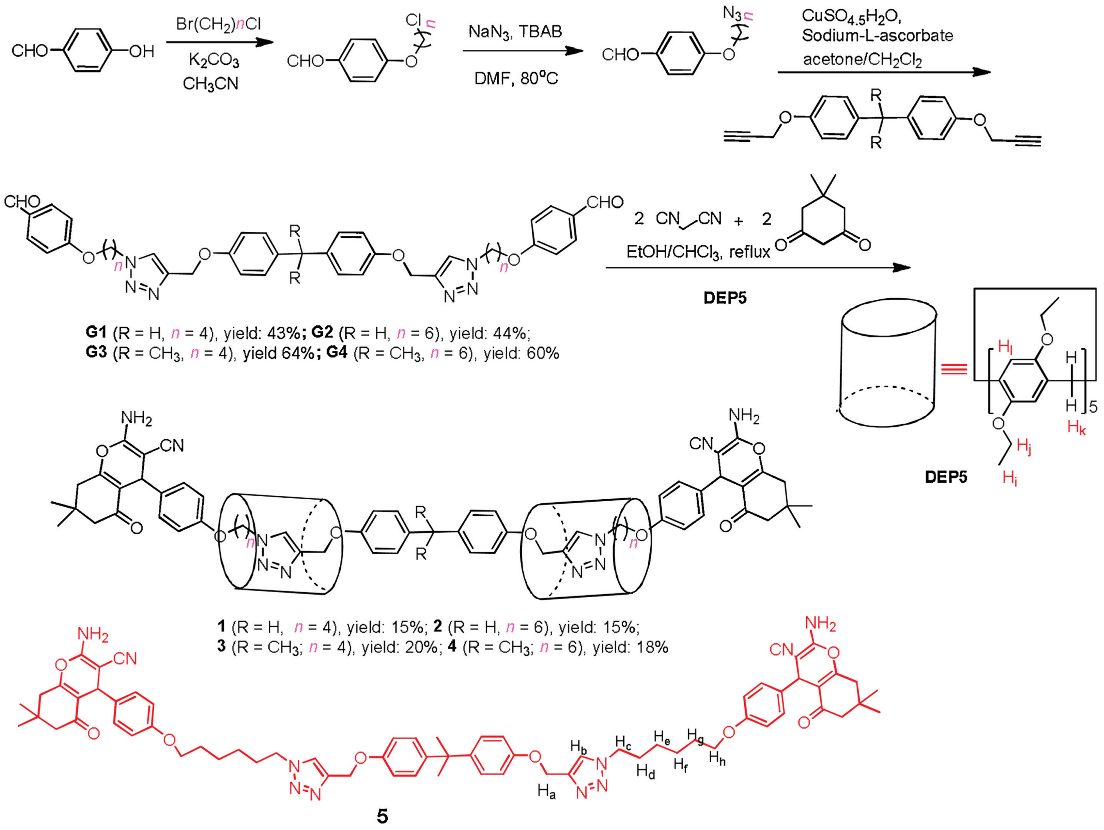
https://doi.org/10.1016/j.cclet.2019.11.041



Scheme 1. A synthetic route to guests **G1-G4** and [3]rotaxanes **1–4**.

