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A New pH-Switchable Dimannosyl[c2]Daisy Chain Molecular Machine

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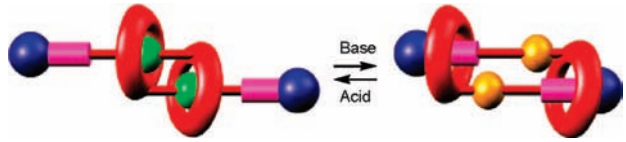
ABSTRACT



The preparation of a dimannosyl[c2]daisy chain molecular machine containing an ammonium and a triazolium station is described. The both stretched and contracted states of the molecular machine can be obtained by variation of the pH, thus localizing the mannosyl stoppers closer or farther away.

Carbohydrate-lectin recognitions play a key role in many biological events.[1] As a result, many studies concerning this kind of interaction have been conducted in the past decades, especially because a better understanding of these recognition phenomena could be used to target infected cells, viruses, bacteria, or other pathogenic foreign bodies. It has already been demonstrated that lectin affinity is enhanced by increasing the number of glucidic ligands in a single molecule.[2] This effect has been called the multivalent or cluster effect. Orientation and the distance between carbohydrate units constitute two important factors to control in order to increase the affinity of glucidic ligands for their receptor.[3] With this aim, many chemists have designed synthetic multivalent glycomimetics by varying, in a single molecule, the number of glucides and the distance or the nature of the link between carbohydrates. However, to date, very few groups have envisaged the preparation of molecules of higher degrees of freedom, including two or more glucidic moieties, and in which the two carbohydrates are not covalently bound together.[4] Such compounds are of great interest since they should adapt their shape to their putative receptor depending on different factors (pH, solvent polarity, temperature, etc.).

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Interlocked molecules like [2]rotaxanes present the advantage of containing two components that are not covalently linked (Figure 1a). These molecules have received much attention

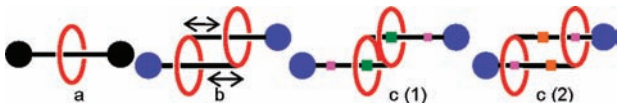
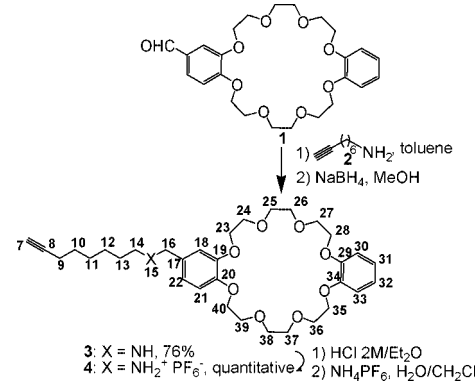


Figure 1. Cartoon representing (a) a [2]rotaxane, (b) a [c2]daisy chain without any molecular station, (c) the [c2]daisy chain molecular machine targets in (1) the stretched conformation and (2) the contracted conformation. The different colors correspond to the mannosyl stopper (blue), the macrocycle (red), the *N*-benzylammonium station (green), the triazolium station (pink), and the *N*-benzylamine (orange).

during the past years, especially in the domain of nanotechologies and materials.[5] As very few papers have been devoted to those that could be used in medicinal field,[6] we recently published a very efficient synthesis of a mannosyl [2]rotaxane derivative[7] and a new glycorotaxane molecular machine.[8] Cyclic rotaxane dimers, also called [c2]daisy chains or "molecular muscles",[9] have attracted our attention because they offer the possibility to incorporate two glucidic stoppers at both extremities of the molecule (Figure 1b and c). These dimers are composed of two interwoven monomers, each of them consisting of a macrocyle linked to a linear chain, which includes one or more template moieties for the macrocycle. The interlocked structure is maintained with the help of the two bulky stoppers. In this paper, we describe the synthesis and the NMR study of an original pH-switchable glyco[c2]daisy chain molecular shuttle. The molecular target contains a mannosidic unit at both extremities of the molecules and two molecular stations having different affinity for the DB24C8 part. The DB24C8 part proved to have a better affinity for the *N*-benzylammonium template than for the triazolium one, and no affinity at all for the *N*-benzylamine moiety, thus allowing the two states of the molecular machine. Two tailored constraints of distances between the two mannosidic moieties can thus be imposed by contracting or stretching the dimer[10] and should make it possible to switch on or off the multivalent effect (Figure 1c).

