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Chiroptical switching of molecular universal joint triggered by complexation/release of a cation: A stepwise synergistic complexation

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ABSTRACT

Pillar[5]arene-based molecular universal joints (MUJs), bearing fused crown ether subring (**MUJ1** and **MUJ3**) or a ring without ether oxygen atom (**MUJ2**), were synthesized and enantio–differentiated. Significant chiral inversion was observed for the crown ether-fused **MUJs** upon the addition of equivalent cations Na^+, showing an anisotropy (g) factor of 0.014, while alkyl subring-fused **MUJ2** showed no CD inversions. Unprecedentedly, sodium ion triggered rolling-in motion of the subring to the pillar[5]arene cavity was verified, and the synergistic noncovalent interaction of cation-π interactions and C–H···π interactions were responsible for the stabilized self-included conformers. The addition of MeOH or competitive hosts 15-crown-5 ether disassembled the complex of **MUJ1** and Na^+ followed by a rolling-out of the subring, which made the sodium-ion triggered chiroptical switching reversible.

The studies on artificial molecular machines/devices and the control of their mechanical motions have attracted significant interest in the recent decades, which displayed promising potential in materials and biological applications [1–4]. To date, a variety of molecular machines/devices based on chemical structures, such as rotaxanes, catenanes and molecular knots, have been built [5–7], which underwent mechanical motions in response to external stimuli, including light [8,9], temperature [10–12], pH [13], redox [14,15] and chemical additives [16,17]. On the other hand, chirality is a fundamental property of nature [18,19], and the regulation of molecular chirality is playing more and more important roles in asymmetric catalysis [20], material science [21], biology and medicine science [22]. Chiral molecular devices often show circular dichroism (CD) spectral responses, which have significant advantages of allowing for distinctively determining mechanical motions on the basis of the sign of CD spectra over the intensity-based absorptive or emissive detection [23,24]. Recently, bicyclic pillar[n]arene derivatives, in which a subring is fused in one hydroquinone unit, has attracted great attention [25,26]. We defined these type of bicyclic compounds as molecular universal joints (MUJs) due to the subring's flexible rolling in/out property [27]. Such pillar[n]arene-based bicyclic structure has been demonstrated to undergo self-included/excluded conformational change, accompanying by the chirality switching of the pillar[n]arene core upon the variation of solvent, ion, and pH [28–31]. We have recently reported a series of MUJs showing chirality switching induced by stimuli, including temperature [32], pressure [33], redox [34] or light [35]. In these cases, the subring was often regarded as a guest for the pillar[n]arene and exerting external stimulus which resulted in the change of host-guest binding properties of the pillar[n]arene was mainly responsible for rolling in/out of the subring. Cooperative complexation of a guest by the pillar[n]arene cavity and the subring to regulate mechanical motions accompanying with chirality switching has been rarely reported, as simultaneously manipulating two active site in a single molecule to interact with a guest is challenging despite that such phenomena are widespread in biological systems [36]. Wen and coworkers reported that the two macrocyclic rings of crown ether-fused pillar[5]arene could individually complex guests, but first complexation showed a negative effect towards the second complexation [37]. Lee and coworkers reported a pillar[5]thiacrown whose planar chiral inversion was driven by a Hg^{2+} with rolling-out mechanical motion of a self-included subring upon complexation of Hg^{2+} [38]. Herein, we report a cation triggered rolling-in mechanical motion of a subring with significant chiroptical switching in crown ether-fused **MUJs** by synergisticly stepwise complexing the cation by two macro rings of the **MUJs**.

