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Rotaxanes

A Dibenzoazacyclooctyne as a Reactive Chain Stopper for [2]Rotaxanes

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Abstract: A strained dibenzoazacyclooctyne (DIBAC) derivative was introduced for the preparation of a rotaxane by strain-promoted azide–alkyne cycloaddition (SPAAC), also referred to as a copper-free click reaction. The DIBAC can efficiently act as a bulky reactive chain stopper to transform a pseudorotaxane architecture consisting of a diazo-functionalized dialkox-

naphthalene guest and a tetracationic cyclobis(paraquat-*p*-phenylene) (CBPQT⁴⁺) host into the corresponding [2]rotaxane. Furthermore, the use of the DIBAC is demonstrated to be limited to short rigid macrocycles, as it is unable to act as stopper for a rotaxane featuring a larger crown ether macrocyclic host.

Introduction

The most recently introduced type of isomeric organic molecules^[1] are mechanically interlocked molecules (MIMs) such as catenanes, rotaxanes, and knots, the inspiration for which came from various natural objects and architectures.^[2–5] MIMs have attracted increasing attention for over 50 years owing to their wide range of potential applications in molecular devices such as artificial machines,^[6–10] muscles,^[11] elevators,^[12] switches,^[13,14] and pumps,^[15] and the Nobel Prize was awarded recently for work in this area.^[16–24] The rotaxane structure, as one type of mechanically interlocked molecule, has been considered as a versatile platform for the construction of functional artificial nanomachines.^[25–27] Therefore, the discovery of highly efficient synthetic strategies for the preparation of rotaxanes should facilitate the further development of this research area. The synthetic strategies for the preparation of rotaxanes range from statistical threading to directed template synthesis.^[28,29] In recent years, rotaxanes were mainly synthesized by either “clipping” a partially formed macrocycle around a dumbbell,^[27,30–33] “slipping” the macrocycle over the bulky ends of the dumbbell,^[34] or by single or double “stoppering” of a

pseudorotaxane with bulky stoppers; the double-stoppering strategy employed in this work is illustrated in Figure 1. The stoppering approach is used most widely to make rotaxanes, especially if cyclobis(paraquat-*p*-phenylene) (CBPQT⁴⁺), also named blue box, is employed as the macrocyclic host to construct rotaxanes.^[35–38]

The Cu^I-catalyzed azide–alkyne cycloaddition (CuAAC), often referred to as a click reaction,^[39] has frequently been utilized in the stoppering strategy for the creation of rotaxanes owing to its high regioselectivity, tolerance to sensitive functional groups, and mild reaction conditions.^[35,38,40] However, it is commonly performed in the presence of copper ions, which increase the complexity of the workup procedure and may interfere with the pseudorotaxane formation if metal templates are involved in the assembly process. Therefore, the interest in methods involving metal-free click reactions to replace CuAAC is growing.^[41–43] Rotaxanes have already been prepared by the metal-free cycloadditions of azides with bulky acetylenedicarboxylates^[42] as well as through cucurbituril-catalyzed azide–alkyne cycloaddition.^[44] Several strain-promoted copper-free systems, such as oxanorbornadienes,^[45,46] cyclooctynes,^[47–49] and dibenzocyclooctynes^[50–53] have been developed for fast and selective reactions with azides, commonly referred to as strain-promoted azide–alkyne cycloaddition (SPAAC). To the best of our knowledge, there is only one previous report in which dibenzocyclooctyne was employed to construct a [2]rotaxane.^[54] However, that study only utilized the dibenzocyclooctyne to evaluate a new route for the synthesis of a [2]rotaxane under solvent-free conditions without any further emphasis on its use as a stopper or the evaluation of its scope as a stopper to prepare compact [2]rotaxanes. Herein, we introduced a dibenzoazacyclooctyne (DIBAC) derivative to prepare a compact [2]rotaxane through this methodology and further addressed its scope as a stopper.

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Figure 1. Graphical representation of the double stopping of a pseudorotaxane to form a [2]rotaxane.

