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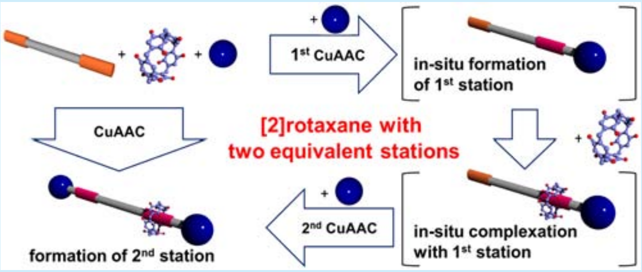
Synthesis of a Pillar[5]arene-Based [2]Rotaxane with Two Equivalent Stations via Copper(I)-Catalyzed Alkyne−Azide Cycloaddition

Tomoki Ogoshi,* Ryo Iizuka, Daisuke Kotera, and Tada-aki Yamagishi

Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

Supporting Information

ABSTRACT: A one-pot synthesis of pillar[5]arene-based [2]rotaxanes containing one and two stations by copper(I)-catalyzed alkyne−azide cycloaddition (CuAAC) reaction is reported. In situ formation of the two stations by two stepwise CuAAC reactions allows for the synthesis of a [2]rotaxane containing two stations with equal energy levels that exhibit shuttling of the pillar[5]arene wheel.



[2]Rotaxanes,[1] which consist of a macrocyclic "wheel" and "axle", are one of the simplest mechanically interlocked molecules. The interlocked macrocyclic wheel in [2]rotaxanes can shuttle between two stations.[2] Therefore, a great deal of interest has been paid to [2]rotaxanes that possess two stations because of their potential use as physical and chemical stimuli-responsive molecular shuttles or switches.[3] However, to synthesize [2]rotaxanes containing two stations, the introduction of a protecting group at one station site is necessary in many cases to inhibit the formation of [3]rotaxanes containing two wheels on two stations.[2a,b] Thus, simple, conventional methods to produce [2]rotaxanes containing two stations are desired.

Pillar[*n*]arenes (Figure 1a),[4] which were first reported by our group in 2008,[4a] are attracting a great deal of interest and are now important macrocyclic hosts in supramolecular chemistry. Pillar[*n*]arenes are easy-to-make synthetic receptors[5] and can be functionalized using various organic reactions.[6] One favorable characteristic of pillar[*n*]arenes is their excellent host−guest behavior.[7] On the basis of their host−guest property, pillar[5]arene-based rotaxanes have been synthesized.[8] However, there are no examples of pillar[5]arene-based [2]rotaxane containing two stations. Li and co-workers reported selective complexation between per-ethylated pillar[5]arene **1** (Figure 1a) and neutral heterocycle-substituted 1,4-butylene guests.[7a] The binding affinity of *n*-butylene with two 1-substituted 1,2,3-triazole moieties at its end **2** [Figure 1b, $K = (1.6 \pm 0.3) \times 10^4\ \mathrm{M}^{-1}$] for **1** is much stronger than that with one 1-substituted 1,2,3-triazole moiety **3** [Figure 1b, $K = (1.0 \pm 0.2) \times 10^2\ \mathrm{M}^{-1}$]. Triazole moieties can be easily prepared by the copper(I)-catalyzed Huisgen alkyne−azide 1,3-dipolar cycloaddition reaction (CuAAC reaction),[9] so we speculated that stepwise CuAAC reaction between diyne and diazide moieties should be practical for the synthesis of [2]rotaxanes. In this study, we synthesized [2]rotaxanes using the stepwise CuAAC reaction. Interestingly, [2]rotaxanes containing two stations with equal energy levels can be synthesized by in situ formation of the two stations through end-capping using the CuAAC reaction.

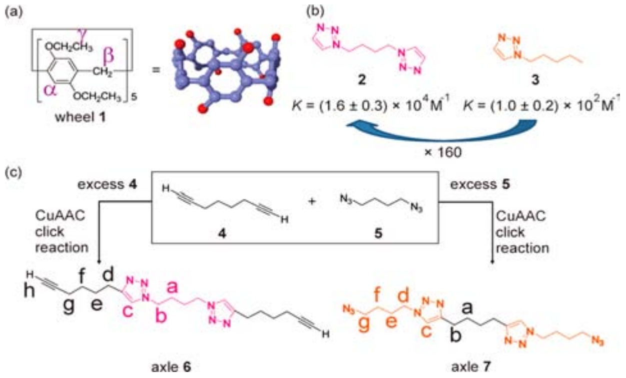


Figure 1. Chemical structures of (a) per-ethylated pillar[5]arene wheel **1** and (b) neutral heterocycle-substituted 1,4-butylene guests (**2** and **3**). (c) Synthesis of axles **6** and **7** by CuAAC reaction between diyne **4** and diazide **5**.

