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Construction of Type III-C Rotaxane-Branched Dendrimers and Their Anion-Induced Dimension Modulation Feature

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ABSTRACT: Starting from a novel rotaxane building block with dendrimer growth sites being located at both the wheel and axle component, we realized the successful construction of a new family of rotaxane-branched dendrimers, *i.e.* Type III-C rotaxane-branched dendrimers up to fourth-generation as a highly branched [46]rotaxane through a controllable divergent approach. In the resultant rotaxane-branched dendrimers, the wheel components of the rotaxane units are located on the branches as well as at the branching points, making them excellent candidates to mimic the amplified collective molecular motions. Thus, taking advantage of the urea moiety inserted into the axle components of the rotaxane units as the binding sites, the addition or removal of acetate anion as stimulus endows the individual rotaxane unit switchable feature that lead to a collective expansion-contraction motion of the integrated rotaxane-branched dendrimers, thus allowing for the remarkable and reversible size modulation. Such three-dimensional size switching feature makes Type III-C rotaxane-branched dendrimers a very promising platform towards the fabrication of novel dynamic smart materials.

INTRODUCTION

Inspired by biomolecular machines in living systems that perform vital biological functions such as synthesis, replication, motion, and transport etc.,¹ a great number of artificial molecular machines² such as molecular shuttle,³ molecular muscle,⁴ molecular motor,⁵ molecular assembler⁶ etc., have been constructed by chemists. As an intriguing feature of biomolecular machines, the remarkable amplification of collective molecular motions of functional nanomechanical moieties with specific arrangements leads to the essential biological functions as outputs.⁷ Taking the macroscopic motion of muscles as a representative example, such process originates from the coordinative movements of sarcomeres in a cooperative manner.⁸ In order to mimic such biological process, the integration of multiple artificial molecular machine units with a delicate arrangement has attracted more and more attentions towards the construction of novel dynamic bio-inspired materials. For instance, by using the rotaxane-based molecular muscles⁹ (especially [c2]daisy chain rotaxanes¹⁰) as key building blocks, a series of muscle-like supramolecular polymers have been constructed, whose macroscopic properties could be modulated by the controllable motions of the molecular muscle units at nanoscale.¹¹ However, in these reports, only onedimensional (1-D) linear arrangements of nanomechanical units were investigated in the most cases, while the construction of novel integrated systems with twodimensional (2-D) or even three-dimensional (3-D) arrangements of artificial molecular machines units have been rarely explored, which might be caused by the lack of facile and efficient synthetic approaches that enable the precise arrangements of multiple mechanically interlocked moieties.



Fig. 1 Cartoon presentation of Type III rotaxane-branched dendrimers: Type III-A, III-B, and III-C, respectively.

Considering the highly branched and star-shaped structure feature as well as the nanometer-scale dimensions of dendrimers,¹² the introduction of rotaxane units, especially ones with the controllable motion behaviors,



Fig. 2 Cartoon representation of the dimensional modulation of Type III-C rotaxane-branched dendrimer upon the addition or removal of external stimuli.

into the branches of dendrimers give rise to rotaxanedendrimers with 3-D branched monodispersed arrangements of rotaxane units within the dendritic skeleton.¹³ The unique collective amplification of molecular motions of each branch might make the resultant rotaxanebranched dendrimers a very promising platform towards the exploration of the amplified collective molecular motions and their applications in the construction of artificial molecular machines and smart materials. It should be noted that, in the original definition by Kim et al.,^{14a} only two types of rotaxane-branched dendrimers, *i.e.* Type III-A and III-B ones, were proposed depending on the position of wheel components either on the branches or at the branching points, respectively. As the last piece of the 'rotaxane-branched dendrimer puzzle', Type III-C rotaxanebranched dendrimers with the combined structural features of both III-A and III-B ones, i.e. the wheel components are located on the branches as well as at the branching points, have been only proposed by Stoddart¹⁵ in 2016 and the construction of high-generation Type III-C rotaxane-branched dendrimers has not been realized yet (Fig. 1). Notably, compared with Type III-A or III-B ones, the relative movement of the wheel and axle components in Type III-C rotaxane-branched dendrimers might lead to the remarkable changes of the length of each branch in a direct way. Furthermore, such collected contraction-extension motion of each branch under the external stimuli will probably result in the remarkable size and microenvironment modulation of the integrated rotaxanebranched dendrimers.

Based on our on-going interests on rotaxane-branched dendrimers,¹⁶ herein, we report the first successful synthesis of dynamic Type III-C rotaxane-branched dendrimers up to fourth-generation with 45 switchable [2]rotaxane units dispersing within the dendrimer skeleton

via a controllable divergent approach. Notably, with the addition of acetate anion as external stimulus, the translational motion of the macrocycle components along the branch was realized. More importantly, due to the existence of rotaxane moieties both on the branches and at the branching points, the anion-triggered switchable feature of the individual rotaxane branches endows the integrated rotaxane-branched dendrimers a three-dimensional switching feature via a collective extension-contraction motion, thus allowing for the remarkable and reversible size modulation (Fig. 2).

