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Controlling the Chair Conformation of a Mannopyranose in a Large-Amplitude [2]Rotaxane Molecular Machine

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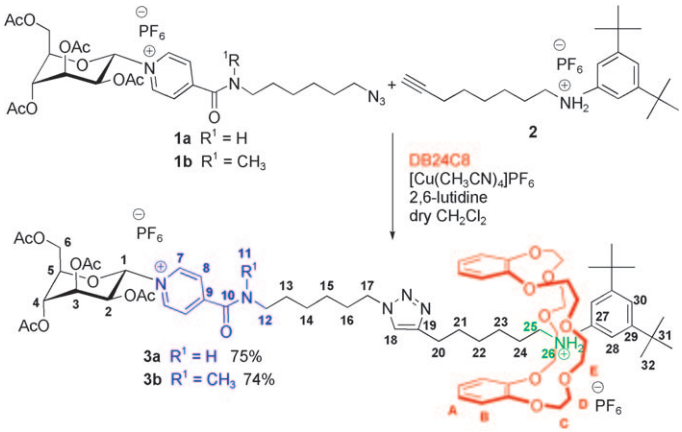
Rotaxanes have received much attention during the past decade, especially because they can be used as molecular machines.[1] As we are involved in the field of structure–activity relationships between glucides and lectines, we recently described very efficient preparations of glycorotaxanes,[2] pH-sensitive glycorotaxane molecular machines,[3] and glycosyl molecular muscles[4] containing an ammonium and a triazolium station. Here, we report the synthesis of two large-amplitude mannosyl [2]rotaxane molecular machines, containing dibenzo[24]crown-8 (DB24C8), an anilinium station, and either a new mono- or disubstituted pyridinium amide station, both derived from isonicotinamide moiety (Scheme 1). Since Busch et al. reported the ability for the DB24C8 to interact strongly with ammonium cations,[5] a wide variety of other template moieties, such as benzylic ammonium,[6] *N*-benzylic anilinium,[7] *N*,*N*′-dialkyl-4,4′-bipyridinium,[8] and 1,2-bis-(pyridinium)ethane cations,[9] have been investigated. However, the use of a monopyridinium amide station for DB24C8 in a molecular machine has never been described so far.[10] As expected, anilinium was found to be a much better station for the macrocycle than the pyridinium amide station. However, upon deprotonation of the anilinium, the macrocycle shuttles toward the pyridinium amide station. More interestingly, the interactions of the pyridinium amide station with DB24C8 proved to be very different depending on the mono- or disubstituted conjugated amide, thus allowing different localizations of the macrocycle around the pyridinium amide station. Whereas the DB24C8 resides around the positive charge of the disubstituted pyridinium amide, it is localized around the NH of the monosubstituted amide. This difference of localization causes the impressive switching of the glucidic conformation from $^1C_4$ to $^4C_1$ upon deprotonation of the anilinium, only in the rotaxane containing the disubstituted pyridinium amide station.



Scheme 1. The synthesis of the large-amplitude mannosyl [2]rotaxane molecular machines **3a–b**.

The mannosyl [2]rotaxane molecular machines **3a**,**b** were successfully obtained from the initially prepared mannoside azide **1a**,**b** containing a pyridinium amide moiety and the alkyne ammonium **2**, by using the copper(I)-catalyzed Huisgen[11] alkyne-azide 1,3-dipolar cycloaddition, also called "CuAAC click chemistry".[12] (Scheme 1)

The reaction was carried out in dichloromethane, at ambient temperature, over a period of 24 h, in the presence of DB24C8 (2 equiv), $[Cu(MeCN)_4]PF_6$ (1 equiv) and 2,6-lutidine (0.1 equiv). In these experimental conditions, only the [2]rotaxanes **3a**,**b** were isolated, as a result of the exclusive very good complexation of the anilinium template with the macrocycle, and no thread or [3]rotaxane were detected. This last observation evidently suggests that mono- and disubstituted pyridinium amides are very weak templates for the macrocycle in comparison with anilinium. The further shuttling of the macrocycle in rotaxanes **3a** and **3b** was car-

