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Click Annulation of Pseudo[2]rotaxane to [2]Catenane Exploiting Homoditopic Nitrile *N*-Oxide

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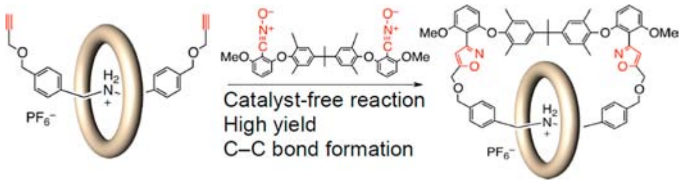
ABSTRACT



A mild annulation reaction of a propargyl-terminated pseudorotaxane with a homoditopic stable nitrile *N*-oxide enabled the efficient synthesis of catenanes consisting of not only dibenzo-24-crown-8-ether (DB24C8) but also dibenzo-30-crown-10-ether (DB30C10) as a wheel component. A dynamic ^{1}H NMR study showed the highly enhanced mobility of the components of the DB30C10-based [2]catenane due to the enlarged wheel cavity.

[2]Catenanes[1] can be obtained from pseudo[2]rotaxane mainly by both a cyclization reaction between reactive end groups and an annulation reaction with a connecting agent. Such reactions usually suffer from dissociation of the pseudo[2]rotaxane with a labile through-space linkage as well as the polymerization to a linear molecule. Therefore, ring-closing olefin metathesis (RCM)[2] and click chemistry based on the Huisgen reaction[3] have long been employed for the synthesis of the catenanes.

From viewpoints of the development of atom-efficient and metal-free procedures without labor-intensive purification, we have previously developed an effective synthesis of [2]rotaxanes and polyrotaxanes via 1,3-dipolar cycloaddition of nitrile *N*-oxide for the end-capping reaction.[4] This method, by exploiting a nitrile *N*-oxide,[5] can be characterized by the catalyst-free, chemoselective, solvent-free, and high-yield synthesis from pseudo(poly)rotaxanes bearing unsaturated bonds, such as $C{=}C$, $C{\equiv}C$, and $C{\equiv}N$ groups at the axle terminus.[4]

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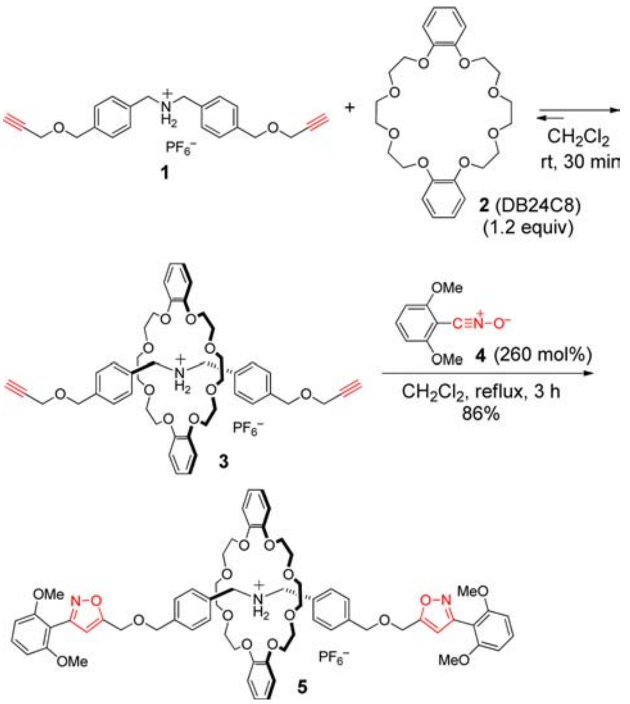
Scheme 1. Model Reaction Using Pseudo[2]rotaxane **3** to [2]Rotaxane **5**



Furthermore, we have also discovered a homoditopic nitrile *N*-oxide as a new chemical ligation agent between unsaturated bond-containing compounds, mainly directed toward both catalyst-free polycycloaddition of bisdipolarophiles and catalyst-free cross-linking reactions of common polymers, such as fibers, rubbers, and resins.[6,7]

Herein, we report the click annulation of pseudo[2]rotaxane using the homoditopic nitrile *N*-oxide as a connecting agent to afford efficiently [2]catenanes. The present click annulation is available to the synthesis of [2]catenane consisting of a large ring dibenzo-30-crown-10-ether (DB30C10) that has a very labile through-space linkage. The ring size effects of the resulting [2]catenanes are also discussed with their dynamic nature.