RESULTS AND DISCUSSION

Synthesis of the switchable [2]rotaxane 3 as key precursor and its anion-switching behavior. To construct Type III-C rotaxane-branched dendrimers, according to the retrosynthetic analysis, a new [2]rotaxane building block with dendrimer growth sites being located at both the wheel and axle component is needed. Following such design strategy, two protected alkynes that can be gently exposed to the alkyne group for the subsequent dendrimer growth were attached at the periphery of the pillar[5]arene (P[5]) macrocycle.¹⁷ thus leading to the new wheel component $\mathbf{1}$ (Scheme S1). In addition, a semi-blocked rod-like compound **2** was further prepared as the axle precursor through a multistep synthetic route (Scheme S2), where the urea moiety was inserted into the axle component as a binding site. By employing threading-followed-bystoppering strategy, the reaction of 1, 2, and $Pt(PEt_3)_2I_2$ in a ratio of 6:1:4 in CHCl₃/*i*-Pr₂NH (v/v, 2:1) in the presence of CuI as

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Fig. 3 Synthesis of [2]rotaxane 3 starting from compounds 1, 2 and Pt(PEt₃)₂I₂, and the anion-induced switching motion of [2]rotaxane 3.

catalyst resulted in the successful preparation of organometallic [2]rotaxane **3** as the basic building block in a good yield (70%) on gram scale (Fig. 3). Notably, in [2]rotaxane 3, the mono-substituted platinum-acetylide moiety not only served as the stopper to prevent dethreading, but also acted as the reactive sites for the subsequent dendrimer growth. The structure of [2]rotaxane 3 was fully characterized by 1-D multinuclear (¹H, ¹³C, and ³¹P), 2-D NMR (¹H-¹H COSY, ROESY) spectroscopy, and MALDI-TOF-MS analysis (Figs. S1-S6).

In organometallic [2]rotaxane 3, the P[5] ring preferred being located at the urea and adjacent methylene moieties due to the stronger hydrogen bonding interactions between methoxy group of P[5] macrocycle and the urea moiety. Considering the ability of urea moiety to serve as hydrogen bonding donor, the addition of hydrogen bonding acceptor, which could compete with P[5] macrocycle to complex with the urea moiety, into the rotaxane system would induce the translational motion of P[5] along the axle from urea to the neutral alkyl chain. To test such hypothesis, acetate anion was selected as the stimulus (Fig. 3). To our delight, by sequentially adding tetrabutylammonium acetate (TBAA) from 1.0 equiv to 5.0 equiv into the solution of [2]rotaxane **3** in tetrahydrofuran- d_8 (THF- d_8), ¹H NMR titration experiments revealed that the signals of the protons H₁₄ and H_{15} on the urea moiety as well as the protons nearby (H_{10} -13) displayed the obvious downfield shifts. While the



Fig. 4 (a) Synthesis of Type III-C rotaxane-branched dendrimer G1 by a CuI-catalyzed coupling reaction of 3 and 1,3,5triethynylbenzene; (b) Schematic representation of a controllable divergent strategy for the synthesis of Type III-C rotaxanebranched dendrimers G2-G4. Reaction conditions: (I) (a) Bu₄NF·3H₂O, THF, r.t., 2h; (b) 3, CuI, Et₂NH, r.t., 8h. 52%; (II) (a) Bu₄NF·3H₂O, THF, r.t., 2h; (b) **3**, CuI, Et₂NH, r.t., 8h. 42%; (III) (a) Bu₄NF·3H₂O, THF, r.t., 2h; (b) **3**, CuI, Et₂NH, r.t., 8h, 29%.

peaks of protons $(H_{4.9})$ attributed to the neutral alkyl chain exhibited the remarkable upfield shifts. These observations suggested the acetate anions replaced the P[5] ring to bind with urea moiety, which thus allowed the macrocycle component moving from the urea moiety to neutral alkyl chain. The binding constant (K) of [2]rotaxane **3** for TBAA was sequentially calculated to be (6.41 \pm 0.08) \times 10³ M⁻¹. Subsequently, upon adding 10.0 equiv. of NaPF₆ into the mixture of [2]rotaxane 3 and TBAA, which could completely remove acetate anion as NaOAc precipitate, the resultant ¹H NMR spectrum was almost the same as the original spectrum of the[2]rotaxane 3, thus suggesting the movement of the macrocycle back to the urea moiety (Figs. S7-S12). Therefore, the anion-triggered translational motion of P[5] ring along the axle in [2]rotaxane 3 was achieved in a reversible manner through the addition and removal of acetate anion, thus allowing for a switchable rotaxane system. Moreover, the theoretical calculation also clearly indicated that the wheel component underwent the translational motion from urea moiety to the neutral alkyl chain upon the binding between urea moiety and acetate anion (Fig. S13). All these results confirmed the anioninduced switchable molecular motion of [2]rotaxane 3, thus laying the foundation of the construction of stimuliresponsive Type III-C rotaxane-branched dendrimers by employing [2]rotaxane **3** as the key building block.