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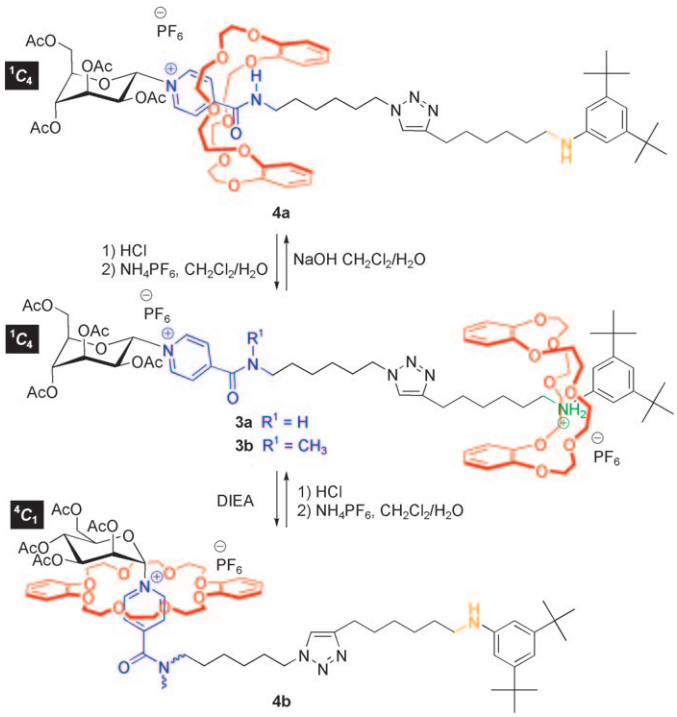

Scheme 2. Shuttling of the macrocycle in the large-amplitude mannosyl [2]rotaxane molecular machines **3**–**4** by variation of pH.

ried out by deprotonation of the anilinium station. (Scheme 2)

The interlocked architecture of glycorotaxanes **3a**,**b** and **4a**,**b** and the localization of the macrocycle at different pH were studied by ^{1}H NMR spectroscopy (Figures 1 and 2). Deprotonation of **3a** was realized by using NaOH and afforded the rotaxane **4a**. As expected, the DB24C8 moved toward the pyridinium amide station upon deprotonation. The localization of the DB24C8 around either the anilinium station in **3a** or around the pyridinium amide station in **4a** was confirmed by the analyses of the ^{1}H NMR spectra of both rotaxanes **3a** and **4a**, and uncomplexed threads **3au** and **4au**. (Figure 1)

Comparison between the spectra of the uncomplexed thread **3au** and the rotaxane **3a** reveals the presence and the localization of the macrocycle. (Figure 1a,b) Apart from the evident appearance of the signals for the macrocycle hydrogen atoms H^A–H^E, the H^{25} atoms experience a downfield shift ($\Delta\delta = 0.95$ ppm), while no chemical shift variations of the hydrogen atoms belonging to the pyridinium station (blue signals) are noticed, indicating that the DB24C8 ring binds exclusively with the monosubstituted *N*-alkylanilinium center. The H^{20}–H^{23} atoms and to a lesser extent H^{18} are more or less shielded in the rotaxane, because they undergo the shielding effect of the aromatic ring of the macrocycle. The other hydrogen atoms of the west part of the molecule (H^1–H^{17}) stay unchanged as they are not surrounded by the macrocycle. Upon deprotonation, the DB24C8 moved to the pyridinium amide station. This was confirmed by comparing ^{1}H NMR spectra of rotaxanes **3a** and **4a**. (Figure 1b,c) Ef-