Results and Discussion

In this work, we introduced a DIBAC derivative for the preparation of [2]rotaxanes, as we anticipated that it could act simultaneously as a reactive group and a bulky stopper to yield very compact [2]rotaxanes. Moreover, the commercial availability of various DIBAC derivatives further expands the applicability of such a synthetic protocol. The occurrence of the SPAAC reaction at room temperature or below is ideal for strong supramolecular binding, for example, of the CBPQT⁴⁺ ring to a variety of thread molecules with π -electron-donating nature, to form pseudorotaxanes efficiently, a prerequisite for efficient rotaxane synthesis, which is often performed at room temperature or below.^[35,55]

As a first step, the reactivity of the DIBAC derivative in acetonitrile at 0 °C was investigated by mixing a stoichiometric ratio of the DIBAC with 1,5-dialkoxynaphthalene (DNP) derivative **1** carrying azide-terminated glycol chains. The reaction solution was stirred for 48 h and then analyzed by ESI-MS without further purification, and the analysis revealed the reactivity of the cyclooctyne stopper, as only the dumbbell formed through the reaction with DIBAC was detected together with a trace amount of free DIBAC stopper molecules (see the Supporting Information, Figure S1). The obtained dumbbell was then mixed with excess CBPQT-4PF₆ in acetonitrile to examine whether the stopper can effectively prevent the threading of the CBPQT⁴⁺ ring over the chain stoppers of the dumbbell molecule to form the rotaxane architecture and provide a first indication of the possible use of the DIBAC as a chain stopper. No color change was observed upon the addition of the CBPQT-4PF₆ macrocycle to the dumbbell, whereas the direct addition of the CBPQT-4PF₆ solution to a solution of DNP **1** caused the appearance of a pink-purple color. These visual observations were confirmed by UV/Vis spectroscopy, which indicated the ability of the DIBAC

to act as chain stopper to prevent the threading of the CBPQT⁴⁺ macrocycle over the dumbbell (see the Supporting Information, Figure S2).

Stimulated by these promising results, we synthesized the [2]rotaxane **3**·4PF₆ by the “threading-followed-by-stopping” strategy (Figure 1 and Scheme 1). Firstly, the two recognition elements, the DNP **1** thread molecule and the CBPQT⁴⁺ macrocycle, were mixed at 0 °C to form the pseudorotaxane, as evidenced by the appearance of the characteristic purple color of the DNP–CBPQT⁴⁺ host–guest donor–acceptor complex. The rotaxane was then synthesized by the addition of the DIBAC stopper **2**, and the pure rotaxane **3**·4PF₆ could be isolated in 61 % yield by preparative TLC after the reaction mixture was stirred for 2 d at 0 °C.

The [2]rotaxane **3**·4PF₆ was characterized by ¹H NMR spectroscopy, matrix-assisted laser-desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, and size-exclusion chromatography (SEC). Unfortunately, the rather complex structure of the obtained rotaxane, including the possible formation of different triazole isomers as well as different protonation states of the triazole and carboxylic acid groups, possibly in combination with limited mobility of certain parts of the structure led to broadened signals and a complicated ¹H NMR spectrum, which made a full assessment of the purity difficult. Nonetheless, as shown in Figure S3 (see the Supporting Information), the resonance signals of DNP shifted upfield owing to shielding by the CBPQT⁴⁺ ring, as is typical for a rotaxane containing CBPQT⁴⁺ and DNP. The shift and broadening of the resonance signals of CBPQT⁴⁺ further confirmed the formation of a CBPQT⁴⁺–DNP donor–acceptor charge-transfer complex.^[35] The slow rotations of the bipyridinium units and *p*-phenylene rings in CBPQT⁴⁺ are reflected by the broad proton resonances at 298 K. These signals coalesce into narrower peaks at higher

Scheme 1. The general synthetic route to [2]rotaxane **3**·4PF₆ (note that only one triazole isomer is shown for simplicity).

temperature, especially those of the β protons of the bipyridinium groups.

The MALDI-TOF mass spectrum of the [2]rotaxane confirmed its purity (Figure 2) as it only showed the peaks corresponding to the rotaxane with different numbers of PF₆[−] counterions, that is, $[M - 4PF_6 + 3e]^+$, $[M - 3PF_6 + 2e]^+$, and $[M - 2PF_6 + e]^+$.

Figure 2. MALDI-TOF mass spectrum of the [2]rotaxane **3**·4PF₆.