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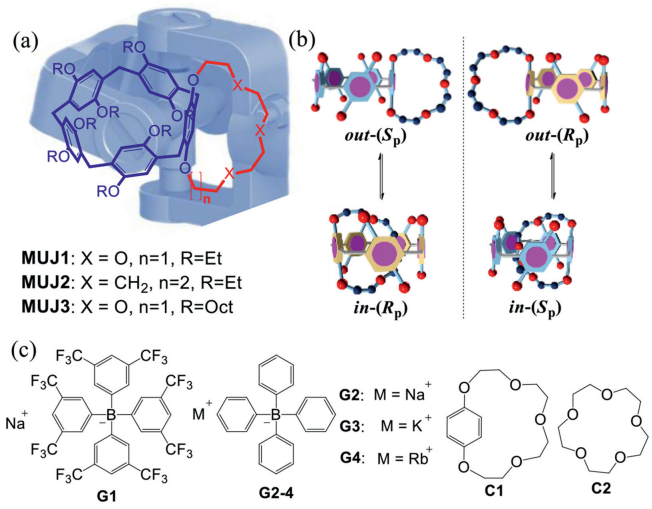

Scheme 1. (a) The chemical structures of the bicyclic MUJs (**MUJ1–3**); (b) schematic illustrations for the in-out equilibrium of the **MUJ1** enantiomeric pair; (c) chemical structures of **G1-G4**.

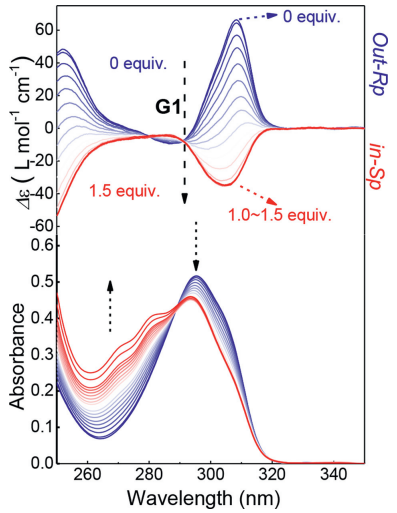

Fig. 1. CD (top) and UV–vis (bottom) spectra of out-(R_p)/in-(S_p)-**MUJ1** (24 μmol/L) with titrations of **G1** in DCM.

The bicyclic compounds based on pillar[5]arene (Scheme 1a), fusing with 17-crown-5 (**MUJ1**) and alkyl ring (**MUJ2**) were synthesized according to our previous report [10]. A new MUJ (**MUJ3)** with increased alkyl chain length grafting on pillar[5]arene was synthesized to investigate the influence of alkyl chain length on the conformational flipping. Enantioseparation of enantiomeric pair of each MUJ, *i.e.*, out-(S_p)/in-(R_p) and out-(R_p)/in-(S_p) pair, was achieved by preparative chiral-phase HPLC. Each enantiomer of the MUJs has two conformational isomers, which can interconvert with each other with accompanying chirality switching by the in-out equilibrium (Scheme 1b) [28,29].

The CD spectra of **MUJ3** in different solvents were investigated (Fig. S5c in Supporting information). The out-(R_p)/in-(S_p)-**MUJ3** showed a positive CD signal in DCM, MeCN, THF, *n*-hexane (n-H), $CHCl_3$ and ethyl acetate (EA), which is similar to that of **MUJ1** (Fig. S5a in Supporting information) [32], demonstrating that **MUJ3** also favored the out-configurations in these solvents. The binding of the solvent by the pillar[5]arene cavity [39] and solvation of the subring which stabilized the out-configuration should be responsible for the positive CD signal, as changing the solvent to cyclohexane (CH) and decalin (DECA) with large size, the CD sign of the MUJs inverted, indicating the inversion of planar chirality to the in-configurations, showing a unique character for MUJs that solvent could lead to a reversal of unimolecular chirality [40,41].