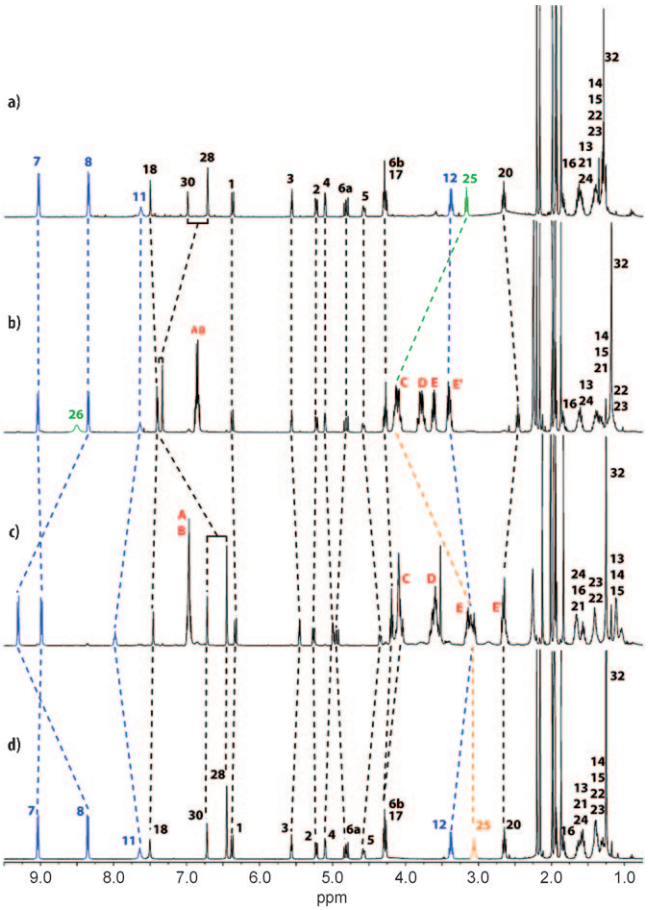

Figure 1. ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) the uncomplexed dumbbell-shaped thread **3au**, b) the rotaxane **3a**, c) the rotaxane **4a**, and d) the uncomplexed dumbbell-shaped thread **4au**. The lettering and numbering correspond to the proton assignments indicated in Scheme 1.

fectively, the chemical shift of H^{25} is shifted upfield as a result of both the deprotonation of the anilinium and the shuttling of the macrocycle, whereas pyridinium H^8 atoms and to a lesser extent the amide hydrogen atom H^{11} are simultaneously shifted downfield ($\Delta\delta = 0.96$ and 0.34 ppm, respectively), due to hydrogen bonding with the DB24C8. This is corroborated by a slight upfield shift of H^{12}–H^{16}, which now undergo the shielding effect of the aromatic ring of the DB24C8 to the detriment of H^{20}–H^{23}, which experience a downfield shift. Interestingly, no variation of the pyridinium hydrogen atoms H^7 is observed, which indicates the absence of any kind of interaction between H^7 and the DB24C8. No ion–dipole interactions occur between the cationic charge of the pyridinium and the oxygen atoms of the macrocycle. Eventually, a tremendous upfield shift is observed in **4a** for the signals of H^E, probably because they experience the shielding effect of the aromatic pyridinium ring. The localization of the DB24C8 around the pyridinium amide station is corroborated by the direct comparison of the rotaxane **4a** with the uncomplexed thread **4au**. (Figure 1c,d) In the rotaxane **4a**, the chemical shift of H^{25} stays unchanged, while the signals for H^{11} and H^8 are simulta-

neously shifted downfield due to hydrogen bonding with the DB24C8 and that for H^{12} is shifted slightly upfield, as they experience the shielding effect of the aromatic ring of the DB24C8.

Deprotonation of the rotaxane **3b** was carried out with diisopropylethylamine (DIEA) and the resulted shuttling of the macrocycle was studied by ^{1}H NMR spectroscopy (Figure 2). The interlocked architecture of rotaxane **3b** was

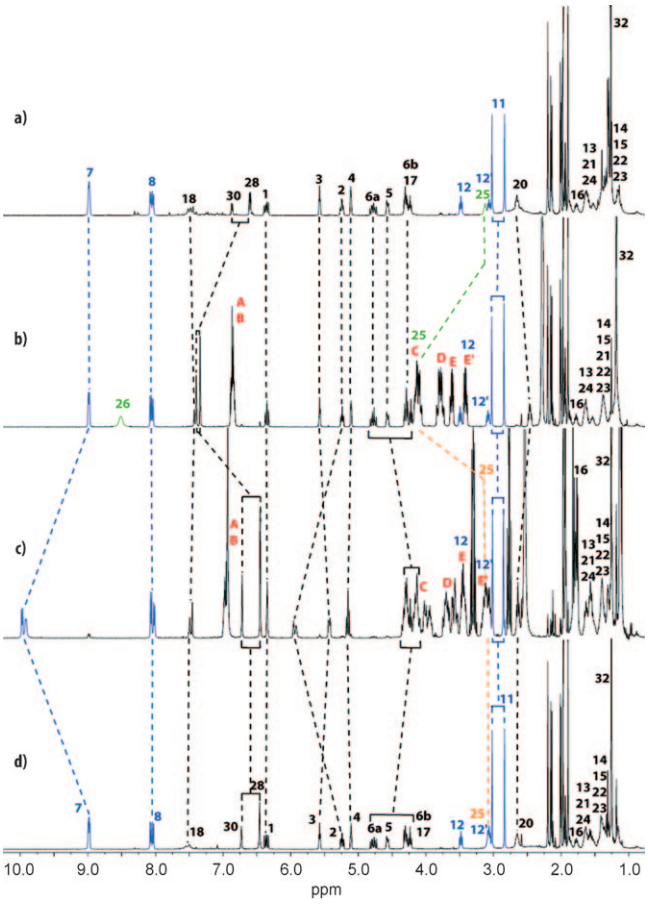

Figure 2. ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) the uncomplexed dumbbell-shaped thread **3bu**, b) the rotaxane **3b**, c) the rotaxane **4b**, and d) the uncomplexed dumbbell-shaped thread **4bu**. The lettering and numbering correspond to the proton assignments indicated in Scheme 1.

