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A New Glycorotaxane Molecular Machine Based on an Anilinium and a Triazolium Station

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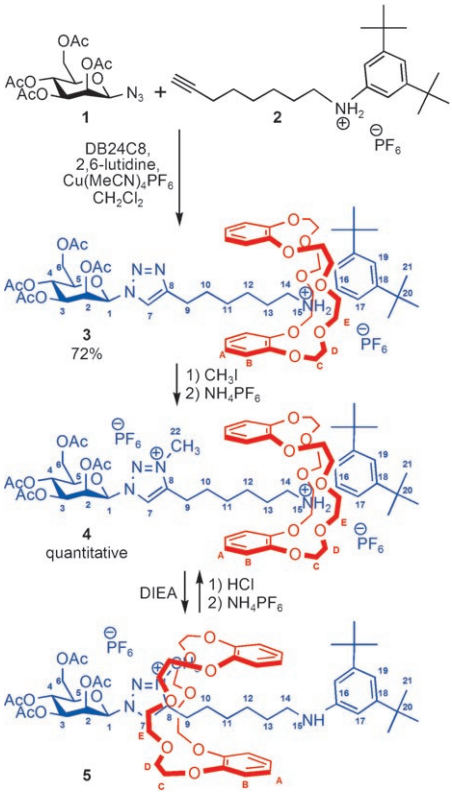
Rotaxanes have received much attention during the past decade, especially because they can be used as molecular machines.[1] Although many efforts have been carried out to design and synthesize molecular machines for nanotechnology, very few papers have been devoted to those, which could be used in the medicinal field.[2] Since glycosides are involved in a wide range of biological recognition processes, we recently published a very efficient synthesis of a mannosyl [2]rotaxane derivative using the Schmidt glycosylation method.[3] Glycorotaxanes, in which a glycosyl moiety is used as a stopper,[3,4] constitute a class of molecules of great interest, as localization of the macrocycle along the glycosyl thread could influence the recognition towards their lectine receptors. Effectively, masking or unmasking the glycoside part, by moving the macrocycle more or less far from the glycoside end depending on the extracellular physiological pH of a cell, would allow for the subsequent study of the structure–activity relationship of the glycosidic molecular machine for its specific receptor. With this aim, we describe in this paper the readily preparation of a mannosyl two-station molecular machine derivative, via the end-capping method of a semirotaxane. We also report the pH-controlled shuttling of the dibenzo[24]crown-8 (DB24C8) around the two very different binding sites. The synthetic strategy is based on the copper(I)-catalyzed Huisgen[5] alkyne–azide 1,3-dipolar cycloaddition, also called "the CuAAC click chemistry",[6] and on the subsequent alkylation of the 1,2,3-triazole. Although recent papers described on one hand the use of the "click chemistry" as an efficient route to triazolrotaxanes[7] and on another hand the recognition study of anions by 1,2,3-triazolium receptors,[8] the *N*-methyltriazolium moiety has never been described as a molecular station for DB24C8 so far. However, since Busch et al. reported the ability for the DB24C8 to interact strongly with ammonium cation,[9] a wide variety of other template moieties, such as benzylic ammonium,[10] *N*-benzylic anilinium,[11] *N*,*N*′-dialkyl-4,4′-bipyridinium,[12] 1,2-bis(pyridinium)ethane cations,[13] have been investigated. Our targeted rotaxane **4** contains two molecular stations with different affinity for the DB24C8. (Scheme 1)



Scheme 1. Template synthesis of the mannosyl [2]rotaxane **3** and its derivatization to pH-sensitive molecular machines **4** and **5**.

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The already reported *N*-alkylanilinium was chosen as the templated moiety for the preparation of the [2]rotaxane **3**, and, at the same time, as the best molecular station for DB24C8 in the targeted molecular machine **4**. The cationic electron-poor aromatic ring *N*-methyltriazolium should be able to interact with the DB24C8 either by π–π stacking with the electron-rich catechol ring, by ion-dipole interactions between the cationic charge and the oxygens of the macrocycle or by hydrogen bond between the vinylic hydrogen of the triazolium and the oxygens of the macrocycle.