Synthesis and characterization of Type III-C rotaxane-branched dendrimers. Starting from the switchable [2]rotaxane **3**, a controllable divergent strategy was employed to construct the targeted Type III-C rotaxane-branched dendrimers. Fig. 4 outlines the detailed synthetic route. Firstly, by utilizing 1,3,5-triethynylbenzene as the scaffold core and CuI as catalyst, the coupling reaction of [2]rotaxane **3** with 1,3,5-triethynylbenzene in diethylamine (Et₂NH) resulted in the formation of firstgeneration Type III-C rotaxane-branched dendrimer (G1) in 70% yield, which contained three rotaxane units in the dendrimer skeleton. Subsequently, the deprotection of G1 with tetrabutylammonium fluoride trihydrate (Bu₄NF · 3H₂O) allowed for the generation of the intermediate G1-**YNE** with six alkyne groups at the periphery of the P[5] ring. The sequential employment of coupling reaction of G1-YNE with [2]rotaxane 3 in the presence of CuI as catalyst in Et₂NH generated the second-generation Type III-C rotaxane-branched dendrimer (G2) with nine rotaxane units dispersed in the dendrimer skeleton in a yield of 52%. repeating such iterative deprotection-coupling By reactions, the construction of the third-generation and rotaxane-branched fourth-generation Type III-C dendrimers (G3 and G4) were achieved through a divergent approach (Scheme S3-S6). All the obtained Type III-C rotaxane-branched dendrimers were neutral and soluble in common organic solvents, which made the purification process facile and efficient through the combination of flash column chromatography and preparative gel permeation chromatography (GPC). Notably, for the resultant **G4** with a molecular weight as high as 95,371 Da., forty-five individual switchable rotaxane units were distributed in the dendrimer skeleton in a monodispersed manner to afford a highly branched [46]rotaxane system.

The identity of these Type III-C rotaxane-branched dendrimers **Gn** (n = 1-4) was firstly determined by 1-D NMR measurements. In the ¹H NMR spectra of **G1-G4**, no proton signal ascribed to the free terminal acetylenes was observed, indicating the full conversion of the terminal acetylenes towards the formation of platinum-acetylide bonds¹⁸ during the dendrimer growth process. In addition, the peaks below 0.0 ppm that are attributed to the protons on the axle of the rotaxane units remained, suggesting that the rotaxane units were intact during the synthetic processes. In the case of ³¹P NMR analysis, compared with the building block [2]rotaxane 3, G1 displayed a remarkable downfield shift from 8.91 to 11.64 ppm, which directly supported the formation of platinum-acetylide bonds as the dendrimer growth step. Similarly, the higher-generation **G2-G4** also featured a signal peak at 11.68 ppm (**G2**), 11.86 ppm (G3), and 11.66 ppm (G4), respectively, revealing the high symmetry feature of the resultant Type III-C rotaxanebranched dendrimers (Figs. S14-S27). The matrix-assisted desorption/ionization-time of flight laser mass spectrometry (MALDI-TOF-MS) and gel permeation chromatography (GPC) experiments further confirmed the successful synthesis of the targeted Type III-C rotaxanebranched dendrimers. In the MALDI-TOF-MS spectrum of **G1** (Fig. 5a), peaks of m/z = 6,952.7 and m/z = 3,476.5 were found, which agreed with the theoretical values of [G1 +Na]⁺ ion (m/z = 6,953.5) and [G1 + H + Na]²⁺ ion (m/z =3,477.2), respectively. In the case of **G2**, the peaks of m/z =19.592.5 and m/z = 9.809.0 were observed, which fitted well with the theoretical values of $[G2 + Na]^+$



Fig. 5 MALDI-TOF-MS spectra of (a) **G1** and (b) **G2**. GPC (c) and DLS (d) spectra of Type III-C rotaxane-branched dendrimers **G1-G4**.

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ion (m/z = 19,592.7) and $[G2 + 2Na]^{2+}$ ion (m/z = 9,807.9)(Fig. 5b), respectively. For the higher-generation **G3** and **G4**. because of their high molecular weight and low ionizationefficiency, we didn't obtain the satisfied data even after continuous attempts. Thus GPC experiments were performed to confirm the formation of G3 and G4. In the GPC spectra (Figs. 5c and S28-S31), all rotaxane-branched dendrimers G1-G4 displayed a single peak and narrow distributions for the number-averaged molecular weight (M_n) and the polydispersity index (PDI) (for **G1**, PDI = 1.02; for **G2**, PDI = 1.04; for **G3**, PDI = 1.03; for **G4**, PDI = 1.04), indicating the monodispersity of **G1-G4**. In addition, with the increase of the generation, the M_n values significantly increased (for **G1**, *M*_n = 6, 614; for **G2**, *M*_n = 14,465; for **G3**, $M_{\rm n}$ = 29,997; for **G4**, $M_{\rm n}$ = 46,548). Such changes are in accord with the expected trend, which indirectly proved the successful synthesis of G3 and G4. Notably, the absolute molecular weight of G4 was determined as 105,800 Da. (Fig. S31), which was quite close to the $M_{\rm w}$ value (95,371 Da.), thereby again supporting the successful synthesis of the [46]rotaxane-branched dendrimer G4.

Moreover, the 2-D diffusion-ordered spectroscopy (DOSY) spectra of all Type III-C rotaxane-branched dendrimers, especially for G3 and G4, revealed one set of signals, respectively, indicating the monodispersity of G1-**G4**. In addition, when compared with the precursor [2]rotaxane 3, the diffusion coefficient (D) decreased significantly from $(14.13 \pm 0.14) \times 10^{-10} \text{ m}^2\text{s}^{-1}$ (3) to $(10.96 \pm$ 0.24 × 10⁻¹⁰ m²s⁻¹ (G1), (5.13±0.12) × 10⁻¹⁰ m²s⁻¹ (G2), (2.75) ± 0.16) × 10⁻¹⁰ m²s⁻¹ (G3), and (1.66 ± 0.15) × 10⁻¹⁰ m²s⁻¹ (G4), respectively. Considering the fact that diffusion coefficient is inversely proportional to the hydrodynamic size, such progressive increase of the hydrodynamic size along with the increase of the dendrimer generation provided the additional support for the existence of Type III-C rotaxanebranched dendrimers G1-G4 (Figs. S32-S36). Dynamic light scattering (DLS) is also a useful technique to determine the dimension of rotaxane-branched dendrimers in solution. The hydrodynamic size $(D_{\rm h})$ of **G1** was determined as 2.11 \pm 0.10 nm, and a size progression was clearly observed with the increase of dendrimer generation $(3.67 \pm 0.14 \text{ nm for})$ G2; 5.36 ± 0.08 nm for G3; 7.12 ± 0.10 nm for G4) (Figs. 5d and \$37-\$40).