Furthermore, the observation of the intact rotaxane by MALDI-TOF MS indicates that the DIBAC-based stoppers are large enough to block the CBPQT⁴⁺ macrocycle on the chain. Finally, the obtained [2]rotaxane in 1,1,1,3,3,3-hexafluoroisopropanol was analyzed by SEC; the intact rotaxane eluted over the column, as detected by the UV signal at $\lambda = 520$ nm (see the Supporting Information, Figure S4), which further confirmed the stability of the obtained rotaxane.

To evaluate further the stability of the formed rotaxane **3**·4PF₆, the rotaxane solution was heated from 10 to 80 °C and monitored by UV/Vis spectroscopy. The temperature-dependent UV/Vis spectra are shown in Figure 3 and revealed that the absorption intensity of the rotaxane was constant at ca. 0.55 during the heating process. The minor decrease in absorption can be ascribed to the faster exchange between the complexed and uncomplexed forms of DNP and CBPQT⁴⁺ resulting from the movement of CBPQT⁴⁺ along the chain. In contrast, the heating of a solution of the precursor pseudorotaxane consisting of DNP **1** and CBPQT⁴⁺ led to a strong decrease in absorption intensity upon heating, and this indicates dethreading and loss of the pseudorotaxane structure. Thus, these comparative results indicate that rotaxane **3**·4PF₆ is stable at elevated temperatures and confirm that the DIBAC-based stopper is large enough to stabilize the rotaxane structure. Furthermore, these

Figure 3. Temperature-dependent UV/Vis spectra of (a) rotaxane **3-4PF₆** and (b) the corresponding pseudorotaxane of DNP **1** with CBPQT⁴⁺ in acetonitrile.

results also confirmed the purity of the product and again suggested that no semi(pseudo)rotaxane is present.

In addition to its thermal stability, the stability of the rotaxane **3-4PF₆** was also studied towards a competing guest molecule, tetrathiafulvalene (TTF), which has a much higher association constant for complexation with CBPQT⁴⁺ than that of the dialkoxynaphthalene present in the rotaxane. Moreover, the host-guest complex formed by CBPQT⁴⁺ and TTF exhibits a distinct green color, which is readily distinguishable from the purple CBPQT⁴⁺-DNP complex and allows the straightforward evaluation of the competition experiments. Upon the addition of some drops of concentrated TTF solution to a solution of rotaxane **3-4PF₆**, no clear color change was observed; therefore, no exchange was possible, and the stability of the rotaxane was confirmed (Figure 4). The minor change in color is most likely caused by the partial charge-transfer interaction between TTF and the CBPQT⁴⁺ ring through the complexation of TTF to the outer part of the CBPQT⁴⁺ ring. However, the addition of TTF to the solution of the pseudorotaxane immediately resulted in the formation of a green solution, which is characteristic of the for-

mation of the CBPQT⁴⁺ complex with TTF.^[56] These competition experiments were also monitored by UV/Vis spectroscopy, which supported the visual observations. The UV/Vis spectra for the competition experiment with the rotaxane suggest that the naphthalene-CBPQT⁴⁺ charge-transfer absorption band, centered at $\lambda \approx 520$ nm, did not decrease upon the addition of TTF, although a new absorption band at $\lambda \approx 800$ nm most likely results from the charge-transfer interaction between TTF and the outside of the CBPQT⁴⁺ ring. For the pseudorotaxane, the absorption band of the CBPQT⁴⁺ complex with DNP disappeared upon the addition of TTF, and a new quite strong absorption band at $\lambda = 800$ nm was ascribed to the CBPQT⁴⁺ complex with TTF. These observations demonstrate that the rotaxane is stable against the competing guest and give further evidence that the DIBAC derivative is large enough to act as stopper for the preparation of rotaxanes.

To investigate the broader scope of the use of the DIBAC for the construction of macrocyclic host-based rotaxanes, it was evaluated for the preparation of a [2]rotaxane based on 1,5-dinaphtho[38]crown-10 (DNP38C10; see Scheme 2) as a macro-

Figure 4. UV/Vis spectra of (a) rotaxane **3-4PF₆** and (b) the corresponding pseudorotaxane of DNP **1** with CBPQT⁴⁺ in the absence and presence of an excess of TTF in acetone at 25 °C.