In view of the strong binding ability of crown ether with alkali metal ions [42], **G1–4** (Scheme 1c) were employed to investigate the stimuli-responsibility of MUJs toward cations and, therefore to regulate the mechanical behavior and the planar chirality of MUJs. Out-(R_p)/in-(S_p)-**MUJ1** showed a positive CD signal (CD_{ex}) at the extremum (308 nm) in DCM, demonstrating an out conformation. Interestingly, upon adding guest **G1,** the intensive positive CD signal at *ca.* 308 nm decreased sharply firstly and then inverted to a strong negative CD signal when adding 1.0∼1.5 equiv. of **G1** (Fig. 1). The CD spectral changes were directly proportional to the amount of **G1** and reached a plateau at **[G1]/[MUJ1]** = 1.0 (Fig. S6 in Supporting information). The anisotropy (*g*) factor varied as much as 0.014 (Fig. S7 in Supporting information). In addition, the UV–vis absorption at *ca.* 300 nm of out-(R_p)/in-(S_p)-**MUJ1** decreased upon adding **G1**, and the changes also stopped when the amount of **G1** exceeded 1.0 equiv. (Fig. 1). These results suggested a strong 1:1 host-guest complexation between **MUJ1** and **G1** in DCM, and the inversion of the CD signal suggested a conformational flipping from out-(R_p)-**MUJ1** to the in-(S_p)-**MUJ1**, for which the binding of sodium ion by the fused 17-crown-5 should be responsible, as changing the side ring to an alkyl ring induced only decrease of CD signal but no inversion even in the presence of an excess amount of **G1** (Fig. S8 in Supporting information), demonstrating a significant chiral reversal induced by cation complexation.

The solvent effect on the **G1**-induced CD changes was further investigated (Figs. S9–S17 in Supporting information). The CD signal of out-(R_p)/in-(S_p)-**MUJ1** in $CHCl_3$ also showed inversion which was similar with that in DCM. However, in the polar solvents, including MeOH, MeCN, THF and EA, almost no CD changes for both **MUJ1** and **MUJ2** could be observed. We ascribe this to the strong solvation of **G1** with the polar solvents, which prevent the complexation of **G1** by the **MUJs**.

For the **MUJ3**, an analog decorated with bulky octyl group on the portal of pillar[5]arene, CD inversion was also observed for out-(R_p)/in-(S_p)-**MUJ3** upon adding guest **G1** (Fig. S19 in Supporting information), and absorption and CD changes also reached a plateau when equal proportion of **G1** was added (Figs. S20 and S21 in Supporting information). The varied *g* factor was similar (Fig. S22 in Supporting information). These phenomena indicated that the alkyl substitutions on the portal of pillar[5]arene exert little effect on the chirality switching of MUJs triggered by **G1**. Instead, the subring of crown ether played a pivotal role.

The rolling of the side ring into the cavity of pillar[5]arene induced by **G1** complexation was verified by the NMR titration. As can be seen in Fig. 2, increasing the concentration of **G1** led to broadening and upfield shift of all proton signals of the subring, with the protons a and a' showing the largest upfield shift of −0.76 ppm shifts when 1.0 equiv. of **G1** was added (Fig. 2b). This is in good consistent with the fact that the rolling-in subring will suffer from the shielding effect of benzene rings when was located in the cavity of the pillar[5]arene, and the protons a and a' should insert mostly deep into the cavity, thus, suffer from the strongest shielding effect. The broadening and shifting of the proton signals demonstrated a fast equilibrium of the threading/unthreading of the side ring in the pillar[5]arene cavity. The aromatic protons of the pillar[5]arene, however, showed unsynchronous shifting, with three shifting upfield and the other two showing significant downfield shift (Fig. 2c). This was a little bit unexpected as the inclusion of just a crown ether subring will only result in upfield shifting. Considering the strong binding ability of crown ether with Na^+, cation-π interaction was primarily responsible for downfield shifting of the aromatic protons. This deduction was validated by the NMR titration of **C1** with **G1**. As can be seen in Fig. 3, both the aromatic and methylene protons of **C1** showed significant downfield