The strategy used to prepare the interwoven target molecules is based on the end-capping of pseudo[c2]daisy chains by the copper(I)-catalyzed Huisgen[11] alkyne-azide 1,3-dipolar cycloaddition, also called "CuAAC click chemistry".[12] Reductive amination between the preliminary synthesized aldehyde **1** and the primary amine **2**[13] using sodium borohydride afforded, after protonation and counterion exchange, the [c2]daisy chain precursor **4** (Scheme 1).

Scheme 1. Synthesis of [c2]Daisy Chain Precursor **4**



The self-assembling behavior of compound **4** was studied by ^{1}H NMR in different solvents (Figure 2). In a polar solvent

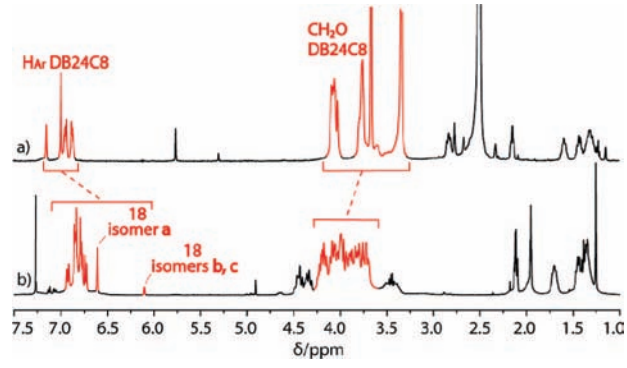


Figure 2. ^{1}H NMR spectra (400 MHz, 298 K) of compound **4** in (a) DMSO-d_6 and (b) $CDCl_3$. The numbering corresponds to the proton assignments indicated in Scheme 1.

like DMSO-d_6 (Figure 2a), simple ^{1}H NMR signals are observed, which indicate the presence of the uncomplexed

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monomer. However, when ^{1}H NMR was carried out in a hydrogen bond promoting solvent like $CDCl_3$, (Figure 2b), the molecules of **4** are shown to interact, either through ion−dipole interactions or hydrogen bonds between the oxygens of the macrocycle and, respectively, the ammonium template and the closest methylene hydrogens or by $\pi-\pi$ stacking between aromatic rings. The ^{1}H NMR signals of the DB24C8 part are then split and become much more complicated. This observation results from both the formation of several interlocked molecular architectures and the nonmagnetic equivalence of the CH_2O hydrogens in the crown ether part, which is due to their different orientations toward the two nonsymmetrical ends of the pseudo daisy chain.

As already mentioned by Stoddart et al. with an analogous molecule, three possible dimeric interlocked stereoisomers are possible (Figure 3): they arise from the nonsymmetrical

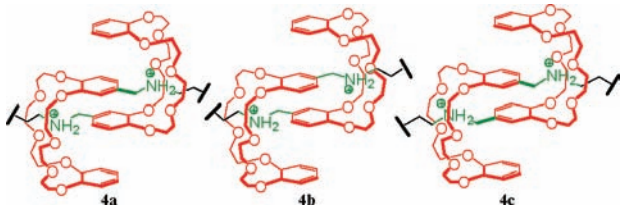
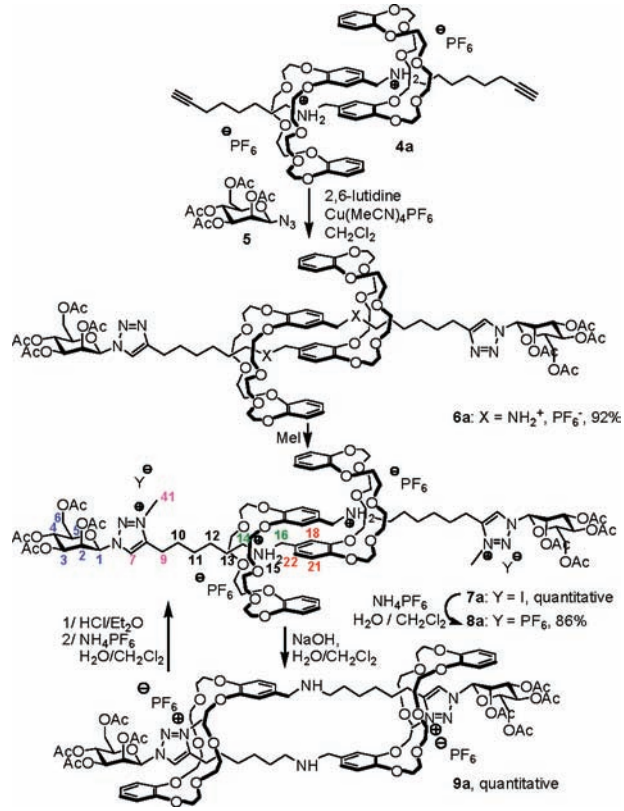