To evaluate the feasibility of the click annulation protocol to give directly [2]catenane, we first investigated the model reaction, i.e., a double end-capping reaction of bispropargyl-terminated pseudo[2]rotaxane **3** using monofunctional stable nitrile *N*-oxide **4**[5a−c] (Scheme 1). Treatment of *sec*-ammonium salt **1** in the presence of dibenzo-24-crown-8-ether (DB24C8, **2**) in CH_2Cl_2 at room temperature gave pseudorotaxane **3** possessing alkyne moieties at both termini. Subsequent catalyst-free 1,3-dipolar cycloaddition reactions of nitrile *N*-oxide **4** to **3** underwent nicely the isoxazole formations to give the corresponding [2]rotaxane **5** in 86% yield. The structure of **5** was determined by ^{1}H NMR, ^{13}C NMR, IR, and ESI−TOF MS spectra as a single regioisomer.[8]

From the high yielding synthesis of **5**, we next examined the catenane synthesis by the click annulation reaction of **3** using the homoditopic nitrile *N*-oxide **6**.[6] After the preparation of the pseudo[2]rotaxane **3** in a 0.1 M CH_2Cl_2 solution, the mixture was diluted with an arbitrary amount of CH_2Cl_2 before the annulation reaction. Table 1 summarizes the effect of the concentration on the annulation reaction to give [2]catenane **7**. As a first attempt, a stoichiometric amount of **6** was directly added to a 0.1 M solution of **3** without any dilution, and the mixture was refluxed until the complete comsumption of **3** and **6**, which was detected by a TLC analysis (Table 1, entry 1). After 5 h, the mixture was concentrated in vacuo and purified by gel permeation chromatography (GPC) to yield the corresponding catenane **7** (12%) and the polymeric materials (74%) caused by a polycycloaddition reaction between **3** and **6**. To avoid the polymerization reaction, the high dilution conditions for the annulation reaction were performed as shown in entries 2−5. By the reduction in concentration, the reaction required a prolonged reaction time but resulted in the favorable formation of **7** as a main product (entries 2, 3, and 5). The higher reaction temperature led to the slight decrease in the yield of **7** (entry 4), probably due to the entropy-dependent deslippage behavior of **3**. From these results, we concluded that the suitable reaction conditions were 0.001 M in CH_2Cl_2 (entry 3, 49% yield). It is possible that the central *gem*-dialkyl group of **6** might induce a Thorpe−Ingold effect to facilitate somewhat the annulation reaction.

According to the optimized conditions, the synthesis of DB30C10-based [2]catenane **10** was performed via the intermediary formation of pseudorotaxane **9** and a one-pot annulation reaction under the high dilution conditions (Scheme 2). As a result, it turned out that the reaction enabled the efficient synthesis of DB30C10-based [2]catenane **10**

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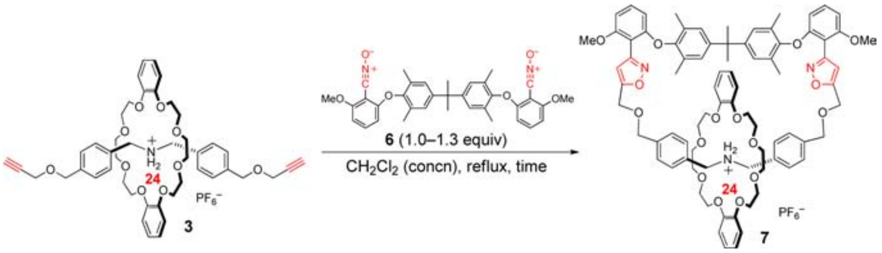
(8) See, Supporting Information.