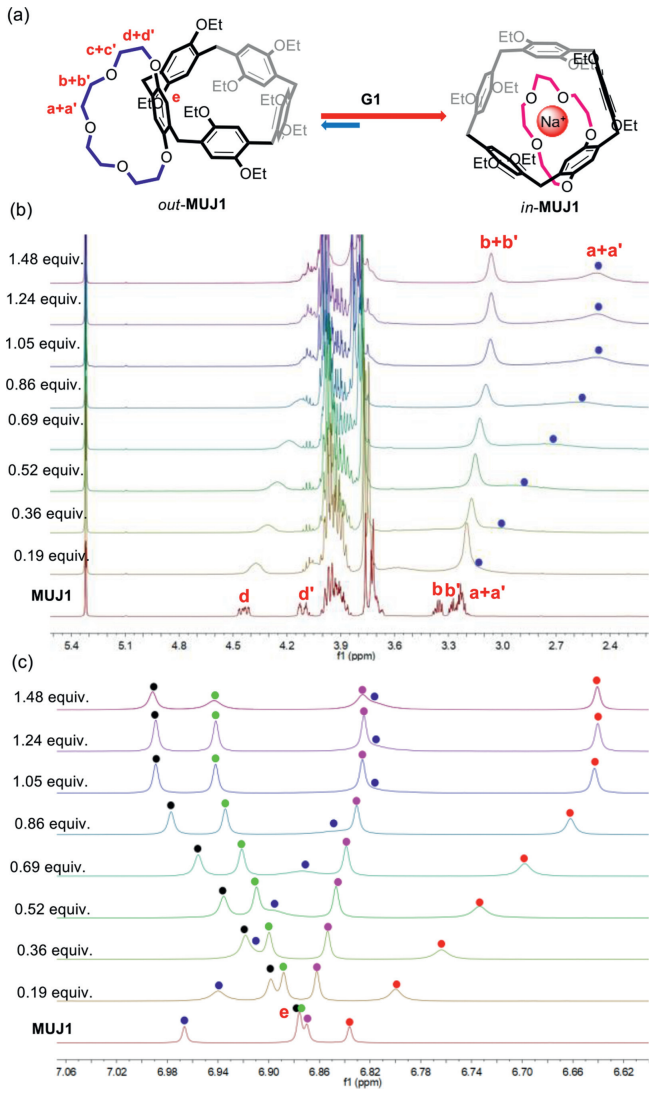

Fig. 2. (a) Schematic illustrations for the in-out equilibrium of the **MUJ1** induced by the binding of Na^+; partial ^1H NMR spectra of **MUJ1** (10 mmol/L) with titrations of **G1** at upfield (b) and downfield (c) regimes, respectively.