Transmission electron microscopy (TEM) and atomic force microscopy (AFM) analysis were then employed to visualize the morphologies of the resultant Type III-C rotaxane-branched dendrimers **G1-G4**. From the TEM analysis (Figs. S41-S44), the discrete and uniform nearspherical morphologies were observed for **G1-G4**, respectively. And along with the increase of the generation, the size of **G1-G4** were determined to be 1.70 \pm 0.20 nm, 2.65 \pm 0.22 nm, 3.60 \pm 0.30 nm, and 4.65 \pm 0.30, respectively. Moreover, spherical particles were also observed in the AFM images (Fig. 6). With the increase of the generation, the average height gradually increased from 1.75 \pm 0.15 nm (**G1**) to 2.45 \pm 0.20 nm (**G2**), 3.30 \pm 0.20 nm (**G3**) and 4.80 \pm 0.25 nm (**G4**), which is similar with the TEM analysis.

Anion-induced dimension modulation of Type III-C rotaxane-branched dendrimers. After confirming the



Fig. 6 AFM images of Type III-C rotaxane-branched dendrimers. (a) **G1**; (b) the height range of **G1** is 1.75 ± 0.15 nm; (c) **G2**; (d) the height range of **G2** is 2.45 ± 0.20 nm; (e) **G3**; (f) the height range of **G3** is 3.30 ± 0.20 nm; (g) **G4**; (h) the height range of **G4** is 4.80 ± 0.25 nm.

successful synthesis of the targeted Type III-C rotaxanebranched dendrimers, their stimuli-responsive properties were then evaluated (Scheme S7-S10). Same as the switchable building block [2]rotaxane 3, acetate anion was selected as the stimulus. ¹H NMR titration experiments of **G1-G4** were recorded in THF- d_8 at 298K. It was found that, upon the addition of TBAA, the obvious chemical shifts of the protons (H_{14}, H_{15}) on the urea moieties as well as the protons (H₄-13) on the axle were observed, which displayed the similar anion-induced switching behaviors with the individual [2]rotaxane 3, thus supporting the feasibility of anion-induced collective switching motion of the individual rotaxane branches. As indicated by ¹H NMR spectra (Figs. S45-S48), for each urea moiety, 5.0 equiv. of TBAA was needed to induce the translational motion of P[5] macrocycle from urea moiety to the alkyl chain. Similarly, NaPF₆ was introduced to promote the macrocycle return back to the original urea station, suggesting the reversible translational motion of macrocycle along the axle on each branch.

As above-mentioned, the addition or removal of acetate anion could reversibly change the location of macrocycle component on the branches. It should be noted that the macrocycles are located both on the branches and at the branching points, the movement of the wheel in the dendrimer skeleton might result in the size extensionintegrated rotaxane-branched contraction of the dendrimers. In order to confirm this hypothesis, 2-D DOSY experiments were carried out in THF- d_8 at 298K, which could provide the direct evidence for the size change of Type III-C rotaxane-branched dendrimers. For instance, it was found that the diffusion coefficient (D) remarkably decreased from $(10.96 \pm 0.24) \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ to (8.91 ± 0.20) $\times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ with the addition of TBAA (Fig. 7), suggesting the increase of the hydrodynamic size of **G1**. Sequentially, the introduction of NaPF₆ into the resultant mixture resulted in the increase of diffusion coefficient ($D = (10.23 \pm$ $(0.25) \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$), which almost returned back to the original value, thus demonstrating the reversibility of such size modulation processes. For the higher-generation rotaxane-branched dendrimers G2, G3 and G4, the change of *D* value showed the same tendency with **G1**. On the basis of the Stokes-Einstein equation, the swelling ratio of different Type III-C rotaxane-branched dendrimers was determined to be 22.9% for G1, 28.8% for G2, 34.7% for G3, and 38.3% for G4, respectively (Figs. S49-S56).

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Furthermore, DLS analysis was also employed to evaluate the stimuli-induced size modulation of rotaxane-branched dendrimers. As shown in Fig. 7, with the addition of TBAA, the size of **G1** increased from 2.11 \pm 0.10 to 2.60 \pm 0.15 nm with a swelling ratio of 23.2%. Upon adding NaPF₆ to remove the acetate anions, the size almost went back to the original value, which was in accord with the 2-D DOSY analysis. Similarly, the swelling ratio of **G2, G3** and **G4** were calculated to be 26.7%, 31.3%, and 36.7%, respectively (Figs. S57-S64). In addition, according to the AFM analysis,



Fig. 7 2-D DOSY (THF- d_8 , 298 K, 500 MHz) (*top*) and DLS (*bottom*) results of anion-induced size switching of Type III-C rotaxane-branched dendrimers **G1-G4**.

upon the addition of TBAA, the increase of the averaged height for each generation rotaxane-branched dendrimer was observed (Figs. S65-S68), which demonstrated the anion-induced swelling behaviors with the swelling ratios of 20.0% for **G1**, 24.4% for **G2**, 30.0% for **G3**, and 34.8% for **G4**, respectively. Through the combination of 2-D DOSY, DLS and AFM analysis, two trends were clearly revealed: (1) the addition or removal of acetate anion could reversibly regulate the expansion and contraction of the integrated Type III-C rotaxane-branched dendrimers; (2) along with the increase of dendrimer generation, the swelling ratio increased simultaneously, which might be attributed to the amplification of the responsiveness through the integration of multiple switchable rotaxane moieties within the dendrimer skeleton.