The mannosyl [2]rotaxane **3** was successfully synthesized, at room temperature in dichloromethane, from the tetra-*O*-acetyl-α-D-mannosyl azide **1**[14] (1 equiv) and the anilinium alkyne **2** (1 equiv) in the presence of DB24C8 (2 equiv), $Cu(MeCN)_4PF_6$ (1 equiv) and 2,6-lutidine (0.1 equiv). Compound **3** was isolated in a 72% yield after chromatographic column purification. The interlocked architecture of **3** was confirmed by comparing the ^{1}H NMR spectra of the uncomplexed dumbbell-shaped thread **3u**, the rotaxane **3** and the uncomplexed DB24C8 (Figure 1). In comparison with the free DB24C8, the chemical shifts of the complexed crown ether hydrogens H_C and H_E of the rotaxane **3** are split, indicating that they are facing the two non-symmetrical ends of the threaded mannoside. Methylene hydrogens H_D are shifted slightly upfield; the upfield shift of hydrogen H_E is more pronounced. Comparison between the spectra of the uncomplexed thread **3u** and the rotaxane **3** reveals the presence and the localization of the macrocycle. Apart from the evident appearance of the macrocycle hydrogen signals, the hydrogens H_{14} experience a downfield shift ($\Delta\delta = 0.65$ ppm), indicating that the DB24C8 ring binds with the secondary *N*-alkylanilinium center. Most of the other chemical shifts of the other hydrogens are more or less shielded in the rotaxane, because they undergo the shielding effect of the aromatic ring of the macrocycle.

Subsequent regioselective methylation of the [2]rotaxane **3** was carried out at room temperature in iodomethane during four days and afforded quantitatively, after anion exchange, the two-station mannosyl [2]rotaxane **4**. In order to move the ring more or less far from the mannosyl end, variation of the pH was investigated. Deprotonation of the anilinium [2]rotaxane **4** was carried out in acetone with a large excess of diisopropylethylamine and the [2]rotaxane **5** was purified according to the supporting information.[15] As expected, the DB24C8 moved towards the triazolium station upon deprotonation. This was confirmed by the analyses of the ^{1}H NMR spectra of both rotaxanes **4** and **5**, and uncomplexed thread **4u** and **5u** (Figure 2).

The direct comparison of the ^{1}H NMR spectra of both the dumbbell-shaped anilinium thread **4u** and rotaxane **4** indicates the localization of the DB24C8. (Figure 2a, b) Whereas H_{14} is dramatically shifted downfield ($\Delta\delta = 0.72$ ppm) in the rotaxane **4**, no significant variation in the chemical shift of H_7 was noticed, pointing out that the DB24C8 mainly resides around the anilinium station. This result suggests that the affinity of DB24C8 is much better for the anilinium station than for the triazolium. Moreover, and similarly to the comparison between **3u** and **3** (Figure 1), ^{1}H NMR signals of the alkyl chain (H_9, H_{10}, H_{11}, H_{12} and H_{13}) are shifted upfield ($\Delta\delta$ range from −0.22 to −0.49 ppm) because of the shielding effect of the aromatic rings of the crown ether. This result is consistent with the very slight variations of the chemical shift observed for H_{17} and H_{19} in **3u** and **3**. Actually, the DB24C8 may probably prefer to sit over the alkyl chain, rather than over the hindered di-*tert*-butyl phenyl group.[16] Deprotonation of the anilinium moiety made the DB24C8 move towards the triazolium station. (Figure 2b, c) By comparing rotaxane **5** with

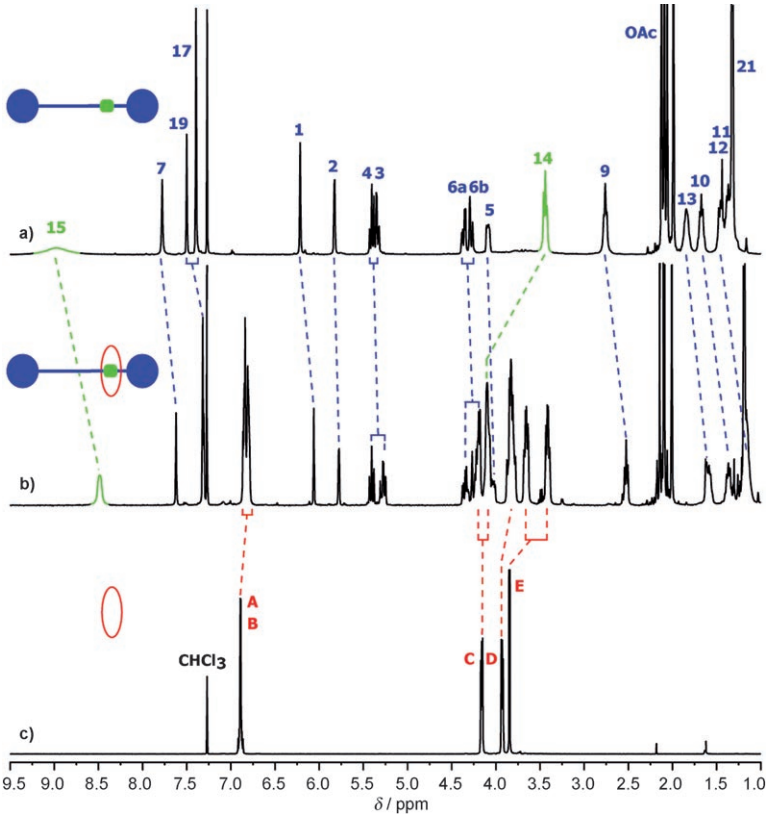

Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of: a) the uncomplexed dumbbell-shaped thread **3u**; b) the rotaxane **3**; c) the uncomplexed DB24C8. The lettering and numbering correspond to the proton assignments indicated in Scheme 1. The green colour signals are part of the anilinium binding-site.