per-Ethylated pillar[5]arene **1** as a ring component and 1,7-octadiyne **4** and 1,4-diazidobutane **5** as starting compounds were used to synthesize axles (Figure 1). CuAAC reaction of an excess of diyne **4** (20 equiv) with diazide **5** (1 equiv) afforded axle **6** containing alkyne moieties at both ends (yield 84%). CuAAC reaction between excess diazide **5** (20 equiv) and diyne **4** (1 equiv) gave axle **7** bearing azido moieties at both ends (yield 68%). Purification of these axles was simple: Starting compounds **4** and **5** were soluble in hexane, but the axles were not, so washing the mixture with hexane allowed the axles to be isolated. Host−guest complexation was assessed by ^{1}H NMR spectroscopy (Figure 2). When pillar[5]arene wheel **1** was added to axle **6** (Figure 2b), new peaks appeared from the *n*-butylene linker

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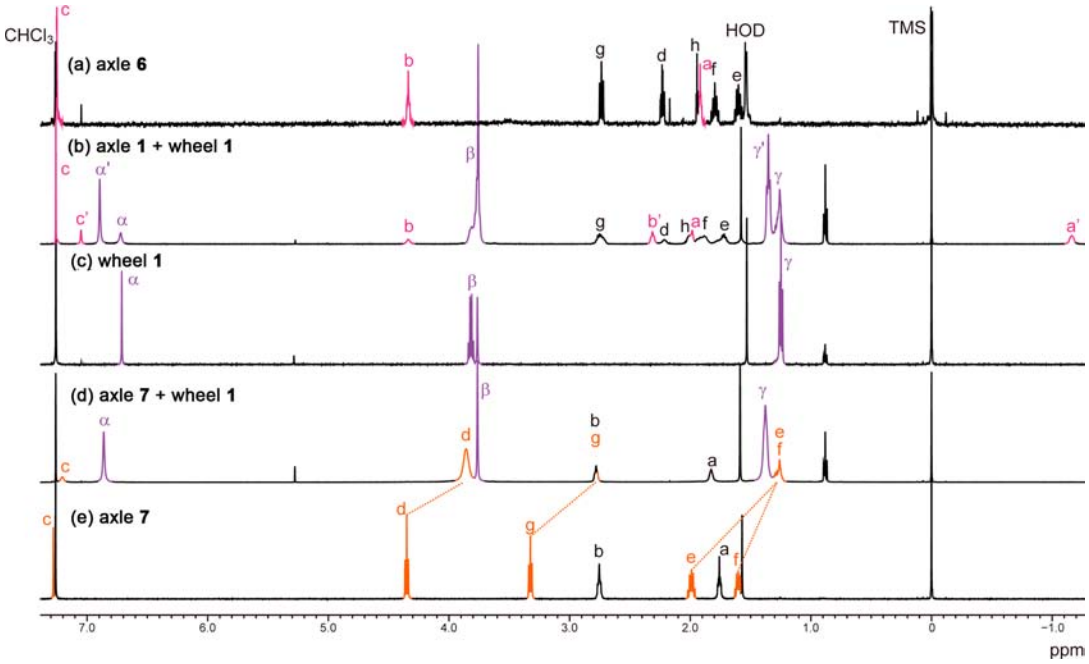

Figure 2. ^{1}H NMR spectra (CDCl$_3$, 25 °C, 5 mM) of (a) axle **6**, (b) 1:1 mixture of axle **6** and wheel **1**, (c) wheel **1**, (d) 1:1 mixture of axle **7** and wheel **1**, and (e) axle **7**.

between 1-substituted 1,2,3-triazole moieties in axle **6**, which is defined as N-ended butylene linker (pink peaks a′, b′, and c′) and pillar[5]arene wheel **1** (purple peaks α' and γ'), indicating slow complexation on the NMR time scale and formation of a pseudorotaxane type inclusion complex with **1** on the N-ended butylene linker in axle **6**. The stoichiometry of the complex determined from a Job plot was 1:1 (Figure S8). The association constant K for the host−guest complex formed between wheel **1** and axle **6** determined from the ^{1}H NMR data was $K = (1.9 \pm 0.003) \times 10^4$ M^{-1}, which is of the same order of magnitude as that of the complex between pillar[5]arene **1** and N-ended butylene linker **2**.[7a]