Scheme 2. The general synthetic route to dumbbell **6**; only one triazole isomer is shown for simplicity (the inset shows the structure of host macrocycle DNP38C10).

cyclic host with a larger and more flexible cavity than that of CBPQT⁴⁺. Therefore, a dumbbell was prepared by reacting the 2,7-bis(2-[2-(2-(2-azidoethoxy)ethoxy)ethoxy]ethyl)benzo-*[lmn]*[3,8]phenanthroline-1,3,6,8(2*H*,7*H*)-tetraone (**5**) guest molecule with DIBAC **2**. The ESI-MS results of the reaction solution (see the Supporting Information, Figure S5) revealed the quantitative formation of the double-stoppered dumbbell, in addition to a minor excess of DIBAC that would not interfere with the formation of the host–guest rotaxane. As depicted in Figure S6 (see the Supporting Information), the exposure of this dumbbell solution to a concentrated DNP38C10 solution in CDCl₃ revealed the immediate appearance of a pink color, which indicates the donor–acceptor host–guest complexation of DNP38C10 and the naphthodiimide unit. This observation was further confirmed by UV/Vis spectroscopy, which revealed the characteristic charge-transfer absorption band of the DNP38C10–**5** complex centered at $\lambda \approx 520$ nm. These results suggest that the cavity size of DNP38C10 is significantly larger than that of the DIBAC derivative in the dumbbell, which no longer acts as an efficient stopper. A comparison of the ¹H NMR spectrum of the bare dumbbell with that of the mixture with DNP38C10 revealed the expected partial upfield shift of the naphthodiimide proton resonances, similar to those for a mixture of DNP38C10 with **5** (see the Supporting Information, Figure S7). These ¹H NMR spectroscopy results confirm that the DIBAC derivative cannot be used to construct rotaxanes with this larger macrocyclic ring.

Conclusions

A DIBAC derivative was introduced as a new reactive stopper for the preparation of small [2]rotaxanes by combining the high

reactivity of DIBAC towards azides through SPAAC with a large steric bulky stopper. Several methods were employed to assess the efficiency of the stopper for the construction of a [2]rotaxane based on CBPQT⁴⁺ as a macrocyclic host, and the results clearly demonstrated that we have developed a new, highly efficient approach for the development of rotaxanes. The DIBAC was demonstrated to be limited to small rigid hosts as it was insufficient as a stopper for a rotaxane based on the larger and more flexible DNP38C10 macrocyclic host. Nonetheless, this straightforward synthetic strategy provides the opportunity to prepare mechanically interlocked molecules efficiently. Last but not least, the commercial availability of various DIBAC derivatives facilitates their use as stoppers for the construction of rotaxanes.

Experimental Section

General Methods: All reagents were purchased from Sigma–Aldrich and used without further purification unless otherwise noted. 1,5-Bis(2-[2-(2-(2-azidoethoxy)ethoxy)ethoxy]naphthalene (**1**),^[35,57] cyclobis(paraquat-*p*-phenylene),^[58] 2,7-bis(2-[2-(2-azidoethoxy)ethoxy]ethyl)benzo-*[lmn]*[3,8]phenanthroline-1,3,6,8(2*H*,7*H*)-tetraone (**5**),^[59] 1,5-dinaphtho[38]crown-10,^[60] and 5-[11,12-didehydridibenzo[*b,f*]azocin-5(6*H*)-yl]-5-oxopentanoic acid (**2**)^[53] were prepared according to previously reported procedures. Thin layer chromatography (TLC) plates were purchased from Macherey–Nagel (precoated TLC plates SIL G-25 UV₂₅₄).

