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Straightforward Synthesis of a Double-Lasso Macrocycle from a Nonsymmetrical [c2]Daisy Chain

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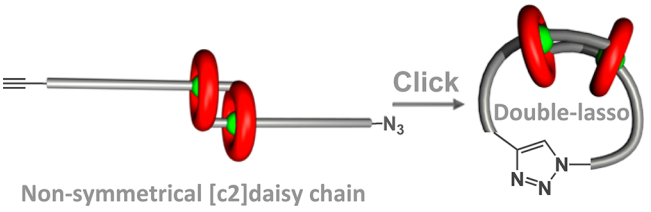
ABSTRACT



The straightforward synthesis of a double-lasso macrocycle from a nonsymmetrical [c2]daisy chain, using the copper(I)-catalyzed Huisgen alkyne–azide 1,3-dipolar cycloaddition, is described. The preparation of the nonsymmetrical alkyne azide [c2]daisy chain precursor was realized in situ via the exchange of the monomers contained in both symmetrical alkyne and azide [c2]daisy chains and was followed by mass spectrometry.

Interlocked and interwoven molecules constitute a class of fascinating compounds which have been intensively studied in the past decades. Whereas some potential applications in the material[1] or biological field[2] shed light on the interest of such molecules, chemical access to new molecular interlocked architectures still represents a synthetic challenge. Therefore, several interlocked molecules such as rotaxanes,[3] catenanes,[4] foldaxanes,[5] [c2]daisy chains,[6] "molecular muscles",[7] "molecular jump rope",[8] and knots[9] have been synthesized up to date. On the contrary, very few molecular lassos have been the subject of targeted molecules. However, their chemical synthetic access is of high interest, especially because such interlocked compounds can be found in nature. This is the case of lasso peptides,[10] which exhibit biological activities as receptor antagonist or enzymatic inhibitor. It is suggested that their biological role and their resistance against protease degradation would be essentially due to their constrained bent conformation. We recently reported the

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preparation, tightening, and loosening of a double-lasso molecule from a symmetrical ends-activated [c2]daisy chain.[8] Here, we report on a novel straightforward synthetic route to a double-lasso molecular architecture from a nonsymmetrical [c2]daisy chain. The chosen synthetic strategy to yield the targeted molecular double lasso is based on the pseudocyclization of a nonsymmetrical alkyne azide [c2]daisy chain, using the copper(I)-catalyzed Huisgen alkyne−azide 1,3-dipolar cycloaddition,[11] also called "CuAAC click chemistry".[12] The two needed symmetrical diazide and dialkyne[c2]daisy chain precursors **3** and **5** were both synthesized from the already reported[13] dibenzo-24-crown-8(DB24C8)-based macrocycle **1** holding an aldehyde moiety (Scheme 1). Reductive amination by, first, refluxing the aldehyde **1** with, respectively, the 12-azidododecan-1-amine or the tridec-12-yn-1-amine and, second, reducing the intermediate imine using sodium borohydride afforded the secondary amines **2** and **4**. These latter were then submitted to a protonation using a hydrochloride solution in ether and then to an anion exchange with hexafluorophosphate to yield "hermaphrodite" monomers which interwove in the less polar hydrogen-bond promoting solvent like CD_2Cl_2 or CD_3CN to form "meso" supramolecular S_2-symmetric pseudo rotaxane dimers **3** and **5** in, respectively, 70 and 87% overall yield.

The interwoven molecular architectures of the pseudo rotaxane dimers **3** and **5** were elucidated by ^{1}H NMR spectroscopy and mass spectrometry (Figures 1 and 2, a and b).

In the polar solvent DMSO-d_6, simple ^{1}H NMR signals were observed for the DB24C8 moieties, indicating the presence of the uncomplexed "hermaphrodite" monomers, hence the absence of any [c2]daisy chain self-assembling (Figure 1, a and e). In the hydrogen-bond-promoting solvent like CD_3CN, the ^{1}H NMR spectra become much more complicated (Figure 1, b and d). In particular, the hydrogen signals of the methylenic hydrogens of the DB24C8 parts are split, indicating their nonmagnetic equivalence, which is directly due to the interwoven structure. Indeed, when the macrocycles surrounds the molecular axles, the methylenic hydrogens of the DB24C8 are facing the two nonsymmetrical ends of the pseudo daisy chain. Concerning the hydrogens of the aromatic rings of the DB24C8, the highfield chemical shift of hydrogen H_E should be noted, which experiences the shielding effect of the aromatic rings of the [c2]daisy arrangement. Moreover, the hydrogens H_2 and $H_{2'}$ are detected at high chemical shift because they interact by hydrogen bonds with the oxygen atoms of the dibenzo-24-crown-8 parts. The same