The CuAAC reaction was then used to synthesize the corresponding [2]rotaxane (Figure 3). To a mixture of wheel **1** (5 equiv) and axle **6** (1 equiv), an azide-terminated stopper **8** (3 equiv) was added together with [CuCH$_3$CN)$_4$PF$_6$] and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA). Purification of the resulting mixture by silica gel chromatography afforded [2]rotaxane **9** containing one wheel and one axle (yield 54%). A high-resolution electrospray ionization mass spectrum of [2]rotaxane **9** contained a peak at m/z 1766, corresponding to M$^+$, and confirming formation of [2]rotaxane **9**. Dumbbell **10** was also synthesized in the absence of wheel **1**.

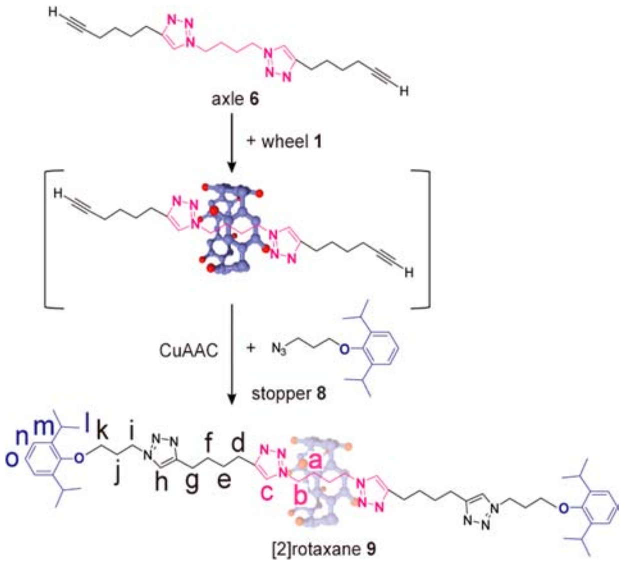

Figure 3. Synthesis of [2]rotaxane **9** via end-capping by the CuAAC reaction.

Comparison of the ^{1}H NMR spectra of [2]rotaxane **9**, wheel **1**, and dumbbell **10** indicates the location of the wheel in [2]rotaxane **9** (Figure 4). Upfield shifts of the proton signals from the N-ended butylene linker moieties (Figure 4b, pink peaks a, b, and c) and downfield shifts of the proton signals from the phenyl and methyl moieties of the wheel (Figure 4b, purple peaks α and γ) were found compared to the corresponding signals of dumbbell **10** (Figure 4a) and wheel **1** (Figure 4c) because these protons were shielded by the wheel. Meanwhile, the chemical shifts of the other proton signals were almost the same as those of dumbbell **10**. These results indicate that the wheel was not located on the *n*-butylene linker between 4-substituted 1,2,3-triazole moieties, which is defined as C-ended butylene linker, but instead on the N-ended butylene linker moieties. The driving forces for the formation of these host−guest systems include multiple CH/π interactions and CH/N hydrogen bonds.[7a] Thus, the N-ended butylene linker moiety is a better station site compared with that between C-ended butylene linker moiety because it can bond more strongly to wheel **1**.

Host−guest complexation between wheel **1** and axle **7** was also investigated by ^{1}H NMR spectroscopy. Upon the addition of pillar[5]arene **1** to axle **7** (Figure 2d), the proton signals from the *n*-butylene linker between azido and 1-substituted 1,2,3-triazole moieties in axle **7** showed upfield shifts (orange peaks d−g), indicating that the complexation is fast in the NMR time scale. The stoichiometry of this host−guest complex determined from a Job plot was 2:1 (Figure S9), indicating that two pillar[5]arenes **1** were located on the *n*-butylene linker between azido and 1-