In order to further confirm such amplified anion-induced dimension modulation of Type III-C rotaxane-branched dendrimers, a semi-empirical method PM6-D3H4 with the dispersion corrections was used in the geometry optimizations for G2 before and after the addition of TBAA using the program MOPAC2016.¹⁹ To predict the surface areas and volumes of different complexes, a series of probe radii were carried out by 3V: Voss Volume Voxelator program.²⁰ For ideal spheres, the ratio of their lengths could be presented as the ratios of the cube roots of their volumes. When we assume the thicknesses of these rotaxanebranched dendrimers are similar, their size difference is calculated as the ratio of the square roots of their surface areas or volumes instead of the ratio of the cube roots of their volumes. If the probe radius is large enough, the ratios of square roots of the surface areas should be close to those of the volumes. As shown in Table S1-S2, the square root of converges to 1.28 when the probe radius is 80 Å. We found that the ratio of the square roots of the volumes of G2 is close to that of surface areas when the probe radius is larger than 70 Å. This means that 70 Å as a probe radius is large enough to compare the sizes of different rotaxanebranched dendrimers. As a prediction by our computational modeling, the sizes of G2 is increased by 28% after the anion is included in the dendrimer, which is in accord with the swelling ratio determined by 2-D DOSY and DLS analysis, thus confirming the amplified anion-switched dimension modulation of these novel Type III-C rotaxanebranched dendrimers (Fig. 8).

To gain more insight into such size modulation phenomenon, the model dendrimer G1-a without urea moieties was prepared from the corresponding model [2]rotaxane 3-a via the same divergent approach (Scheme S11). For both 3-a and G1-a, due to the absence of binding site, the ¹H NMR spectra showed no obvious changes with the addition of TBAA (Figs. S70-S71), suggesting that neither **3-a** nor **G1-a** showed anion-responsiveness. More importantly, the diffusion coefficient (D) from 2-D DOSY experiments and hydrodynamic size from DLS analysis, respectively, were almost the same with the addition of TBAA (for **G1-a**, $D = (1.55 \pm 0.14) \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$, and the size was 1.54 ± 0.10 nm; for the mixture of **G1-a** and TBAA, D = $(1.48\pm0.12) \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$, and the size was $1.52 \pm 0.17 \text{ nm}$) (Figs. S72-S75). The control experiment indicated that the size modulation of rotaxane-branched dendrimers was

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attributed to the collective translational motion of macrocycle along the axle on each branch.



Fig. 8 Optimized structures of Type III-C rotaxane-branched dendrimer **G2** before *(left)* and after *(right)* the addition of TBAA as stimulus by using the program MOPAC2016.

CONCLUSION

In conclusion, by employing a controllable divergent approach, we have realized the successful synthesis of a brand-new Type III-C rotaxane-branched dendrimers as the last member of the proposed rotaxane-branched dendrimer family¹⁵ up to the fourth-generation with 45 individual switchable rotaxane units dispersing within the dendrimer skeleton. In particular, with the addition or removal of the acetate anion, the collective expansion-contraction motion on each branch led to the reversible size switching of the integrated rotaxane-branched dendrimers. Herein we provide another prototype of stimuli-responsive rotaxanebranched dendrimers with the controllable switching features that may mimic the amplified collective molecular motions in biomolecular machines. Such unique dynamic supramolecular systems may find promising applications in the controllable cargo release/capture and switchable supramolecular catalysis in the future.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Additional information concerning the synthesis, characterization, and other experimental details.

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Notes

The authors declare no competing interest.

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REFERENCES

(1) (a) Kinbara, K.; Aida, T. Toward intelligent molecular machines: directed motions of biological and artificial molecules and assemblies. *Chem. Rev.*, **2005**, *105*, 1377-1400. (b) Schliwa, M.; Woehlke, G. Molecular motors. *Nature*, **2003**, *422*, 759-765.

(2) (a) Erbas-Cakmak, S.; Leigh, D. A.; McTernan, C. T.; Nussbaumer, A. L. Artificial molecular machines. *Chem. Rev.*, 2015, *115*, 10081-10206. (b) Sauvage, J.-P. From chemical topology to molecular machines (Nobel Lecture). *Angew. Chem. Int. Ed.*, 2017, *56*, 11080-11093. (c) Stoddart, J. F. Mechanically interlocked molecules (MIMs)—molecular shuttles, switches, and machines (Nobel Lecture). *Angew. Chem. Int. Ed.*, 2017, *56*, 11094-11125. (d) Feringa, B. L. The art of building small: from molecular switches to motors (Nobel Lecture). *Angew. Chem. Int. Ed.*, 2017, *56*, 11060-11078. (e) Zhang, L.; Marcos, V.; Leigh, D. A. Molecular machines with bio-inspired mechanisms. *Proc. Natl. Acad. Sci. USA.*, 2018, *115*, 9397-9404. (f) Neal, E. A.; Goldup, S. M. Chemical consequences of mechanical bonding in catenanes and rotaxanes: isomerism, modification, catalysis and molecular machines for synthesis. *Chem. Commun.*, 2014, *50*, 5128-5142.

