Molecular Shuttles

Controlled Submolecular Translational Motion in Synthesis: A Mechanically Interlocking Auxiliary**

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In memory of Norma A. Stoddart

As well as being prototypical design elements for various types of molecular machines,[1–5] rotaxanes (molecules in which one or more rings are held on one or more threads by bulky stoppers[6]) often dramatically change the properties of their components (including solubility,[7] fluorescence,[8] electroluminescence,[9] and membrane transport[10]) and can protect encapsulated regions of threaded substrates from chemical attack[11] and degradation.[12] Interestingly, since they are molecular compounds—not supramolecular[13] complexes (i.e., the atoms cannot be separated without breaking covalent bonds)—rotaxane architectures also, in principle, circumvent patents that only claim derivatives that branch out from a principal structure through continuous sequences of covalent bonds. Despite such attractive characteristics, practical exploitation of the property-changing and patent-breaking features of rotaxanes have been slow to develop. This is probably because most efficient strategies for rotaxane synthesis require specific recognition elements to be built into each noncovalently linked unit,[14,15] thus limiting the types of chemical structures that can be interlocked. In other words, up to now it has not been possible to make a mechanically interlocked derivative of any particular pharmaceutical, dye, chromophore, catalyst, or reagent that one might choose. Herein we describe a practical rotaxane synthesis that has the potential to be more general than previous methods because it does not depend on a strong recognition motif existing between the ultimately interlocked components. A synthetic auxiliary is used to mechanically interlock a macrocycle around a suitable template, followed by translation of the ring to a position over the desired substrate and, finally, cleavage of the auxiliary to leave a rotaxane (e.g. **1**) with no designed noncovalent interactions