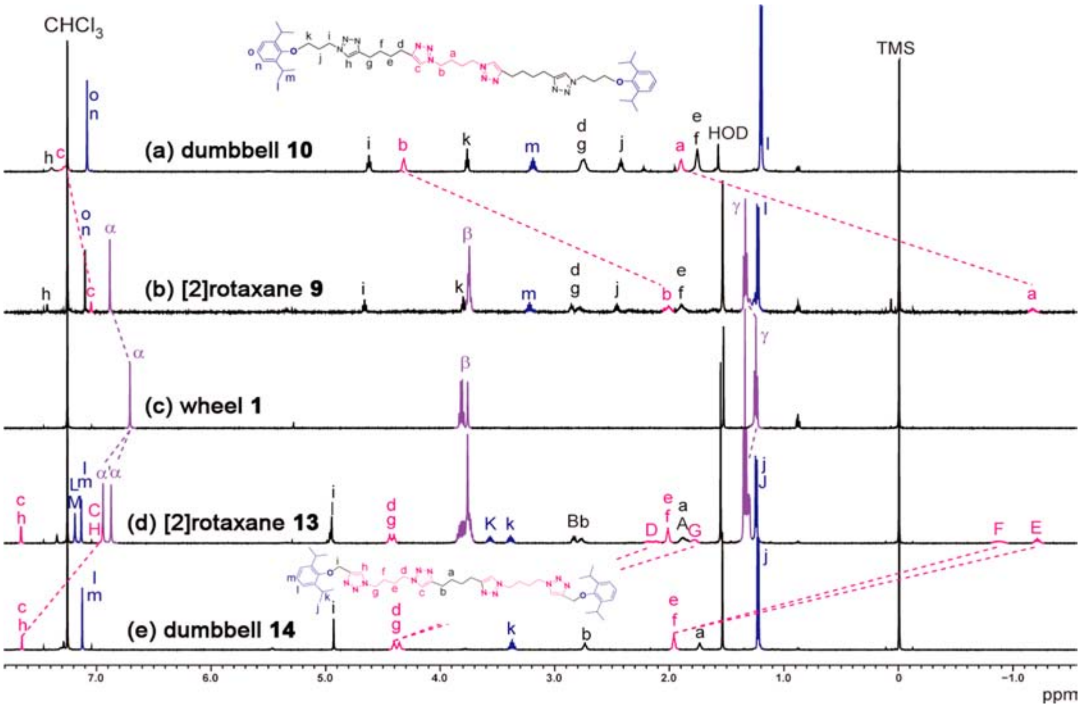

Figure 4. ^{1}H NMR spectra (CDCl$_3$, 25 °C, 5 mM) of (a) dumbbell **10**, (b) [2]rotaxane **9**, (c) wheel **1**, (d) [2]rotaxane **13**, and (e) dumbbell **14**.

substituted 1,2,3-triazole moieties in axle **7**. The association constants K_1 and K_2 calculated for the host−guest complex between wheel **1** and axle **7** were $K_1 = (4.4 \pm 1.8) \times 10^2$ M^{-1} and $K_2 = (2.0 \pm 0.3) \times 10^2$ M^{-1}, which are of the same order of magnitude as those for the complex between pillar[5]arene **1** and mono-1,2,3-triazole substituted *n*-butylene **3** and smaller than the association constants for **1** with a N-ended butylene linker moieties (**2** and axle **6**). *n*-Butylene between azido and 1-substituted 1,2,3-triazole moieties is a better station compared with *n*-butylene between 4-substituted 1,2,3-triazole moieties because of the formation of multiple CH/π interactions and CH/N hydrogen bonds of the azido and 1-substituted 1,2,3-triazole moieties with wheel **1**.[7a]

The CuAAC reaction was also used to synthesize a rotaxane using axle **7**. Axle **7** has azido moieties at both ends, so alkyne stopper **11** was used to produce the corresponding rotaxane. The rotaxane formed by CuAAC reaction of axle **7** (1 equiv) and stopper **11** (3 equiv) in the presence of pillar[5]arene wheel **1** (5 equiv) was not [3]rotaxane **12** consisting of two pillar[5]arene wheels and one axle, but [2]rotaxane **13** with one pillar[5]arene wheel and one axle. Purification of the resulting mixture by silica gel chromatography afforded [2]rotaxane **13** (yield 42%). A high-resolution electrospray ionization mass spectrum of [2]rotaxane **13** contained a peak at *m*/*z* 1766, corresponding to M$^+$, consistent with the formation of [2]rotaxane **13**. The proposed mechanism for the formation of [2]rotaxane **13** is shown in Figure 5. First, CuAAC reaction between axle **7** and stopper **11** affords the intermediate **15**. The N-ended butylene linker moiety in intermediate **15** is a stable station for wheel **1**, so a pseudo[2]rotaxane structure forms. A second CuAAC reaction between intermediate **15** and stopper **11** then affords [2]-rotaxane **13**. This second CuAAC reaction also generates the second station; that is, the N-ended butylene linker moieties. However, wheel **1** cannot slip over the stopper ends. Therefore, stepwise CuAAC reactions are needed to form [2]rotaxane **13** with two stations. Figure 4d shows a ^{1}H NMR spectrum of