verified by comparison of spectra of uncomplexed thread **3bu** and rotaxane **3b** (Figure 2a,b). Similar observations to those seen for the monosubstituted amide **3au** and **3a** concerning the downfield and upfield shifts of characteristic hydrogen atoms are evidenced. The only difference resides in the more complicated spectrum for compounds **b**, which is due to the *cis*/*trans* isomerism of the disubstituted amide bond.[13] In comparison with the deprotonation of **3a**, the deprotonation of **3b** makes the DB24C8 move toward the pyridinium unit, but with a slightly different localization of the macrocycle, which involves a tremendous change of the conformation of the mannosyl extremity. This difference of localization can be explained by the comparison of ^{1}H NMR spectra of **3b** and **4b** (Figure 2b,c), which shows a downfield shift of $\Delta\delta = 0.96$ ppm for H^7, whereas no variations of signal are noted for H^8, indicating hydrogen bonding between the oxygen atoms of the DB24C8 and H^7. This is confirmed by the upfield shift of H^7 when comparing rotaxane **4b** and thread **4bu** (Figure 2c,d). Furthermore, and in contrast to the deprotonation of rotaxane **3a**, very important changes in both the chemical shifts and the vicinal coupling constants of the mannosyl hydrogen atoms are noted after deprotonation of **3b** (Figure 3, Table 1) These important variations of chemical shifts and vicinal coupling constants indicate a conformational change of the chair-like pyranose from the $^1C_4$ to a $^4C_1$ conformation upon deprotonation.

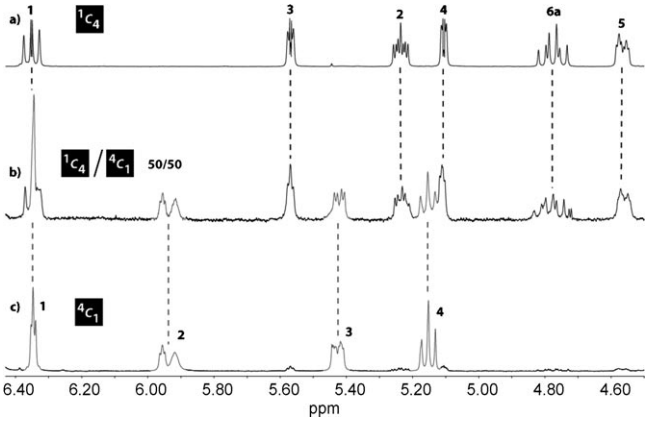

Figure 3. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) showing the conformational change of the mannoside: a) the rotaxane **3b**; b) rotaxane **3b**+DIEA (0.5 equiv); c) the rotaxane **4b** after the addition DIEA (2.5 equiv). The numbering corresponds to the proton assignments indicated in Scheme 1.

Table 1. Vicinal coupling constants of mannosyl hydrogens H^1–H^4 in rotaxanes **3b** and **4b**.

	$^3J(H^1,H^2)$[a]	$^3J(H^2,H^3)$[a]	$^3J(H^3,H^4)$[a]	$^3J(H^4,H^5)$[a]
rotaxane **3b**	9.4	3.2	3.2	3.2
rotaxane **4b**[b]	2.3/3.0	–[c]/3.0	8.4/8.4	8.4/8.4

[a] The coupling constant is given in Hz. [b] Due to the *cis*/*trans* isomerism of the amide bond, rotaxane **4b** exists as a mixture of two diastereomers, hence a value of coupling constant for each diastereomer is reported. [c] Coupling constant could be measured only for one stereoisomer because of broad multiplet.