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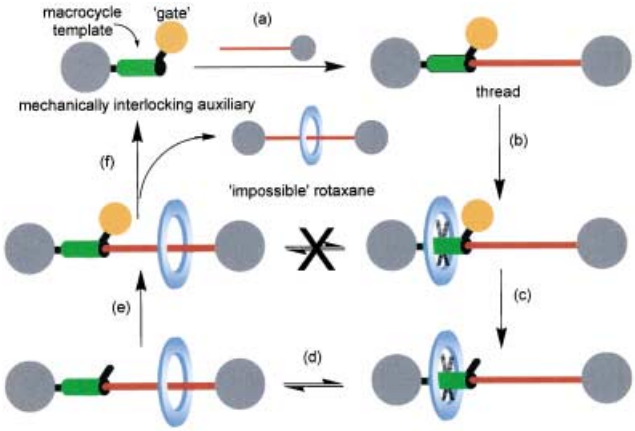
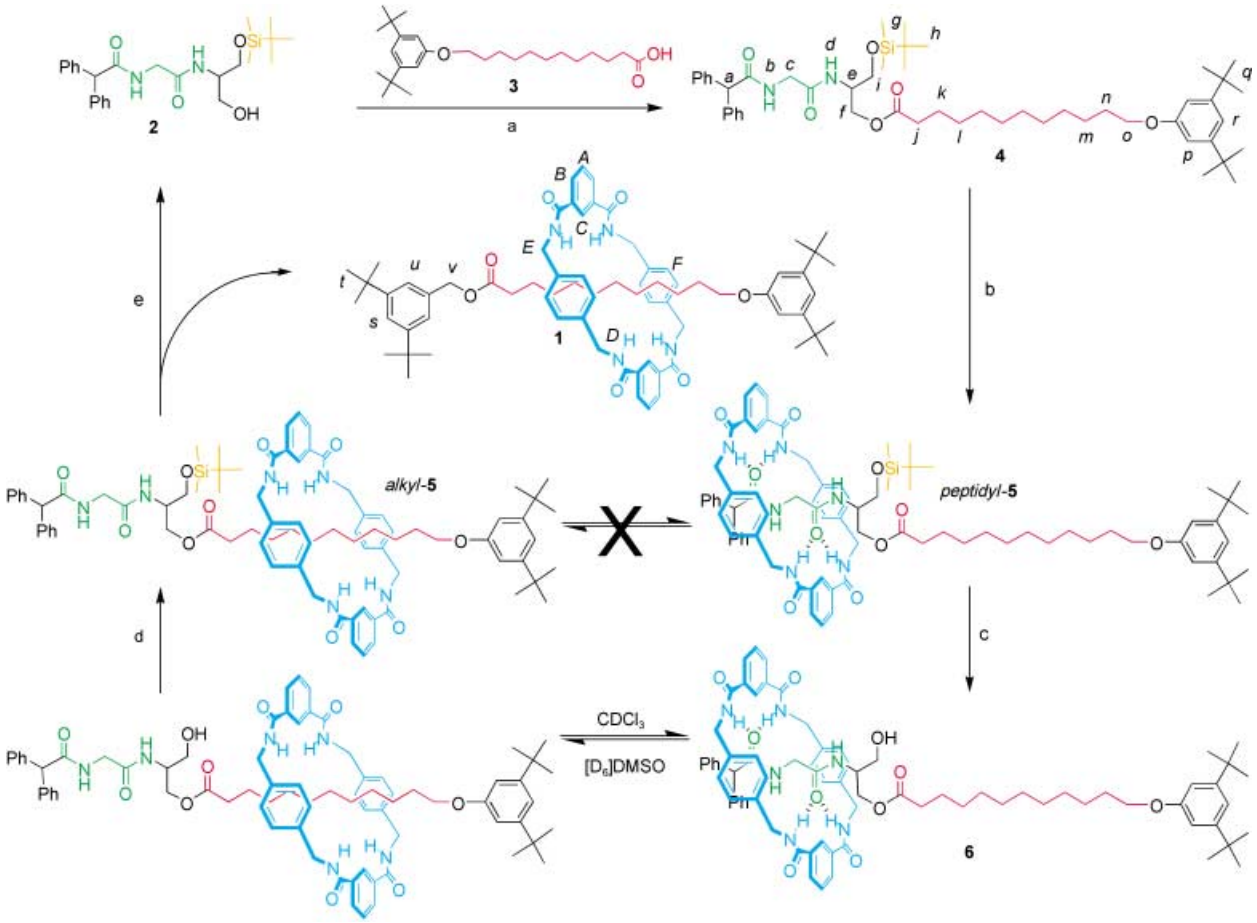
between macrocycle and thread (Scheme 1). As well as providing a synthetic route to otherwise difficult or impossible to obtain structures, a consequence of such unnatural geometries upon molecular fragments is seen in the X-ray crystal structure of rotaxane **1**, which features the first example of an NH amide to *alkyl* O ester hydrogen bond.



Scheme 1. Schematic preparation of a rotaxane that is otherwise difficult or impossible to obtain by using a mechanically interlocking auxiliary. a) Attach substrate to auxiliary; b) formation of rotaxane about template; c) open gate; d) shuttle macrocycle from template to substrate; e) close gate; f) cleave auxiliary.

Switching of the position of a macrocycle between nonequivalent sites in a rotaxane can be achieved by using a variety of stimuli in bistable "molecular shuttles".[1,6] In one such system, a benzylic amide macrocycle is assembled around a glycine-containing peptide template through intercomponent hydrogen bonding in nonpolar solvents.[11,16,17] The macrocycle can be subsequently decomplexed from the peptide by changing to a highly polar medium, which solvates the peptide and macrocycle hydrogen-bonding sites more strongly than they bind to each other.[18,19] We decided to investigate whether this solvent effect could be used to move the macrocycle from its template site to a desired substrate during synthesis, thus providing a means to a "mechanically interlocking auxiliary" (Scheme 2).[20]