Dumbbell Molecule 4: Diazide DNP derivative **1** (0.93 mg, 2.4 μ mol) and DIBAC **2** (1.61 mg, 5.0 μ mol) were dissolved in CH₃CN (4 mL) at 0 °C. The reaction solution was stirred at 0 °C for 2 d. Then, the reaction solution was analyzed by ESI-MS without further purification. ¹H NMR (500 MHz, [D₆]Acetone): δ = 7.96–7.91 (m, 2 H,

Ph from DIBAC), 7.88–7.81 (d, 2 H, DNP *p*-O), 7.61–7.55 (m, 2 H, DNP, *m*-O), 6.99–6.87 (m, 2 H, DNP, *o*-O), 7.77–7.70, 7.50–7.44, 7.29–7.13 (m, 14 H, Ph from DIBAC), 6.14–6.00 (m, 4 H, PhCH₂N), 4.78–4.56 (m, 4 H, CH₂O–DNP), 4.10–3.95 (m, 4 H, OCH₂CH₂O–DNP), 4.35–4.21 (m, 4 H, OCH₂CH₂–triazole), 3.95–3.82 (m, 4 H, OCH₂CH₂–triazole), 2.16–2.10 [m, 4 H, CH₂C(O)N], 1.95–1.75 [m, 4 H, CH₂C(O)OH], 1.68–1.56 [m, 4 H, CH₂CH₂C(O)OH] ppm. ¹³C NMR (125 MHz, [D₆]Acetone): δ = 174.0, 170.6, 161.7, 155.0, 142.9, 141.4, 137.0, 135.2, 132.1, 130.8, 130.1, 128.9, 127.7, 126.1, 114.8, 106.4, 69.3, 55.3, 33.2, 20.9 ppm. ESI-MS: *m/z* = 513.3 [M + 2H]²⁺, 1025.4 [M + H]⁺.

[2] Rotaxane 3-4PF₆: Diazide DNP derivative **1** (9.5 mg, 0.025 mmol) and CBPQT-4PF₆ (35.21 mg, 0.032 mmol) were dissolved in CH₃CN (25 mL) at 0 °C to yield a pink-purple solution. A solution of DIBAC **2** (16.5 mg, 0.052 mmol) in acetonitrile (7 mL) was added after the pink-purple solution was stirred for 0.5 h. The reaction solution was stirred at 0 °C for 48 h, and then the acetonitrile was removed under reduced pressure to give a purple solid. The purple solid was washed with CH₂Cl₂ to remove the trace amount of free stopper **2**. Then, the crude product was dissolved in CH₃CN and purified by preparative TLC with 1 % w/v NH₄PF₆ solution in CH₃CN as the mobile phase. The product was obtained by washing the silica gel with excess eluent followed by the concentration of the CH₃CN solution under reduced pressure and precipitation in cold water. The pure rotaxane **3-4PF₆** was isolated as purple solid (27 mg, 61 %). ¹H NMR (500 MHz, CD₃CN, 325 K): δ = 9.21–8.65 (m, 8 H, α-CBPQT⁴⁺), 8.01 (s, 8 H, β-CBPQT⁴⁺), 7.83 (m, 8 H, aryl-CBPQT⁴⁺), 7.60–7.06 (m, 16 H, aryl-DIBAC), 6.34–6.19 (m, 2 H, DNP *o*-O), 6.08–5.96 (m, 8 H, CH₂–CBPQT⁴⁺), 5.79–5.65 (m, 2 H, DNP *m*-O), 4.985 (br s, 4 H, CH₂N DIBAC), 4.90–4.60 (m, 4 H, alkyl-DNP), 4.59–4.38 (m, 4 H, alkyl-DNP), 4.29–4.10 (m, 4 H, alkyl-DNP), 4.09–3.94 (m, 4 H, alkyl-DNP), 3.67–3.51 (br s, 4 H, alkyl-DIBAC), 3.51–3.37 (br s, 4 H, alkyl-DIBAC), 2.58–2.44 (m, 2 H, DNP *p*-O), 1.70–1.50 (br s, 4 H, alkyl-DIBAC). MS (MALDI-TOF): *m/z* = 1547.1 [M – 4PF₆[–] + 3e]⁺, 1691.8 [M – 3PF₆[–] + 2e]⁺, 1836.8 [M – 2PF₆[–] + e]⁺.

Dumbbell Molecule 6: Compound **5** (1.3 mg, 1.9 μmol) and DIBAC **2** (1.27 mg, 4.0 μmol) were dissolved in CH₃CN (4 mL) at 0 °C. The reaction solution was stirred at 0 °C for 2 d. Then, the reaction solution was analyzed by ESI-MS (see the Supporting Information, Figure S5) without further purification.

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