Table 1. Effect of Concentration on the Annulation Reaction of Pseudorotaxane **3** To Afford [2]Catenane **7**

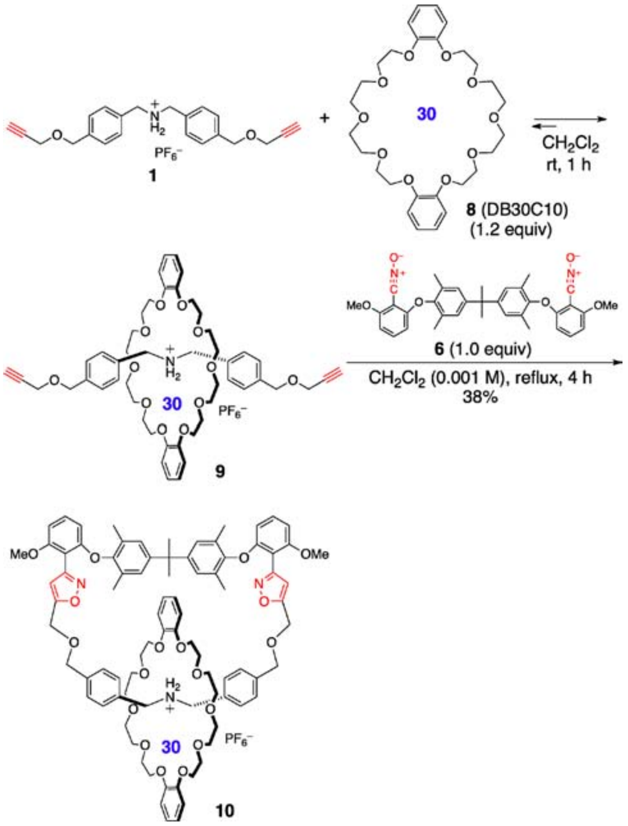


entry	concn/M	time	yield of **7** /%	polymer /%
1[a]	0.1	5 h	12	74
2[a]	0.01	31 h	40	–[d]
3[a]	0.001	72 h	49	38
4[b,c]	0.001	43 h	46	–[d]
5[b]	0.0005	8 d	47	–[d]

[a] 1.3 equiv of **6** were used. [b] 1.0 equiv of **6** was used. [c] The reaction was performed in $ClCH_2CH_2Cl$ under reflux. [d] Not estimated.

(38% yield).[8] The cavity of DB30C10 (**8**) is sufficiently large to penetrate the bulky isoxazole moieties, which was evaluated by CPK model studies. It is also supposed that the through-space linkage of **10** would be weaker than that of DB24C8-based [2]catenane **7**.[9]

Scheme 2. Synthesis of [2]Catenane **10**



To evaluate the differences of circumrotation behaviors between two catenanes **7** and **10**, *N*-acetylation reactions of these *sec*-ammonium moieties were performed to eliminate the through-space interactions (Scheme 3).

Figure 1 shows the ^1H NMR spectra of the axle **1** and the [2]catenanes **7**, **10**, **11**, and **12**. In the spectra (B) and (D), the formations of [2]catenanes were directly evidenced by the signals (f) of the isoxazole skeletons along with the disappearance of the signals of terminal alkynes of axle **3** ($C\equiv C-H$) in addition to the good agreement of the observed HRMS with the theoretical value.[8] Moreover, the characteristic signals of benzyl protons (c) of the axle component of **7** and **10** appeared as broad peaks due to the geminal coupling, strongly supporting the formation of the interlocked structure in accordance with the literature.[10] As shown in the spectra of (C) and (E), the signals of the acetyl group clearly support the *N*-acetylated structures of **11** and **12**. The signals of **11** in the spectrum (C) appeared as complicated peaks, implying the slow circumrotation of the components relative to the NMR time scale. In contrast, the simple signal patterns of **12** except for signals (c) in spectrum (E) suggest the high mobility of the DB30C10 moiety and its ability to be unhindered by the steric hindrance of the bulky isoxazole moieties.

To evaluate the reason why signals (c) were split in spectrum (E), the variable-temperature ^1H NMR spectra (VT-NMR) of **11** and **12** were compared with those of crown ether free macrocycle **13** as a model compound.[8] Figure 2 shows the VT-NMR of **12**. The coalescent

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(9) For related reports, see: (a) Tokunaga, Y.; Yoshioka, M.; Nakamura, T.; Goda, T.; Nakata, R.; Kakuchi, S.; Shimomura, Y. *Bull. Chem. Soc. Jpn*. **2007**, *80*, 1377–1382. (b) Zhu, K.; Vukotic, N.; Noujeim, N.; Loeb, S. J. *Chem. Sci.* **2012**, *3*, 3265–3271.