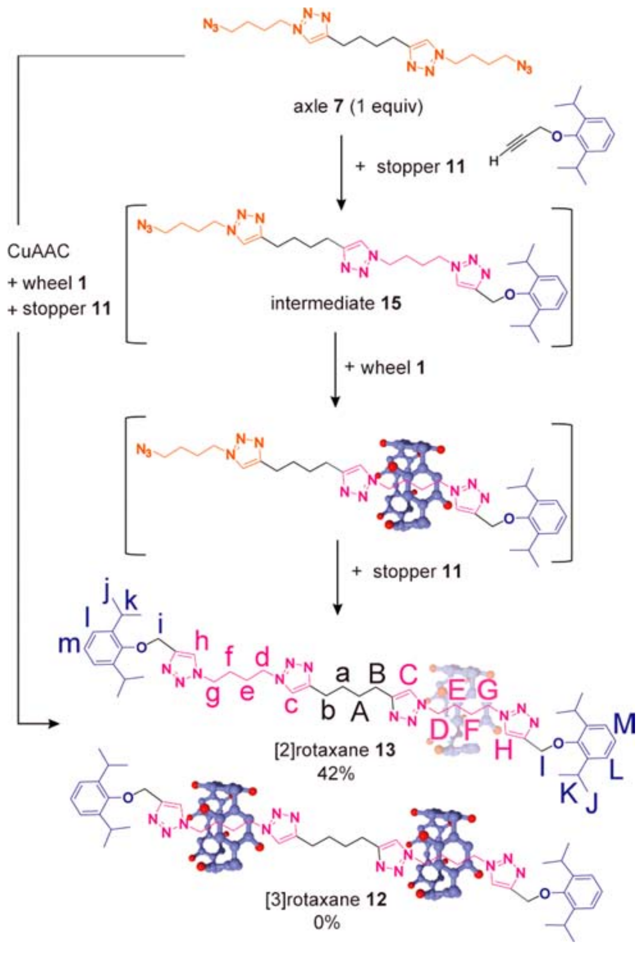

Figure 5. Synthesis of [2]rotaxane **13** by in situ formation of two stations with equal energy levels.

[2]rotaxane **13**. Proton signals from the N-ended butylene linker moieties (pink peaks C−H) were upfield compared with those of dumbbell **14**. Downfield shifts of the proton signals from wheel **1** were also observed (purple peaks α, α', and γ) compared with those of wheel **1** (Figure 4c). In addition, proton signals from [2]rotaxane **13** have two sets of signals. These sets of signals are assigned as the complexed and uncomplexed sides of the molecule, indicating shuttling of the wheel between the two stations is slow on the NMR time scale at 25 °C. The shuttling behavior of the wheel between two stations was investigated by variable temperature ^{1}H NMR measurements. The wheel shuttling remained slow on the NMR time scale in $CDCl_3$ at 45 °C (Figure S12, the limit of temperature in this experiment). In contrast, coalescence of the complexed and uncomplexed signals was found at 51 and 78 °C in DMSO-d_6 and toluene-d_8, respectively (Figures S13 and S14). From the coalescence temperature, the rate constant of wheel shuttling in **13** at 25 °C (k) was 11.0 s^{-1} in DMSO-d_6. k in toluene-d_8 was 0.5 s^{-1}, which is approximately 22 times slower than that in DMSO-d_6. This is because solvation of the stations competes more effectively with the noncovalent interaction between pillar[5]arene and the stations in polar solvent (DMSO-d_6) compared with nonpolar solvent (toluene-d_8). Coalescence was not observed in [2]-rotaxane **9** (Figure S11), indicating that shuttling of wheel **1** did not occur because [2]rotaxane **9** has only one station in the axle segment.

In conclusion, we synthesized pillar[5]arene-based [2]-rotaxanes with one and two stations by multiple CuAAC reactions. This is the first example in which a pillar[5]arene-based [2]rotaxane contained two stations with equal energy levels. The synthesis of a [2]rotaxane with two stations did not require the introduction of protecting groups. The functional groups can be installed in the axle segments because the axle was synthesized by the CuAAC reaction. Therefore, this synthetic method will be of great use in the formation of various pillar[5]arene-based [2]rotaxanes that show wheel shuttling between two stations and will be extended to develop stimuli-responsive degenerate [2]rotaxanes by introducing stimuli-responsive groups and [n]rotaxanes having nonequivalent multistations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental section, characterization data, ^{1}H NMR, Job plots, ^{1}H NMR titration, and variable temperature ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +81-76-234-4775. Fax: +81-76-234-4800. E-mail: ogoshi@se.kanazawa-u.ac.jp.

Notes

The authors declare no competing financial interest.

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