Figure 3. The three possible [c2]daisy chain stereoisomers **4a**−**c**.

substitution of the crown ether by the alkyne ammonium chain. When interlocked into dimers, the alkyne ammonium chain can bind the DB24C8 either by a forward or a backward covalent link, resulting in the formation of a "meso" supramolecular S_2-symmetric stereoisomer **4a** and a "threo" supramolecular racemic C_2-symmetric mixture of **4b**/**4c**. The ratio **4a**:**4b,c** in $CDCl_3$ was directly measured by integrating the H_{18} NMR signals (Figure 2). The major supramolecular stereoisomer was found to be the "meso" supramolecular stereoisomer **4a**. Our result is based on the following incorporation of the chiral D-mannosyl moieties during the synthesis (Scheme 2). Effectively, by analyzing the ^{1}H NMR spectrum of the crude **6**, we note that only the prior minor NMR signals become split, proving in this way that they belong to the minor diastereoisomers **6b**:**6c** 50:50 and come from the enantiomers **4b**:**4c**. It is corroborated by the single major signals observed for the major stereoisomer **6a**, which can only arise from **4a**. Complete conservation of ratio was observed between **4a**:**4b,c** 86:14 and **6a**:**6b**:**6c** 86:7:7.

The introduction of the mannosyl stopper was efficiently carried out in dichloromethane via a "click reaction" between the acetylated D-mannosyl azide **5**[14] and dimers **4**, in the presence of $Cu(MeCN)_4PF_6$ (1 equiv) and 2,6-lutidine (0.1

Scheme 2. Synthesis of pH-Switchable Mannosyl[c2]Daisy Chains **8a** and **9a**



equiv). The resulting [c2]daisy chain **6** was successfully obtained in a 92% yield after chromatographic column purification. Subsequent quantitative methylation of the triazole of **6a** allowed for the formation of a second molecular station after anion exchange. The so-obtained [c2]daisy chain molecular shuttle **8a** was studied with the aim of modifying the distance between the two mannosyl ends by variation of the pH. As recently reported by us with a single glycorotaxane[8] and similarly to an anilinium template, the ammonium station proved to have a better affinity for the DB24C8 than the triazolium. It follows that both the stretched and the contracted state could be obtained upon protonation or deprotonation. Deprotonation of the ammonium caused the displacement of the DB24C8 part around the triazolium station, whereas the macrocycle shuttled back around the ammonium station upon protonation of the amine with a solution of HCl in diethylether followed by anion exchange.

The ^{1}H NMR spectroscopy evidence of the localization of the DB24C8 part around the two molecular stations is reported in Figure 4. As it is based upon the comparison of both the uncomplexed protonated and deprotonated monomers with the protonated and deprotonated [c2]daisy chains, the preparation of uncomplexed monomers **8u** and **9u** was carried out.[15] The direct comparison of the ^{1}H NMR spectra of both the uncomplexed monomer **8u** and the [c2]daisy

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(13) The syntheses of compounds **1** and **2** are described in Supporting Information.