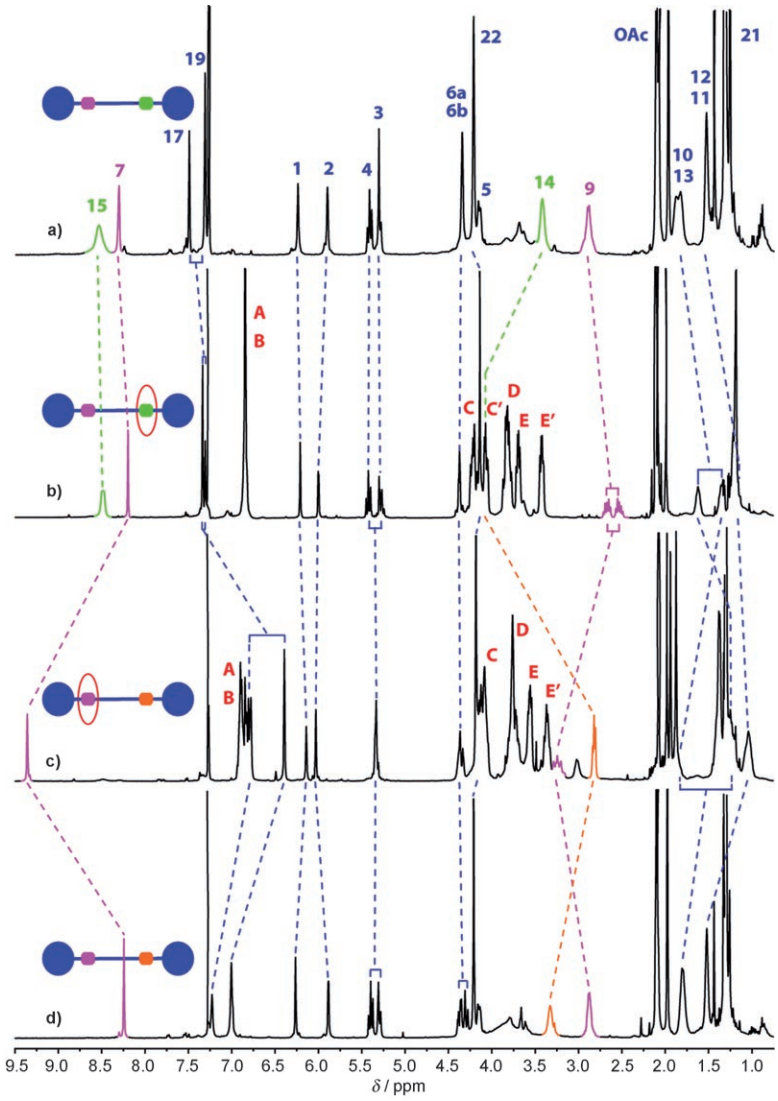

Figure 2. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of: a) the uncomplexed dumbbell-shaped anilinium thread **4u**; b) the rotaxane **4**; c) the rotaxane **5**; d) the uncomplexed dumbbell-shaped aniline thread **5u** . The lettering and numbering correspond to the proton assignments indicated in Scheme 1. The different colored signals are part of: the binding-site of the anilinium station (green); the triazolium station (pink); the aniline moiety (orange).

rotaxane **4**, ^{1}H NMR signal for H_{14} of rotaxane **5** is shifted upfield ($\Delta\delta = -1.26$ ppm) as a result of both the deprotonation of the neighbouring anilinium and the shuttling of the macrocycle. Tremendous downfield shifts are observed at the same time for the signals H_7 ($\Delta\delta = 1.16$ ppm) and in a lesser proportion H_9 ($\Delta\delta = 0.62$ ppm) in the deprotonated rotaxane **5**, indicating their hydrogen bonding with the oxygens of the DB24C8. The localization of the crown ether macrocycle is corroborated by the direct comparison between the rotaxane **5** and the uncomplexed dumbbell-shaped thread **5u**. For the rotaxane **5**, the chemical shifts of H_7 and H_9 are both shifted downfield, whereas the methylene hydrogens H_{11}, H_{12}, H_{13} and H_{14} of the alkyl chain are shifted upfield, exhibiting the shielding effect of the aromatic ring of the DB24C8.