(3) (a) Anelli, P. L.; Spencer, N.; Stoddart, J. F. A molecular shuttle. *J. Am. Chem. Soc.*, **1991**, *113*, 5131-5133. (b) Bissell, R. A.; Córdova, E.; Kaifer, A. E.; Stoddart, J. F. A chemically and electrochemically switchable molecular shuttle. *Nature*, **1994**, *369*, 133-137. (c) Zhu, K.; O'Keefe, C.; Vukotic, V. N.; Schurko, R. W.; Loeb, S. J. A molecular shuttle that operates inside a metal-organic framework. *Nat. Chem.*, **2015**, *7*, 514-519. (d) Vukotic, V. N.; Zhu, K.; Baggi, G.; Loeb, S. J. Optical distinction between "slow" and "fast" translational motion in degenerate molecular shuttles. *Angew. Chem. Int. Ed.*, **2017**, *56*, 6136-6141. (e) Zhu, K., Baggi, G.; Loeb, S. J. Ring-through-ring molecular shuttling in a saturated [3]rotaxane. *Nat. Chem.*, **2018**, *10*, 625-630. (f) Goldup, S. M. Molecular machines swap rings. *Nature*, **2018**, *557*, 39-40.

(4) (a) Jiménez, M. C.; Dietrich-Buchecker, C.; Sauvage, J.-P. Towards synthetic molecular muscles: contraction and stretching of a linear rotaxane dimer. *Angew. Chem. Int. Ed.*, **2000**, *39*, 3284-3287. (b) Collin, J.-P.; Dietrich-Buchecker, C.; Gaviña, P.; Jimenez-Molero, M. C.; Sauvage, J.-P., Shuttles and muscles: linear molecular machines based on transition metals. *Acc. Chem. Res.*, **2001**, *34*, 477-487. (c) Fang, L.; Hmadeh, M.; Wu, J.; Olson, M. A.; Spruell, J. M.; Trabolsi, A.; Yang, Y.-W.; Elhabiri, M.; Albrecht-Gary, A.-M.; Stoddart, J. F. Acid-base cctuation of [c2]daisy chains. *J. Am. Chem. Soc.*, **2009**, *131*, 7126-7134. (d) Iwaso, K.; Takashima, Y.; Harada, A. Fast response dry-type artificial molecular muscles with [c2]daisy chains. *Nat. Chem.*, **2016**, *8*, 625-632.

(5) (a) Kassem, S.; van Leeuwen, T.; Lubbe, A. S.; Wilson, M. R.; Feringa, B. L.; Leigh, D. A. Artificial molecular motors. *Chem. Soc. Rev.*, **2017**, *46*, 2592-2621. (b) van Leeuwen, T.; Lubbe, A. S.; Stacko, P.; Wezenberg, S. J.; Feringa, B. L. Dynamic control of function by light-driven molecular motors. *Nat. Rev. Chem.*, **2017**, 1, 0096. (c) Roke, D.; Wezenberg, S. J.; Feringa, B. L. Molecular rotary motors: unidirectional motion around double bonds. Proc. Natl. Acad. Sci. U SA, 2018, 115, 9423-9431.