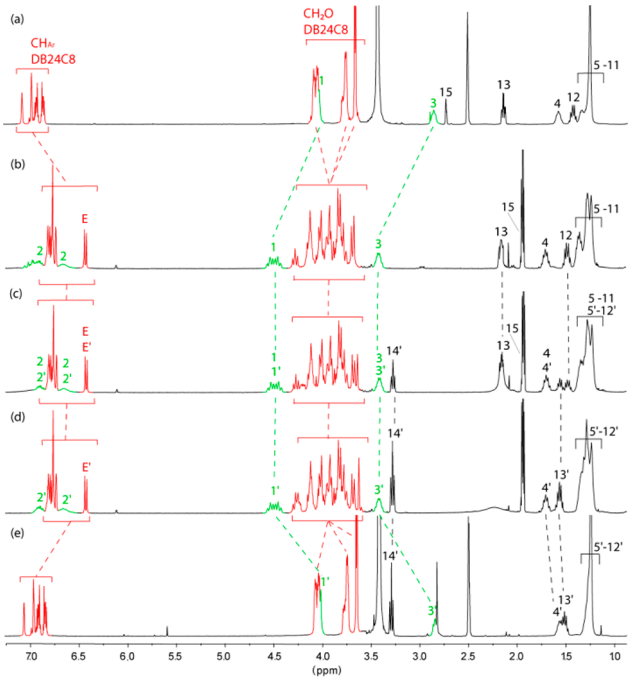

Figure 1. ^{1}H NMR spectra (400 MHz, 298 K) of (a) the uncomplexed alkyne compound **5u** in DMSO-d_6, (b) the dialkyne pseudo rotaxane dimer **5** in CD_3CN, (c) the stoichiometric mixture of pseudorotaxane dimers **3** and **5** in CD_3CN, (d) the diazido pseudo rotaxane dimer **3** in CD_3CN, and (e) the uncomplexed azido compound **3** in DMSO-d_6. The coloring, lettering, and numbering correspond to the proton assignments indicated in Scheme 1.

trend is observed for hydrogens H_1, $H_{1'}$, H_3, and $H_{3'}$ for identical reasons.

The equilibrium between the pseudorotaxanes **3** and **5** and the nonsymmetrical enantiomers **6**/**6′** was then investigated (Scheme 1). It is noteworthy that **6** and **6′** exist as a pair of enantiomers. Indeed, contrary to compounds **3** and **5**, pseudo rotaxane dimers **6** and **6′** do not have any S_2 symmetry because of the two different alkyne and azide ends of the [c2]daisy chain.

In a first instance, we compared the ^{1}H NMR spectra in CD_3CN of the isolated pseudo rotaxanes **3** and **5** with the ^{1}H NMR spectrum of a stoichiometric mixture of **3** and **5** (Figure 1, b−d). Unfortunately, the *ratio* between the four possible exchangeable pseudo rotaxanes were impossible to determine, since the spectrum of the mixture matches exactly with the superimposition of the spectra of the two isolated symmetrical diazido and dialkyne pseudo rotaxanes **3** and **5**. No other ^{1}H NMR signal corresponding to the nonsymmetrical pseudo rotaxane enantiomers **6**/**6′** was detected. Nevertheless, this observation does not mean that no exchange is possible between pseudo rotaxane dimers. It rather results from the fact that an alkyne or an azide moiety located at one extremity of the pseudo rotaxane dimer has no influence on the chemical shift of hydrogen atoms located at the other extremity. This assumption was corroborated by a kinetic study of