As already mentioned in the literature, with metals and diamine glucidic derivatives,[14] and with silylated protecting group of glucidic hydroxyle,[15] the pyranose moiety can be flipped between $^4C_1$ and $^1C_4$ chair conformation. On the other hand, it is also known that glycosyl pyridinium compounds undergo the reverse anomeric effect (RAE), because a cationic charge, located at the anomeric position of a glucide, forces the aglycone chain to sit in the energetically preferred equatorial position, even though more protected hydroxyl groups are in axial orientations on the pyranose.[16] If vicinal hydrogen atoms are both axial, the coupling constant generally observed is 8–10 Hz; however it is

usually between 2–4 Hz if at least one of the two vicinal hydrogen atoms is equatorial.[17] For the mannosyl rotaxanes **3a**,**b** and **4a** and for all uncomplexed threads, the vicinal coupling constants measured for the hydrogen atoms of the glucidic scaffold unambiguously indicate that the glucide adopts a $^1C_4$ chair conformation, whereas they indicate a $^4C_1$ chair conformation for **4b** (Figure 3, Table 1). It is worth noting that the tremendous NMR downfield shift observed for H^2 ($\Delta\delta = 0.70$ ppm) between rotaxanes **3b** and **4b** is consistent with the flipping of the pyranose from the $^1C_4$ to the $^4C_1$ conformation, since H^2 can only experience the deshielding effect of the aromatic pyridinium ring in **4b**.[18]

The conformational change to $^4C_1$ observed for **4b** can result from the following effects. Besides the interaction between the DB24C8 and H^7, the $^4C_1$ chair is stabilized by one more equatorial bond, which is energetically favorable. Moreover, it can be assumed that the interactions of the oxygen atoms of the DB24C8 with the pyridinium charge would result in the masking of the cationic charge and, as a consequence, the switching off of the reverse anomeric effect. Such an induced conformational effect was not observed with the rotaxane containing the monosubstituted pyridinium amide **4a**, in which the DB24C8 is located farther from the mannopyranose and interacts preferentially with the NH of the amide moiety and with H^8. Finally, it is worth noting that, upon deprotonation of rotaxane **3b** with diisopropylethylamine (0.5 equiv), two sets of ^{1}H NMR signals were detected, pointing to a slow exchange at room temperature on the NMR time scale between the protonated rotaxane **3b** and the deprotonated rotaxane **4b**.

In conclusion, we have synthesized large-amplitude mannosyl [2]rotaxane molecular machines based on an anilinium and mono- or disubstituted pyridinium amide stations. In both cases, DB24C8 initially resides around the anilinium station. After deprotonation, DB24C8 moves toward the pyridinium station and interacts very differently depending on the amide substitution. With the monosubstituted amide, the amide hydrogen NH and the neighboring H^8 atoms of the pyridinium unit interact with the oxygen atoms of the crown ether by hydrogen bonding. However, with the disubstituted amide, DB24C8 forms hydrogen bonds with the pyridinium H^7 atoms, which are located near the cationic nitrogen atom, and interacts by ion–dipole contacts with the cationic charge. It results in an impressive conformational change of the mannopyranose from $^1C_4$ to $^4C_1$. To the best of our knowledge, rotaxanes **3b** and **4b** constitute unique rotaxane examples of synthetic molecular machines that are able to bring about important conformational changes of a glucidic stoppering extremity by the translation of a macrocycle, resulting from a pH stimulus. This domino effect from one extremity of the molecule to the other (deprotonation of the anilinium stoppering station/translation of the macrocycle/conformational isomerization of the mannosyl stopper) consists of a nice synthetic molecular mimic of an allosteric biomacromolecule, and could be of great interest for structure–activity relationship studies with lectins.

Experimental Section

Compound 3b: $[Cu(CH_3CN)_4]PF_6$ (81 mg, 0.22 mmol, 1 equiv) and 2,6-lutidine (2.5 μL, 0.02 mmol, 0.1 equiv) were added successively to a solution of the mannosyl azide **1b** (160 mg, 0.22 mmol, 1 equiv), alkyne **2** (100 mg, 0.22 mmol, 1 equiv), and DB24C8 (194 mg, 0.44 mmol, 2 equiv) in dry CH_2Cl_2 (3 mL). The mixture was stirred for 24 h at RT, then the solvent was removed under vacuo. The crude mixture was directly purified by column chromatography (SiO_2: solvent gradient elution: acetone/CH_2Cl_2 20:80, then 30:70) to afford the pure rotaxane **3b** (266 mg, 74%) as a white solid.

Keywords: chair conformation · click chemistry · glycosides · molecular devices · pyridinium amides · rotaxanes

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