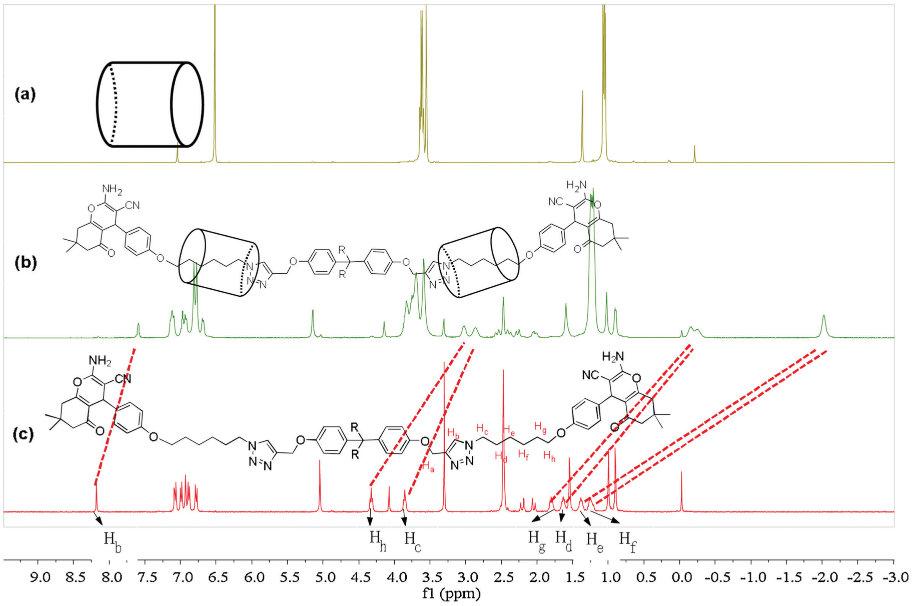


Fig. 1. ^{1}H NMR spectra (room temperature, 400 MHz, DMSO-d_6) of 2.00 mmol/L **DEP5** (a), 2.00 mmol/L **4** (b), and 2.00 mmol/L axle **5** (c).

those of compound **5** due to the encapsulation induced shielding effects [11]. On the other hand, the protons H_i, H_j and H_k of the wheel **DEP5** shifted downfield compared with free pillar[5]arene, which was due to the deshielding effects. It should be pointed that the ^{1}H NMR experiments were investigated in highly polar DMSO-d_6, indicating that the obtained stopper is bulky enough for the [3]rotaxane.

Furthermore, 2D NOESY spectrum of [3]rotaxane **4** in DMSO-d_6 showed clearly NOE correlation signals between protons H_i, H_j, H_k, and H_l of the wheel pillar[5]arene and protons H_b, H_c, H_d, H_e, H_f, H_g, and H_h of the linear axle (Fig. 2). In addition, mass spectrometry also confirmed the formation of [3]rotaxane. In the mass spectrum of [3]rotaxane **4** (Fig. S24), a base peak at *m/z* 1479.8145 (100%) corresponding to $[M+2H]^{2+}$ was observed. All the above NMR

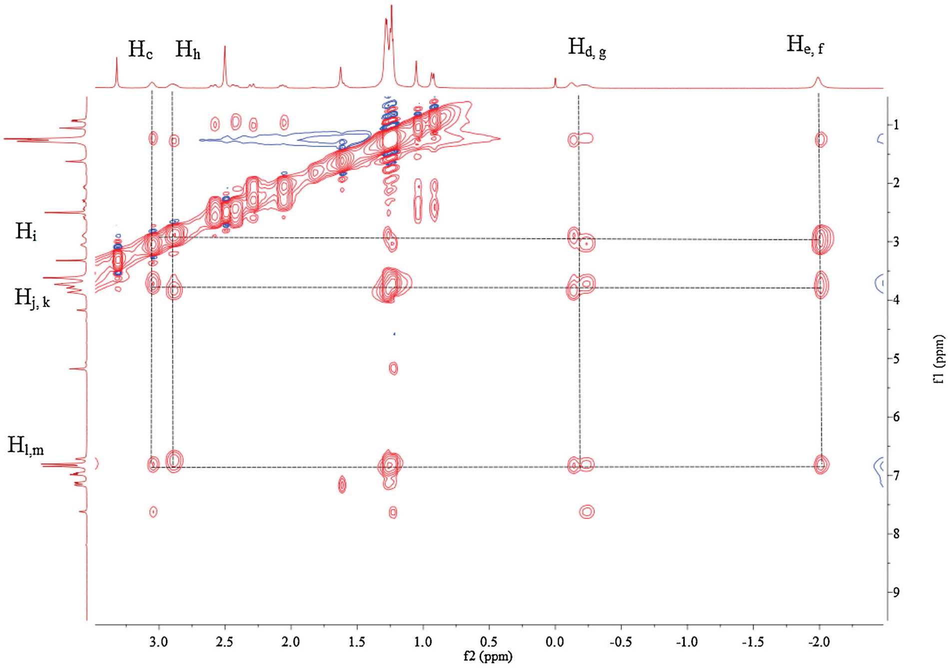


Fig. 2. Partial 2D NOESY NMR spectrum of [3]rotaxane **4**.

and mass investigations led us to conclude the formation of [3]rotaxane. [3]Rotaxanes **1–3** were also confirmed by the similar NMR and mass studies (Figs. S13-S21).