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60

- (6) (a) Lewandowski, B.; De Bo, G.; Ward, J. W.; Papmeyer, M.; Kuschel, S.; Aldegunde, M. J.; Gramlich, P. M. E.; Heckmann, D.; Goldup, S. M.; D'Souza, D. M.; Fernandes, A. E.; Leigh, D. A. Sequence-specific peptide synthesis by an artificial small-molecule machine. Science, 2013, 339, 189-193. (b) De Bo, G.; Kuschel, S.; Leigh, D. a; Lewandowski, B.; Papmeyer, M.; Ward, J. W. Efficient assembly of threaded molecular machines for sequence-specific synthesis. J. Am. Chem. Soc., 2014, 136, 5811-5814. (c) De Bo, G.; Gall, M. A. Y.: Kitching, M. O.: Kuschel, S.: Leigh, D. A.: Tetlow, D. I.: 10 Ward, J. W. Sequence-specific β -peptide synthesis by a rotaxanebased molecular machine. J. Am. Chem. Soc., 2017, 139, 10875-10879. (d) De Bo, G.; Gall, M. A. Y.; Kuschel, S.; De Winter, J.; 12 Gerbaux, P.; Leigh, D. A. An artificial molecular machine that builds 13 an asymmetric catalyst. Nat. Nanotechnol., 2018, 13, 381-385.
- 14 (7) (a) Vale, R. D.; Milligan, R. A. The way things move: looking 15 under the hood of molecular motor proteins. Science, 2000, 288, 88-95. (b) Alberts, B. The cell as a collection of protein machines: 16 preparing the next generation of molecular biologists. Cell, 1998, 17 92.291-294. 18
- (8) Krans, J. L. The sliding filament theory of muscle contraction. 19 Nat. Educ., 2010, 3, 66.
- 20 (9) Bruns, C. J.; Stoddart, J. F. Rotaxane-based molecular muscles. Acc. Chem. Res., 2014, 47, 2186-2199, and references therein. 21
- (10) Goujon, A.; Moulin, E.; Fuks, G.; Giuseppone, N. [c2] daisy chain 22 rotaxanes as molecular muscles. CCS Chemistry, **2019**, *1*, 83-96.
- 23 (11) (a) Du, G.; Moulin, E.; Jouault, N.; Buhler, E.; Giuseppone, N. 24 muscle-like supramolecular polymers- integrated motions from 25 thousands of molecular machines. Angew. Chem. Int. Ed., 2012, 51, 12504-12508. (b) Goujon, A.; Du, G.; Moulin, E.; Fuks, G.; Maaloum, 26 M.; Buhler, E.; Giuseppone, N. Hierarchical self-assembly of 27 supramolecular muscle-like fibers. Angew. Chem. Int. Ed., 2016, 55, 28 703-707. (c) Goujon, A.; Mariani, G.; Lang, T.; Moulin, E.; Rawiso, M.; 29 Buhler, E.; Giuseppone, N. Controlled sol-gel transitions by 30 actuating molecular machine based supramolecular polymers. J. Am. Chem. Soc., 2017, 139, 4923-4928. 31
- (12) (a) Vögtle, F.; Richardt, G.; Werber, N. Dendrimer Chemistry: 32 Concepts, Syntheses, Properties, Applications (Wiley, Weinheim, 33 2009). (b) Newkome, G. R.; Moorefield, C. N. From $1 \rightarrow 3$ dendritic 34 designs to fractal supramacromolecular constructs: Understanding 35 the pathway to the Sierpiński gasket. Chem. Soc. Rev., 2015, 44, 3954-3967. (c) Zhao, G.-Z.; Chen, L.-J.; Wang, W.; Zhang, J.; Yang, G.; 36 Wang, D.-X.; Yu, Y.; Yang, H.-B. Stimuli-responsive supramolecular 37 gels through hierarchical self-assembly of discrete rhomboidal 38 metallacycles. Chem. -Eur. J., 2013, 19, 10094-10100. (d) Xu, L.; 39 Chen, L.-J.; Yang, H.-B. Recent progress in the construction of 40 cavity-cored supramolecular metallodendrimers via coordinationdriven self-assembly. Chem. Commun., 2014, 50, 5156-5170. (e) 41 Chen, L.-J.; Zhao, G.-Z.; Jiang, B.; Sun, B.; Wang, M.; Xu, L.; He, J.; Abliz, 42 Z.; Tan, H.; Li, X.; Yang, H.-B. Smart stimuli-responsive spherical 43 constructed from supramolecular nanostructures 44 metallodendrimers via hierarchical self-assembly. J. Am. Chem. 45 Soc., 2014, 136, 5993-6001.
- (13) (a) Kim, S.-Y.; Ko, Y. H.; Lee, J. W.; Sakamoto, S.; Yamaguchi, K.; 46 Kim, K. Toward high-generation rotaxane dendrimers that 47 incorporate a ring component on every branch: noncovalent 48 synthesis of a dendritic [10]pseudorotaxane with 13 molecular 49 components. Chem. -Asian J., 2007, 2, 747-754. (b) Ho, W. K.-W.; 50 Lee, S.-F.; Wong, C.-H.; Zhu, X.-M.; Kwan, C.-S.; Chak, C.-P.; Mendes, P. M.; Cheng, C. H. K. K.; Leung, K. C.-F. Type III-B rotaxane 51 dendrimers. Chem. Commun., 2013, 49, 10781-10783. (c) Kwan, C.-52 S.; Zhao, R.; Van Hove, M. A.; Cai, Z.; Leung, K. C.-F. Higher-53 generation type III-B rotaxane dendrimers with controlling 54 particle size in three-dimensional molecular switching. Nat. 55 Commun., 2018, 9, 497.
- (14) (a) Lee, J. K.; Kim, K. Rotaxane dendrimers. Top. Curr. Chem., 56 2003, 228, 111-140. (b) Leung, K. C.-F.; Lau, K. N. Self-assembly and 57

thermodynamic synthesis of rotaxane dendrimers and related structures. Poly. Chem., 2010, 1, 988-1000. (c) Chen, C.-F. Highgeneration organometallic rotaxane dendrimer. Sci. China Chem., 2015, 58, 1089.

(15) Bruns, C. J.; Stoddart, J. F. The Nature of the Mechanical Bond (John Wiley & Sons, Hoboken, 2016).

(16) (a) Wang, Y.-X.; Zhou, Q.-F.; Chen, L.-J.; Xu, L.; Wang, C.-H.; Li, X.; Yang, H.-B. Facile construction of organometallic rotaxaneterminated dendrimers using neutral platinum-acetylides as the main scaffold. Chem. Commun., 2018, 54, 2224-2227. (b) Wang, W.; Chen, L.-J.; Wang, X.-Q.; Sun, B.; Li, X.; Zhang, Y.; Shi, J.; Yu, Y.; Zhang, L.: Liu, M.: Yang, H.-B. Organometallic rotaxane dendrimers with fourth-generation mechanically interlocked branches. Proc. Natl. Acad. Sci. USA, 2015, 112, 5597-5601. (c) Wang, X.-Q.; Wang, W.; Li, W.-J.; Chen, L.-J.; Yao, R.; Yin, G.-Q.; Wang, Y.-X.; Zhang, Y.; Huang, J.; Tan, H.; Yu, Y.; Li, X.; Xu, L.; Yang, H.-B. Dual stimuli-responsive rotaxane-branched dendrimers with reversible dimension modulation. Nat. Commun., 2018, 9, 3190. (d) Wang, X.-Q.; Wang, W.; Li, W.-J.; Qin, Y.; Yin, G.-Q.; Jiang, W.-L.; Li, X.; Wu, S.; Yang, H.-B. Rotaxane-branched dendrimers with aggregation-induced emission behavior. Org. Chem. Front., 2019, 6, 1686-1691. (e) He, M.; Chen, L.; Jiang, B.; Tan, H.; Wang, C.; Yang, H. Facile construction of Zn(II)-porphyrin-cored [5]rotaxane and its controllable aggregation behaviours. Chin. Chem. Lett., 2019, 30, 131-134.