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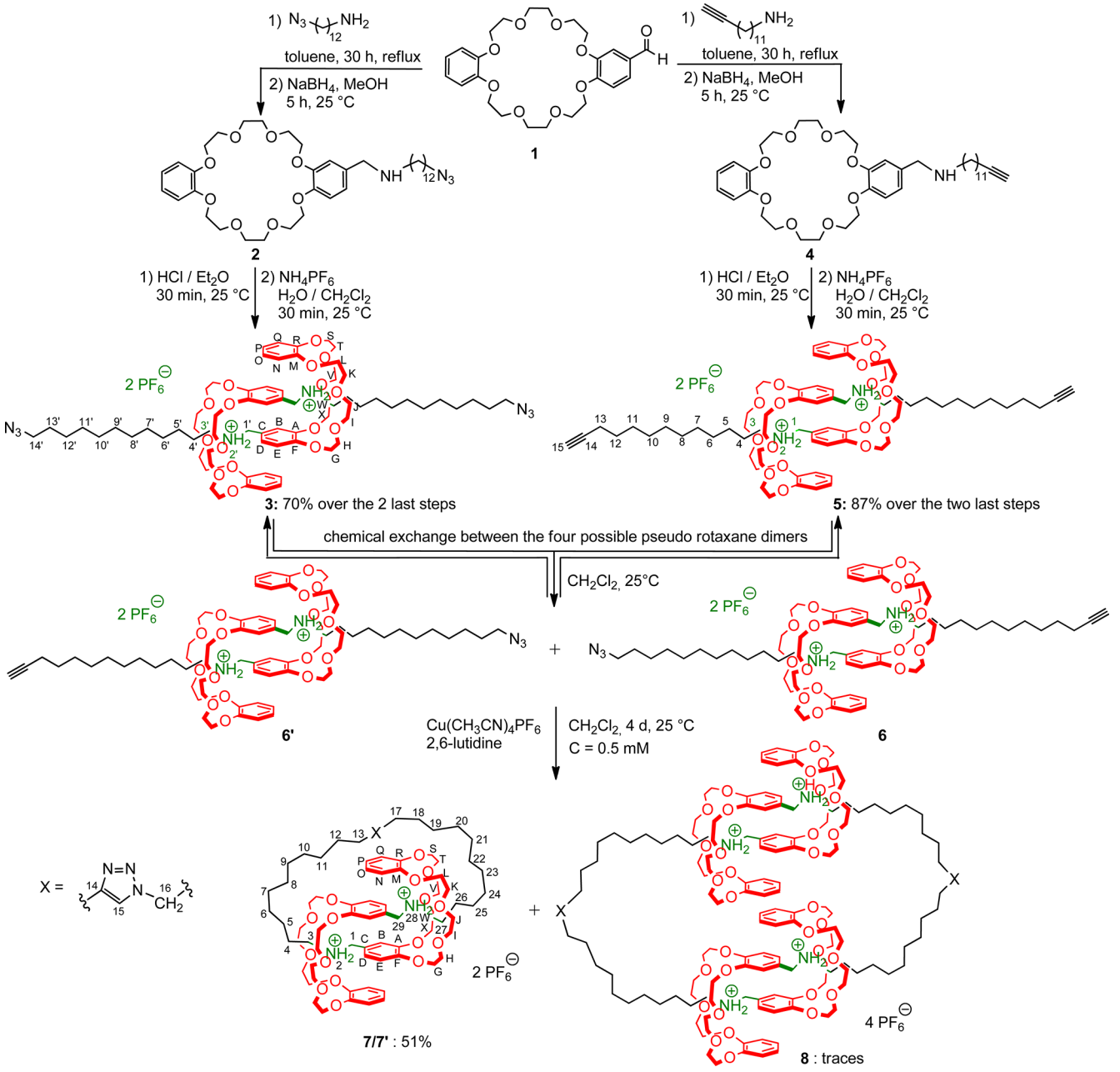
Scheme 1. Synthesis of the Two Symmetrical Diazide and Dialkyne [c2]Daisy Chains **3** and **5**, Equilibrium between Pseudorotaxanes **3**, **5**, and **6**/**6′**, and Synthesis of the Double-Lasso Rotamacrocycle Enantiomers **7**/**7′**



exchange using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) on a stoichiometric mixture of compounds **3** and **5** (Figure 2 c). This way, it was easy to detect each pseudo rotaxane dimer **3**, **5** and **6**/**6′**, since each compound has a different molecular weight.

Over time, the variation observed in the peak intensity gave a good tendency of the rate of the chemical exchange between the pseudo rotaxane dimers. After 1 min, the appearance of a peak corresponding to the enantiomers **6**/**6′** was observed. At the same time, the peak intensities corresponding to the relative abundance of the two symmetrical pseudo rotaxane dimers **3** and **5** decreased, which is consistent with a chemical exchange between the dimer precursors. The concentration of the pseudo rotaxane dimers **6**/**6′** increased until the equilibrium was reached after about 60 min. After that, no significant variation was noticed. By making the assumption that the difference of MS peak intensities of **3** and **5** is due to their different ionization yields (in favor of **5**), one may reasonably suppose that the proportion at the equilibrium exactly matches with a statistical distribution of monomers (i.e., **3**:**5**:**6**/**6′** 25:25:50). Indeed, if the azide or alkyne extremities do not play any role in the interlocking of the structure, which looks to be reasonable to think in the present case, there is twice more chance to yield the two enantiomers **6**