The mechanically interlocking auxiliary, **2**, consists of an *N*-stoppered glycine residue and a monosilylated serinol derivative. The role of the serinol is twofold: the free hydroxy group provides a site for the attachment of a carboxylic acid-terminated substrate (and eventual cleavage of the auxiliary) through an ester linkage, while the bulky *tert*-butyldimethylsilyl ether acts as a closed "gate" through which the macro-



Scheme 2. Synthesis of rotaxane **1**. a) 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride, 4-dimethylaminopyridine (4-DMAP), CH_2Cl_2, 87%; b) isophthaloyl dichloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, 25%; c) tetrabutylammonium fluoride, THF, 95%; d) *tert*-butyldimethylsilyl chloride, imidazole, 4-DMAP, DMSO, 85%; e) di-*tert*-butylbenzyl alcohol, potassium *tert*-butoxide (5 mol%), 78%. Full experimental procedures can be found in the Supporting Information.

cycle cannot pass. Coupling of **2** to the dodecanoic acid **3** gave the composite thread **4**, which was subjected to standard[16–19] hydrogen-bond-directed rotaxane-forming conditions to give the [2]rotaxane *peptidyl*-**5**.[21] Since the xylylene rings of the macrocycle shield the encapsulated region of the thread, the position of the macrocycle in the rotaxane could be unambiguously determined by comparing the nuclear magnetic resonance (NMR) chemical shifts of the thread and rotaxane protons. The ^{1}H NMR spectra in $CDCl_3$ (Figure 1 a and b) and

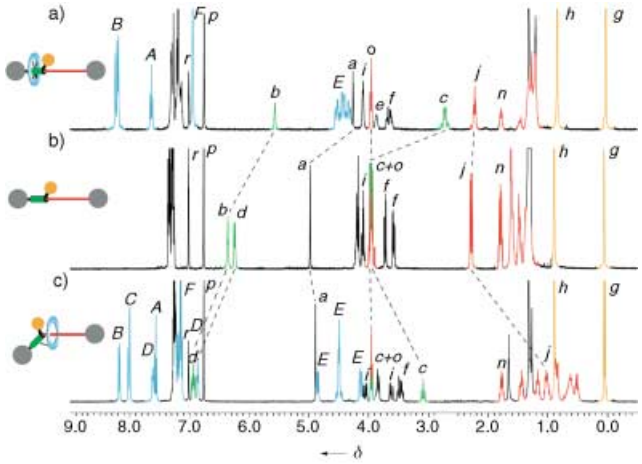


Figure 1. 400 MHz ^{1}H NMR spectra of a) *peptidyl*-**5**, b) **4**, and c) *alkyl*-**5** in $CDCl_3$ at 298 K. The color coding and lettering correspond to the assignments shown in Scheme 2.

[D_6]DMSO (Figure 2 a and b) shows that the closed gate means the macrocycle resides solely on the peptide station in both solvents (for example, the rotaxane H_c glycine protons are shielded by $\delta = -1.26$ ppm in $CDCl_3$ and by $\delta = -1.30$ ppm in [D_6]DMSO with respect to H_c in the thread).

Cleavage of the silyl group of *peptidyl*-**5** with tetrabutylammonium fluoride afforded [2]rotaxane **6**. In **6**, the macrocycle can move through the open gate to get to either the peptide or substrate side of the thread and ^{1}H NMR spectroscopy confirms that its location is determined by the nature of the solvent. Accordingly, **6** was dissolved in anhydrous DMSO and the silyl ether reattached with *tert*-butyldimethylsilyl chloride.[22] A new rotaxane was isolated in 85% yield together with <2% of *peptidyl*-**5**. ^{1}H NMR spectroscopy confirms the new rotaxane to be *alkyl*-**5**, a translational diastereoisomer (identical covalent connectivity but a different spatial arrangement[23]) of *peptidyl*-**5** with the macrocycle locked on the alkyl-chain side of the closed gate, irrespective of the solvent the rotaxane is dissolved in (Figure 1 c and Figure 2 c).[24]