(17) (a) Ogoshi, T.; Kanai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. para-Bridged symmetrical pillar[5]arenes: their Lewis acid catalyzed synthesis and host-guest property. J. Am. Chem. Soc., 2008, 130, 5022-5023. (b) Xue, M.; Yang, Y.; Chi, X.; Zhang, Z.; Huang, F. Pillararenes, a new class of macrocycles for supramolecular chemistry. Acc. Chem. Res., 2012, 45, 1294-1308. (c) Ogoshi, T.; Yamagishi, T.-a.; Nakamoto, Y. Pillar-shaped macrocyclic hosts pillar[n]arenes: new key players for supramolecular chemistry. Chem. Rev., 2016, 116, 7937-8002. (d) Jiang, B.; Wang, W.; Zhang, Y.; Lu, Y.; Zhang, C.-W.; Yin, G.-Q.; Zhao, X.-L.; Xu, L.; Tan, H.; Li, X.; Jin, G.-X.; Yang, H.-B. Construction of π -surface-metalated pillar[5] arenes which bind anions via anion- π interactions. Angew. Chem. Int. Ed., 2017, 56, 14438-14442. (e) Jie, K.; Zhou, Y.; Li, E.; Huang, F. Nonporous adaptive crystals of pillararenes. Acc. Chem. Res., 2018, 51, 2064-2072. (f) Kakuta, T.; Yamagishi, T.-a.; Ogoshi, T. Stimuli-responsive supramolecular assemblies constructed from pillar[n]arenes. Acc. Chem. Res., 2018, 5, 1656-1666. (g) Song, N.; Kakuta, T.; Yamagishi, T.; Yang, Y.-W.; Ogoshi, T. Molecular-scale porous materials based on pillar[n]arenes. Chem, 2018, 4, 2029-2053. (h) Fa, S.; Kakuta, T.; Yamagishi, T.-a.; Ogoshi, T. One-, two-, and three-dimensional supramolecular assemblies based on tubular and regular polygonal structures of pillar[n]arenes. CCS Chemistry, 2019, 1, 50-63.

(18) (a) Leininger, S.; Stang, P. J.; Huang, S. Synthesis and characterization of organoplatinum dendrimers with 1,3,5triethynylbenzene building blocks. Organometallics, 1998, 17, 3981-3987. (b) Wang, W.; Yang, H.-B.; Linear neutral platinumacetylide moiety: beyond the links. Chem. Commun., 2014, 50, 5171-5186. (c) Jiang, B.; Zhang, J.; Ma, J.-Q.; Zheng, W.; Chen, L.-J.; Sun, B.; Li, C.; Hu, B.-W.; Tan, H.; Li, X.; Yang, H.-B. Vapochromic behavior of a chair-shaped supramolecular metallacycle with ultra-stability. J. Am. Chem. Soc., 2016, 138, 738-741. (d) Xu, L.; Yang, H.-B. Our expedition in linear neutral platinum-acetylide complexes: the preparation of micro/nanostructure materials, complicated topologies, and dye-sensitized solar cells. Chem. Rec., 2016, 16, 1274-1297. (e) Chen, L.-J.; Yang, H.-B. Construction of stimuli-responsive functional materials via hierarchical selfassembly involving coordination interactions. Acc. Chem. Res., 2018, 51, 2699-2710. (f) Wong, K. M.-C.; Yam, V. W.-W. Selfassembly of luminescent alkynylplatinum (II) terpyridyl complexes: Modulation of photophysical properties through aggregation behavior. Acc. Chem. Res., 2011, 44, 424-434. (g) Yam, V. W.-W.; Au, V. K.-M. S.; Leung, Y.-L. Light-emitting self-assembled materials based on d^8 and d^{10} transition metal complexes. Chem.

Rev., 2015, 115, 7589-7728. (h) Chan, A. K.-W.; Yam, V. W.-W.
Precise modulation of molecular building blocks from tweezers to rectangles for recognition and stimuli-responsive processes. Acc. Chem. Res., 2018, 51, 3041-3051. (i) Zheng, W.; Wang, W.; Jiang, S.-T.; Yang, G.; Li, Z.; Wang, X.-Q.; Yin, G.-Q.; Zhang, Y.; Tan, H.; Li, X.; Ding, H.; Chen, G.; Yang, H.-B. Supramolecular transformation of metallacycle-linked star polymers driven by simple phosphine ligand-exchange reaction. J. Am. Chem. Soc., 2019, 141, 583-591.

(19) (a) Řezá č, J.; Hobza, P. Advanced corrections of hydrogen bonding and dispersion for semiempirical quantum mechanical methods. *J. Chem. Theory Comput.*, **2012**, *8*, 141-151. (b) Stewart, J. J. P. Stewart Computational Chemistry—MOPAC (Colorado Springs, CO, USA, 2016). In addition, for the geometry simulations of the first-generation Type III-C rotaxane-branched dendrimer **G1** before and after the addition of TBAA, see Fig. S69.

(20) Voss, N. R.; Gerstein, M. 3V: cavity, channel and cleft volume calculator and extractor. *Nucleic Acids Res.*, **2010**, *38*, W555–W562.

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