Considering the symmetrical pillar-like, rigid architecture incorporated in [3]rotaxane **4**, we wondered the potential self-assembly behavior of **4** in water. [3]Rotaxane **4** was dissolved in DMF firstly (10^{-3} mol/L), then 1.00 mL solution of **4** was injected into 99 mL water under vigorous stirring. Dynamic light scattering (DLS) experiment performed with a 1.00×10^{-5} mol/L aqueous solution of **4** over a scattering angle of 90° showed a broad size distribution (Fig. 3a). The average hydrodynamic diameter (D_h) of **4** was observed to be about 500 nm. Then we used transmission electron microscopy (TEM) to investigate the self-assembly behaviors of [3]rotaxane in water. As shown in Fig. 3b, **4** self-assembled into irregular solid particles, whose average diameter was about 500 nm, much larger than the length of the **4**, indicating that the particles self-assembled from tremendous molecules fusing together (Fig. 3c).

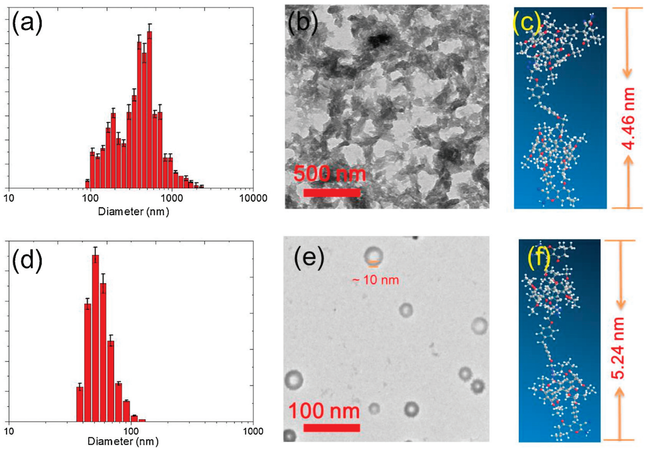


Fig. 3. (a) DLS data of **4**-based aggregates in water. (b) TEM image of **4**-based aggregates in water. (c) Minimize energy structure of **4** (calculated by Gaussian 09 B. 01/B3LYP/6−31 G (d,p)). (d) DLS data of **4**-based assemblies in water after addition of H^+. (e) TEM image of **4**-based assemblies in water after addition of H^+. (f) Minimize energy structure of **4-H** (calculated by Gaussian 09 B. 01/B3LYP/6−31 G (d,p)).

Inspired by the amino groups and triazole units can be protonated by H^+, we then investigated the pH-responsive property of **4** in water. When we added 4 equiv. of HCl into the particles' solution, DLS showed that average hydrodynamic diameter (D_h) of **4-H** was changed to 40 nm with narrow distribution (Fig. 3d). TEM confirmed that the large particles transformed into vesicles with diameter about 40 nm (Fig. 3e). What is more, the thickness of the vesicle' wall is about 10 nm, indicating its bilayer (Fig. 3f). This transformation is due to that when **4** were protonated, it became an amphiphilic compound, so it can self-assemble into regular vesicles through hydrophilic-hydrophobic interactions.

In conclusion, four pillar[5]arene based [3]rotaxanes (**1**-**4**) involving two pillar[5]arene (**P5**) rings and a dumbbell-shaped component were synthesized successfully *via* multicomponent reaction. The structures of [3]rotaxanes were characterized and confirmed by ^{1}H NMR, ^{13}C NMR, NOESY and HR-ESI-MS technologies. Furthermore, take **4** as example, due to the amino groups and triazole units incorporated in **4** can be protonated by H^+, when addition of 4 equiv. of HCl into the aqueous solution of **4**, well-defined vesicles with diameter about 40 nm were observed. We hope that pillar[5]arene based [3]rotaxanes may have potential applications in drug delivery systems and molecular devices.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Nos. 21871227, 21801139), Natural Science Foundation of Jiangsu Province (No. BK20180942), Natural Science Foundation of Nantong University for High-Level Talent (No. 03083004).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.11.041.

References

[1] (a) K.D. Hanni, D.A. Leigh, Chem. Soc. Rev. 39 (2010) 1240–1251;
(b) M.D. Lankshear, P.D. Beer, Acc. Chem. Res. 40 (2007) 657–668;
(c) T. Ikeda, M. Higuchi, D.G. Kurth, J. Am. Chem. Soc. 131 (2009) 9158–9159;
(d) M. He, L. Chen, B. Jiang, et al., Chin. Chem. Lett. 30 (2019) 131–134.

[2] (a) T. Ogoshi, D. Yamafuji, T. Aoki, T.A. Yamagishi, Chem. Commun. (Camb.) 48 (2012) 6842–6844;
(b) Y. Yao, X.J. Wei, Y. Cai, et al., J. Colloid Interf. Sci. 533 (2019) 42–46.