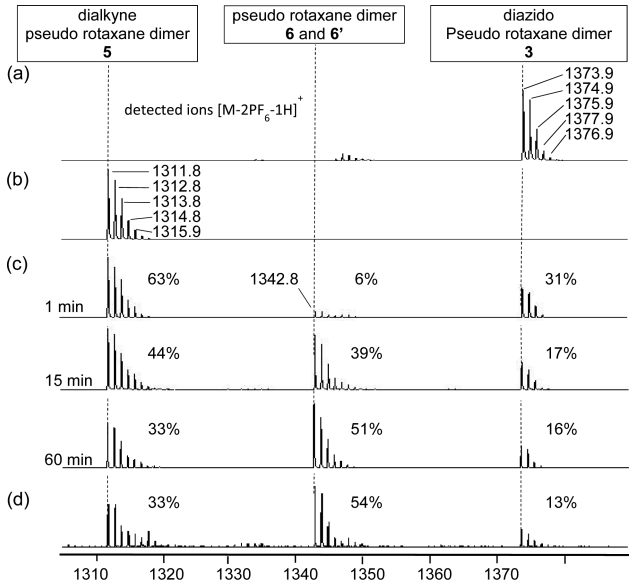


Figure 2. MALDI-TOF mass spectra of (a) the diazido pseudorotaxane dimer **3**, (b) the dialkyne pseudorotaxane dimer **5**, (c) a stoichiometric mixture of pseudorotaxane dimers **3** and **5** over time, and (d) after protonation of a stoichiometric mixture of monomers **2** and **4**.

and **6′** than respectively the compounds **3** and **5**. As it looks rational that the ionization potentials of the nonsymmetrical azidoalkyne pseudo rotaxane dimers **6** and **6′** are comprised between respectively those of the symmetrical diazido and dialkyne pseudo rotaxanes **3** and **5**, the relative abundance of 50% observed by mass spectrometry for **6**/**6′** at the equilibrium should fit with the molar *ratio*, accordingly to a statistical distribution. By comparison, the protonation and the subsequent counteranion exchange of a stoichiometric mixture of deprotonated monomers **2** and **4** was realized and gave very similar results (Figure 2 d).

The pseudo cyclization using "click chemistry" between the azide and alkyne extremities of the nonsymetrical rotaxane dimers **6**/**6′** was envisaged. It was carried out at a concentration of 5×10^{-4} M to minimize the side polymerization reactions and afforded the racemic double-lasso compound **7**/**7′** in a 51% yield after silica gel chromatographic purification, accompanied by traces of the dimeric tetra-lasso **8** which were only detected by MALDI-TOF MS (Scheme 1). No other compound was isolated from the silica gel chromatography, suggesting the side formation of polymers. The comparison between the ^{1}H NMR spectra of the lasso compound **7** and its uncomplexed analogue **7u** revealed the interlocked double-lasso structure (Figure 3).

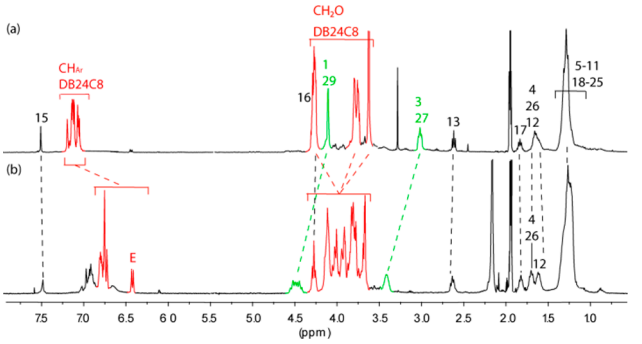


Figure 3. ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of (a) the uncomplexed compound **7u** and (b) the lasso rotamacrocycle **7**. The coloring, lettering and numbering correspond to the proton assignments indicated in Scheme 1.

The hydrogens H_1 and H_{29}, on one hand, and H_3 and H_{27}, on the other hand, are all shifted downfield in the rotamacrocycle **7** because of their hydrogen bonding with the oxygen atoms of the crown ethers. Moreover, the hydrogen H_E belonging to one aromatic ring of a crown ether is shielded by the presence of the aromatic rings of the other crown ether, demonstrating the "sandwich"-type conformation of the [c2]daisy arrangement. The signals of the methylenic hydrogens of the DB24C8 parts are simple in the uncomplexed compound **7u**, whereas they are all split in the rotamacrocycle **7**, indicating their nonmagnetic equivalence due to the nonsymmetrical pseudo macrocycle thread. No other chemical shift variation is observed for the other hydrogens, indicating the localization of the DB24C8 around the ammonium sites.

In conclusion, we have described a straightforward route to a double-lasso rotamacrocycle, based on the cyclization of a nonsymmetrical alkynazide pseudo rotaxane dimer, which was generated by a chemical exchange between two symmetrical dialkyne and diazide pseudo rotaxane dimers. The use of nonsymmetrical [c2]daisy chain precursors could be of real interest for polymerization at high concentration, whereas double-lasso rotamacrocycles could be appealing targets due to their tailorable bent molecular architecture.

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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.

The authors declare no competing financial interest.