In conclusion, we have described a very mild and efficient access to glycorotaxanes using "click chemistry" in a template-directed threading approach. Transformation of the so-created 1,2,3-triazole moiety into the methyl triazolium was successfully realized and allowed for the readily preparation of a mannosyl two-station molecular shuttle. As the affinity of the DB24C8 is much better for the anilinium template than for the triazolium one, the DB24C8 initially resides around the anilinium station. After deprotonation, the macrocycle moves towards the triazolium station, where it can interact by hydrogen bonding. The shuttling process can be inverted by protonation of the aniline moiety. The high simplicity of both the "click chemistry" method and the subsequent *N*-methylation to yield triazolium rotaxanes, besides of the interesting behaviour of the triazolium station for the crown ether, make the route to a wide range of different molecular machines powerful and very easy.

Experimental Section

Compound 3: To a solution of alkyne **2** (240 mg, 0.52 mmol, 1 equiv) and DB24C8 (468 mg, 1.04 mmol, 2 equiv) in dry CH_2Cl_2 (2 mL) were added successively the mannosyl azide **1** (195 mg, 0.52 mmol, 1 equiv), $Cu(CH_3CN)_4PF_6$ (194 mg, 0.52 mmol, 1 equiv) and 2,6-lutidine (6 μL, 0.05 mmol, 0.1 equiv). The mixture was stirred for 24 h at room temperature, then the solvent was removed. The crude was directly purified by column chromatography (silica gel, acetone/CH_2Cl_2 10:90, then 15:85) to afford pure rotaxane **3** (481 mg, 72%) as a white solid. $R_f = 0.22$ (silica gel, acetone/CH_2Cl_2 10:90); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 8.53$–8.41 (br s, 2H; H_{15}), 7.60 (s, 1H; H_7), 7.31 (s, 3H; H_{17}, H_{19}), 6.87–6.78 (m, 8H; H_A, H_B), 6.06 (s, 1H; H_1), 5.77 (d, $^3J(H_2,H_3) = 3.0$ Hz, 1H; H_2), 5.40 (t, $^3J(H_4,H_5) = {}^3J(H_4,H_3) = 10.1$ Hz, 1H; H_4), 5.26 (dd, $^3J(H_3,H_4) = 10.1$, $^3J(H_3,H_2) = 3.0$ Hz, 1H; H_3), 4.35 (dd, $^2J(H_{6b},H_{6a}) = 12.5$ Hz, $^3J(H_{6b},H_5) = 5.1$ Hz, 1H; H_{6b}), 4.25 (br d, $^2J(H_{6a},H_{6b}) = 12.5$ Hz, 1H; H_{6a}), 4.22–4.16 (m, 4H; H_C), 4.13–4.06 (m, 6H; H_{14} H_C), 4.03 (ddd, $^3J(H_5,H_4) = 10.1$, $^3J(H_5,H_{6b}) = 5.1$, $^3J(H_5,H_{6a}) = 1.8$ Hz, 1H; H_5), 3.87–3.77 (m, 8H; H_D), 3.69–3.61 (m, 4H; $H_{E'}$), 3.44–3.37 (m, 4H; H_E), 2.51 (t, $^3J(H_9,H_{10}) = 7.5$ Hz, 2H; H_9), 2.13, 2.09, 2.00 (3s, 12H; CH_3CO), 1.62–1.53 (m, 2H; H_{13}), 1.40–1.28 (m, 4H; H_{10}, H_{11}), 1.18 (s, 18H; H_{21}), 1.27–1.11 ppm (m, 2H; H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 170.7$, 169.8, 169.6, 169.5 ($COCH_3$), 152.6 (C_{18}), 147.9 (C_8), 147.3 ($C_{q\,DB24C8}$), 135.1 (C_{16}), 120.5 (C_7),

123.4, 116.9 (C_{17}, C_{19}), 121.6, 112.3 (C_A, C_B), 84.3 (C_1), 75.4 (C_5), 71.1 (C_3), 70.8 (C_E), 70.2 (C_D), 68.5 (C_2), 68.1 (C_C), 65.0 (C_4), 62.1 (C_6), 50.8 (C_{14}), 34.9 (C_{20}), 31.2 (C_{21}), 28.9, 28.7 (C_{10}, C_{11}), 27.5 (C_{13}), 25.7 (C_{12}), 25.2 (C_9), 20.5, 20.7 ppm (4s, CH_3CO); HRMS (ESI): m/z: calcd for $C_{60}H_{87}N_4O_{17}$: 1135.6066; found: 1135.6042 $[M-PF_6]^+$.

Keywords: click chemistry · glycorotaxanes · molecular machines · template synthesis · triazolium

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