[3] E.M.G. Jamieson, F. Modicom, S.M. Goldup, Chem. Soc. Rev. 47 (2018) 5266–5311.

[4] (a) Y. Liu, Q. Zhang, W.H. Jin, et al., Chem. Commun. (Camb.) 54 (2018) 10642–10645;
(b) T.G. Zhan, H.H. Yin, S.T. Zheng, et al., Chem. Commun. (Camb.) 54 (2018) 9356–9359;
(c) G. Gholami, K. Zhu, G. Baggi, et al., Chem. Sci. 8 (2017) 7718–7723;
(d) W. Wu, S. Song, X. Cui, et al., Chin. Chem. Lett. 29 (2018) 95–98;
(e) R. Zhang, C. Wang, R. Long, et al., Front. Chem. 7 (2019) 508.

[5] T. Ogoshi, S. Kanai, S. Fujinami, et al., J. Am. Chem. Soc. 130 (2008) 5022–5023.

[6] (a) S. Sun, D. Lu, Q. Huang, et al., Colloids Interface Sci. Commun. 533 (2019) 42–46;
(b) S. Sun, M. Geng, L. Huang, et al., Chem. Commun. (Camb.) 54 (2018) 13006–13009;
(c) K. Jie, Y. Zhou, E. Li, et al., Acc. Chem. Res. 51 (2018) 2064–2072;
(d) Y. Zhang, W. Zhu, X. Huang, et al., ACS Sust. Chem. Eng. 6 (2018) 16597–16606;
(e) E. Li, K. Jie, Y. Zhou, et al., J. Am. Chem. Soc. 140 (2018) 15070–15079;
(f) J.R. Wu, A. Mu, B. Li, et al., Angew. Chem. Ing. Ed. 57 (2018) 9853–9858;
(g) M. Zuo, W. Qian, Z. Xu, et al., Small 14 (2018) 1801942;
(h) L.L. Zhao, Y. Han, C.G. Yan, Chin. Chem. Lett. 31 (2020) 81-83;
(i) C.B. Yin, Y. Han, G.F. Huo, et al., Chin. Chem. Lett. 28 (2017) 431–436;
(j) J. Chen, Y. Wang, C. Wang, et al., Chem. Commun. (Camb.) 55 (2019) 6817–6826.

[7] (a) T. Xiao, L. Zhou, L. Xu, et al., Chin. Chem. Lett. 30 (2019) 271–276;
(b) T. Xiao, W. Zhong, L. Xu, X.Q. Sun, X.Y. Hu, L. Wang, Org. Biomol. Chem. 17 (2019) 1336–1350;
(c) Y. Wang, T. Liu, J. Jiang, et al., Dalton Trans. 48 (2019) 6333–6336.

[8] (a) Q. Wang, L. Tian, J. Xu, et al., Chem. Commun. (Camb.) 54 (2018) 10328–10331;
(b) K. Yang, K. Yang, S. Chao, et al., Chem. Commun. (Camb.) 54 (2018) 9817–9820;
(c) H. Shi, X. Cheng, Q. Lin, et al., Chin. J. Org. Chem. 38 (2018) 1718–1724;
(d) Y. Sun, F. Zhang, J. Quan, et al., Nat. Comm. 9 (2018) 2617;
(e) J.Y. Chen, W.W. Hao, M. Zhang, et al., Faraday Discuss. 209 (2018) 149–159;
(f) J. Wu, J. Tian, L. Rui, W. Zhang, Chem. Commun. (Camb.) 54 (2018) 7629–7632.

[9] (a) X.S. Du, C.Y. Wang, Q. Jia, et al., Chem. Commun. (Camb.) 53 (2017) 5326–5329;
(b) S. Dong, J. Yuan, F. Huang, Chem. Sci. 5 (2014) 247–252;
(c) X. Zeng, H. Deng, X. Jia, et al., Chem. Commun. (Camb.) 54 (2018) 11634–11637;
(d) Y. Han, C.Y. Nie, S. Jiang, J. Sun, C.G. Yan, Chin. Chem. Lett. 31 (2020) 725-728.

[10] C.L. Sun, K.X. Teng, L.Y. Niu, Y.Z. Chen, Q.Z. Yang, Acta Chim. Sinica 76 (2018) 779–784.

[11] D. Xia, P. Wei, B. Shi, F. Huang, Chem. Commun. (Camb.) 52 (2016) 513–516.