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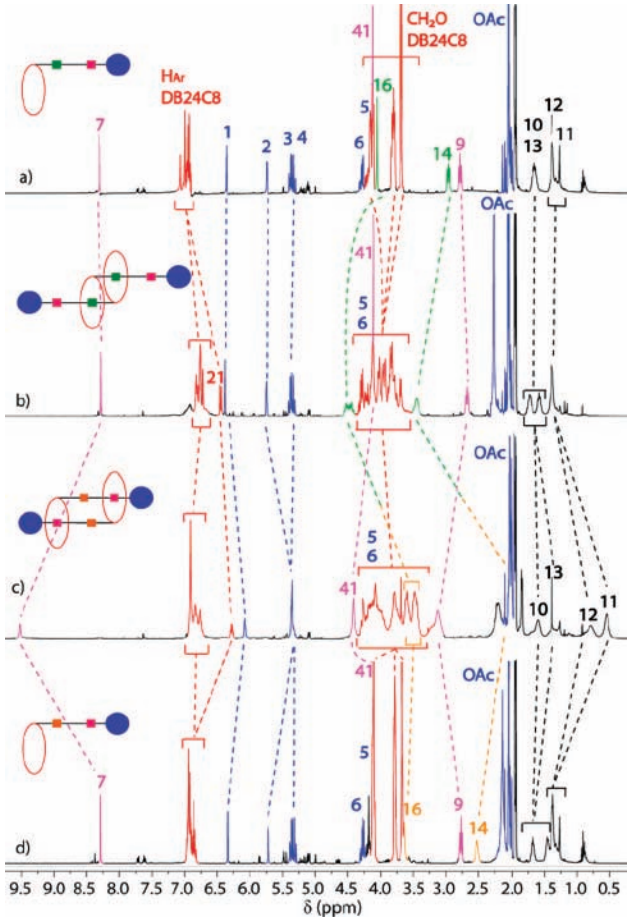

Figure 4. ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of (a) the uncomplexed ammonium monomer **8u**, (b) the [c2]daisy chain containing ammonium **8a**, (c) the deprotonated [c2]daisy chain **9a**, and (d) the uncomplexed deprotonated monomer **9u**. The lettering and numbering correspond to the proton assignments indicated in Scheme 2. The different colored signals are part of the binding site of the ammonium station (green), the triazolium station (pink), the amine moiety (orange), the mannosyl moiety (blue), and the DB24C8 crown ether part (red).

chain **8a** indicates the localization of the DB24C8 part of the molecule in **8a**. Whereas no variation in the chemical shift is noticed for H_7, the methylene hydrogens H_{14} and H_{16} are dramatically shifted downfield (with a $\Delta\delta$ of 0.49 and 0.44 ppm, respectively), pointing out that the DB24C8 exclusively resides around the ammonium station (Figure 4a and b). When the ammonium moiety was deprotonated, the DB24C8 part moved toward the triazolium station (Figure 4b and c). By comparing the [c2]daisy chains **8a** and **9a**, H_{14} and H_{16} are shifted upfield (with a $\Delta\delta$ of -1.40 and -0.98 ppm, respectively) as a result of both the deprotonation of the neighboring ammonium and the shuttling of the macrocycle. Simultaneously, tremendous downfield shifts are observed for H_7 ($\Delta\delta$ 1.24 ppm) and in a lesser proportion H_9 and H_{41} ($\Delta\delta$ 0.51 and 0.29 ppm, respectively) in the deprotonated [c2]daisy chain **9a**, indicating their hydrogen bonding with the oxygen of the crown ether. Eventually, signals for H_1, H_2, H_{11}, H_{12}, and H_{13} are shielded (with a $\Delta\delta$ of -0.30, -0.40, -0.83, -0.59, and -0.38 ppm, respectively), suggesting that they undergo the shielding effect of the aromatic rings of the macrocycle. The localization of the DB24C8 macrocycle was corroborated by the direct comparison between the deprotonated [c2]daisy chain **9a** and the noninterlocked monomer **9u**. For the [c2]daisy chain **9a**, H_7, H_9, and H_{41} are shifted downfield ($\Delta\delta$ 1.22, 0.41, and 0.31 ppm).

In conclusion, we have reported a very efficient access to glyco[c2]daisy chains using the end-capping method via click chemistry. The facile preparation of a mannosyl two-station [c2]daisy chain molecular shuttle was realized by methylation of the 1,2,3-triazole. Depending of the pH, the different affinities of the macrocycle for the two molecular stations allowed the contracted and the stretched co-conformations of the molecule. As the affinity of the macrocycle is much better for the ammonium template than for the triazolium one, the macrocycle initially resides around the ammonium station. After deprotonation, the macrocycle moves toward the triazolium station, where it can interact by hydrogen bonding. Tailoring the distance between sugar units using noncovalent links constitutes an original approach to a multivalent effect biological study.

Supporting Information Available: Characterization data and full experimental procedures for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The preparation of uncomplexed protonated monomers **8u** and **9u** was not straightforward: it is reported in Supporting Information.