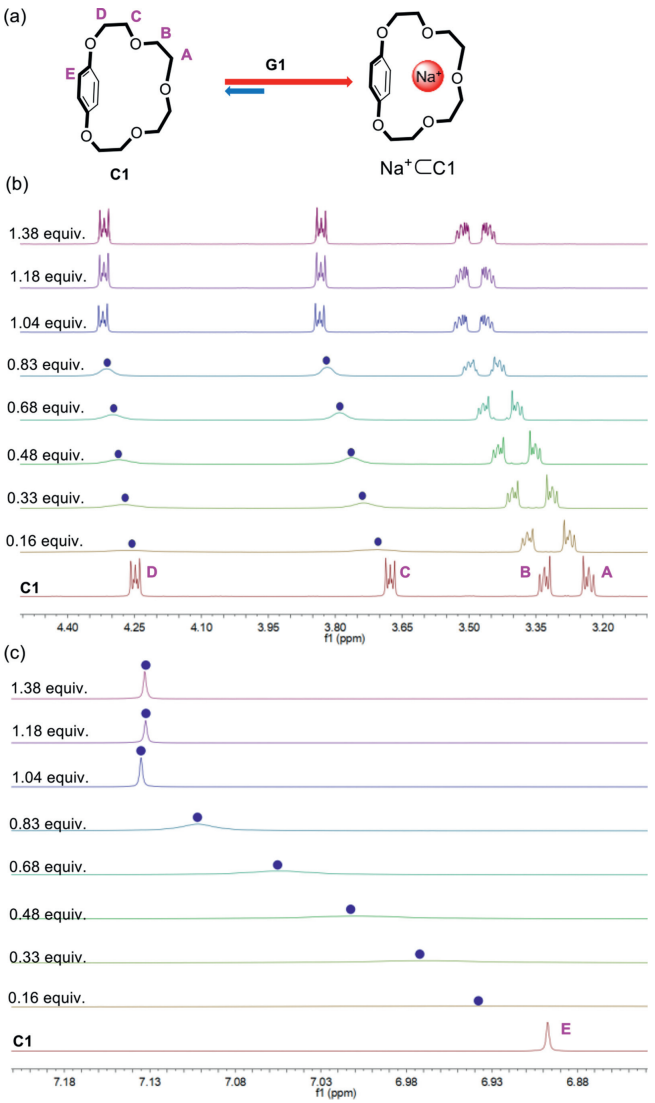

Fig. 3. (a) Schematic illustrations for complexing equilibrium of **C1** with **G1**; partial ^1H NMR (400 MHz, CD_2Cl_2, r.t.) spectra of **C1** (17 mmol/L) with titrations of **G1** at (b) downfield and (c) upfield regimes, respectively.

shifting upon the complexation of **G1**. The protons of **C1** showed extremely broadening effects upon adding **G1**, demonstrating a fast equilibrium of complexation/decomplexation of the sodium ion. More significantly, the proton signals recovered clear and stopped changing after more than 1.0 equiv. of **G1** were added, indicating again a strong 1:1 complexation between **C1** and **G1** in CD_2Cl_2 [43,44].

The sodium ion triggered rolling-in motions with chirality switching of out-(R_p)/in-(S_p)-**MUJ1** was a little bit unexpected. Previously, a pillar[5]thiacrown derivatives showed a rolling-out motion of the subring when complexing with mercury ion [38], for which the expansion of the thiacrown unit upon complexation of Hg^{2+} was responsible. Therefore, the preference of the in-conformation of the present $Na^+\subset$**MUJ1** to the out-conformer was further investigated. NMR titration of **DEP5** with **G1** was carried out in CD_2Cl_2, and the proton signals of methylene at both the waist and on the portal of **DEP5** showed significant upfield shifting and extremely broadening effects (Fig. S27 in Supporting information), demonstrating that **DEP5** exhibited host-guest complexing with **G1**, cation-π and electrostatic attraction between the electron-rich cavity with the electron-defect Na^+ should be the main driving force. The binding constant was determined to be

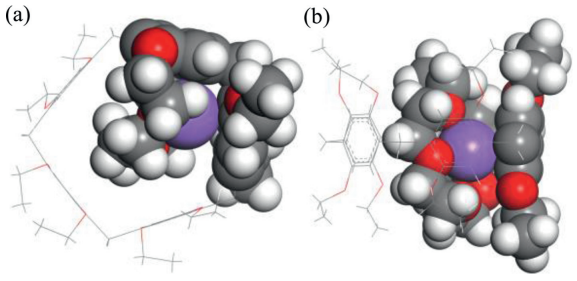

Fig. 4. Top (a) and front (b) view of the optimized structures of $Na^+\subset$out-(R_p)/in-(S_p)-**MUJ1** by DFT at the B3LYP/6–31G(d) level with Gaussian 09 W.

$(5.4 \pm 0.55) \times 10^3$ L/mol (Fig. S28 in Supporting information). Theoretical simulation of the complex $Na^+\subset$out-(R_p)/in-(S_p)-**MUJ1** also showed that the included crown ether subring coordinated with sodium ion could be stabilized by the synergetic cation-π interaction between sodium ion and the aromatic units of pillar[5]arene as well as the strong C–H···π interactions of the positive glycol ether subring with the electron-rich cavity of P[5] (Fig. 4) [44–46]. Therefore, agile rolling in of the subring was realized upon