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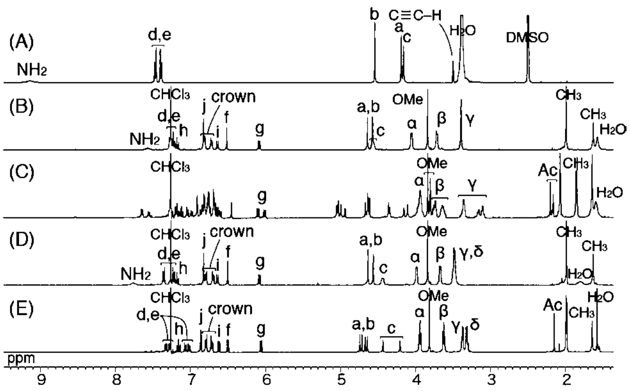
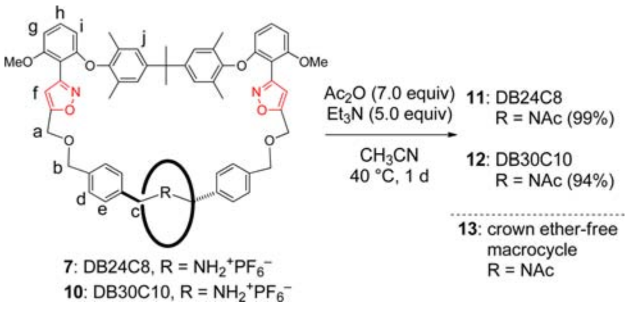


Figure 1. ^{1}H NMR spectra (400 MHz, 298 K) of (A) **1** (DMSO-d_6), (B) **7** ($CDCl_3$), (C) **11** ($CDCl_3$), (D) **10** ($CDCl_3$), and (E) **12** ($CDCl_3$).

Scheme 3. Synthesis of *N*-Acetylated [2]Catenanes **11** and **12**



temperature of signal (c) in the VT-NMR of **12** was in good accordance with that of **13**, strongly indicating that the peak split could be attributed to the rotamers of acetylamide moiety. The VT-NMR analyses of **11** revealed that the wheel component of **11** could not pass through the steric barriers originating from both the central *N*-acetyl group and the bulky isoxazole moieties, since the complicated signals of **11** did not fuse even at high temperature.[8] We also examined the deprotonation reaction of the *sec*-ammonium moiety in **10** using KOH.[4a] The deprotonation

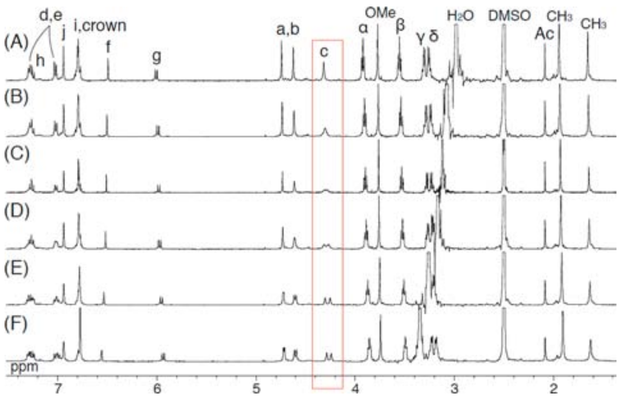


Figure 2. Variable-temperature ^{1}H NMR spectra of **12** (400 MHz, DMSO-d_6) at (A) 373 K, (B) 353 K, (C) 343 K, (D) 333 K, (E) 313 K, and (F) 293 K.

of **10** proceeded easily to give the nonionic [2]catenane in a high yield,[8] while **7** resisted somewhat the same deprotonation conditions, probably due to the proximity effect to intensify the hydrogen bondings and/or the steric hindrance to prevent the approach of the nucleophile. Such results clearly indicate the highly enhanced mobility of **12** accompanied by the enlargement of the wheel cavity.

In conclusion, the present paper has disclosed a simple and powerful synthetic method for [2]catenanes without any catalyst and the evaluation of the ring size effects on the dynamic nature of the resulting [2]catenanes. Further studies directed toward the functionalization of the resulting catenanes based on the chemical modifications of the isoxazole skeletons are currently underway.

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Supporting Information Available. Full experimental details for all new compounds are provided, including ^{1}H NMR, ^{13}C NMR, and IR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.