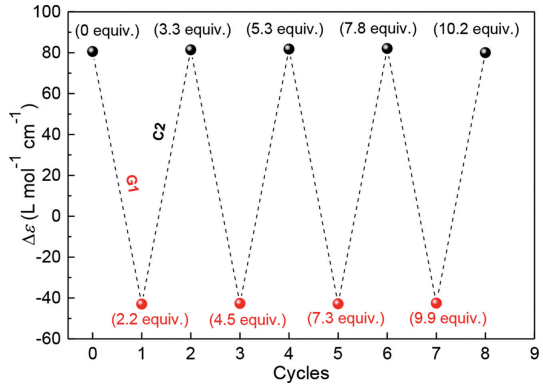

Fig. 5. CD signal changes of out-(R_p)/in-(S_p)-**MUJ1** (20 μmol/L, 307 nm, dichloromethane) with additions of **G1** and **C2** alternately.

adding **G1** and chirality switching of MUJs was achieved firstly by synergistically complexation of **G1** by the two macrocyclic hosts in **MUJ1**.

The counter anion could significantly affect the chiral inversion of the **MUJ1,** as can be seen in Fig. S32 (Supporting information), adding excessive **G2** induced CD inversion but the negative signal was much weaker than that by adding equivalent **G1**, which was reasonable as the ion-pairing strength will affect the host-guest binding affinities. Other alkali metal ions, including K^+ (**G3**) and Rb^+ (**G4**) were also employed to activate the chirality switching of out-(R_p)/in-(S_p)-**MUJ1** (Figs. S33 and S34 in Supporting information), it was found that little changes in the CD spectra were observed even by adding excessive **G3** and **G4,** demonstrating the good selectivity of **MUJ1** with Na^+ over other alkali metal ions.

Polar solvent methanol and competitive host 15-crown-5 ether (**C2**) easily disassembled the complexation between **MUJ1** and **G1** and resulted in the rolling-out of the subring. The CD spectra of Na^+⊂out-(R_p)/in-(S_p)-**MUJ1** recovered to that of free out-(R_p)/in-(S_p)-**MUJ1** after about 3% MeOH was added (Fig. S36 in Supporting information), this is mainly due to the solvation of sodium ion by methanol, which weakens the inclusion of sodium ion by crown ether/pillar[5]arene. Also, adding excessive **C2** to competitively binding with Na^+ recovered the CD signal (Fig. S37 in Supporting information). The CD signs of out-(R_p)/in-(S_p)-**MUJ1** were inverted by adding **G1** and **C1** alternatively for several cycles without obvious fatigue (Fig. 5 and Fig. S38 in Supporting information). These results indicated that the agile rolling in /out of the subring and chirality switching of MUJs could be reversibly manipulated, which will be beneficial for the construction of supramolecular stimuli-responsive systems based on molecular machines [47].

In summary, three MUJs based on pillar[5]arene derivatives fusing with 17-crown-5 ether (**MUJ1**, **MUJ3**) or aliphatic subring (**MUJ2**) were synthesized, planar-chiral enantiomers of **MUJs** were isolated, and the absolute configuration was determined by circular dichroism. Stimuli-responsibility of **MUJs** toward sodium ion was investigated, and the crown ether fused out-(R_p)-**MUJ1** and out-(R_p)-**MUJ3** recognize Na^+ to trigger the chiral inversion to in-(S_p)-**MUJ1** and in-(S_p)-**MUJ3,** respectively. The intensive positive CD signal inverted to a strong negative CD signal upon adding 1.0 equiv. of **G1**, with varied anisotropy factor of as much as 0.014, while the aliphatic subring fused **MUJ2** showed only CD decrease but no inversion**.** NMR titrations and theoretical calculation indicated that the cation-π and C–H$\cdots\pi$ interactions synergistically stabilized the in-conformer of MUJs, thus led to the agile rolling-in motion of the subring upon complexing with **G1**. Other alkali metal ions like K^+ and Rb^+ did not induce the chirality inversion, showing good selectivity of **MUJ1** toward Na^+. The rolling in/out motion of the subring and the chirality switching were reversibly manipulated by adding **G1** and **C2** (or methanol) alternatively. This work opened a new window for manipulating supramolecular equilibria by synergetic complexing of cations and will help understanding the mechanical motion of natural or artificial molecular machines.

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

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.05.072.

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