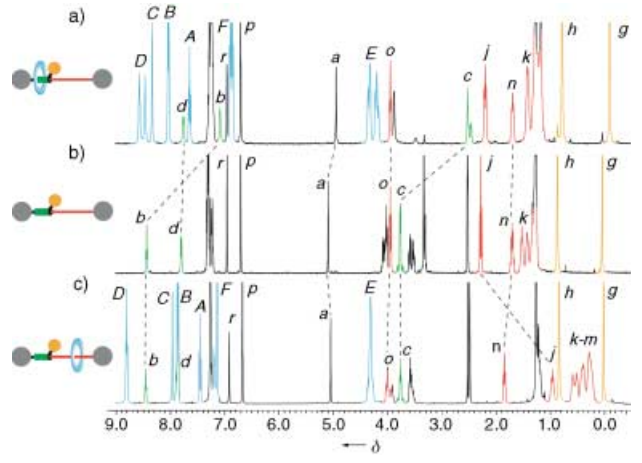


Figure 2. 400 MHz ^{1}H NMR spectra of a) *peptidyl*-**5**, b) **4**, and c) *alkyl*-**5** in [D_6]DMSO at 298 K.

Since there are no strong binding interactions between the macrocycle and thread in *alkyl*-**5**, maintenance of the rotaxane architecture whilst cleaving the mechanically interlocking auxiliary requires a reaction that does not permit unstoppering at any stage.[25] Transesterification with di-*tert*-butylbenzyl alcohol in the presence of catalytic potassium *tert*-butoxide,[26] afforded the desired [2]rotaxane **1** in 78% yield with complete recovery of the regenerated auxiliary and no evidence of any accompanying dethreading.[27] The shielding of all the alkyl chain protons, as revealed in the ^{1}H NMR spectrum of **1** (Figure 3), indicates that the macrocycle is delocalized over the entire length of the substrate, although the greater shielding of H_j indicates that it spends more time nearer the ester end of the molecule in $CDCl_3$.

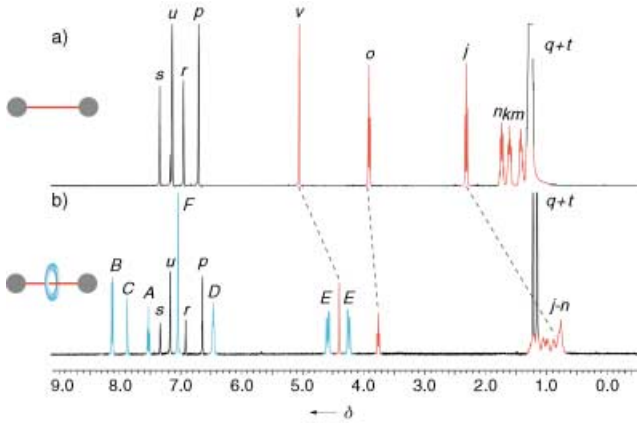


Figure 3. 400 MHz ^{1}H NMR spectra of a) thread and b) rotaxane **1** in $CDCl_3$ at 298 K.

Small single crystals of the rotaxane suitable for X-ray crystallography with a synchrotron source were obtained by slow evaporation of a solution of **1** in acetonitrile. The X-ray crystal structure (Figure 4) confirms the interlocked nature of the rotaxane and shows a remarkable consequence of forcing such unnatural spatial arrangements on submolecular fragments. Although ester groups are normally poor hydrogen-bonding groups,[28] the ester in the thread is the best acceptor available to the macrocycle amide hydrogen-bond donors. Accordingly, the rotaxane exhibits not only a rare[29] example of a solid-state hydrogen bond from the NH group of an amide to an acyl–O atom of an ester but also what appears to be a genuine hydrogen bond from the NH group of an amide to an alkyl–O atom of an ester, which is long (2.60 Å) but

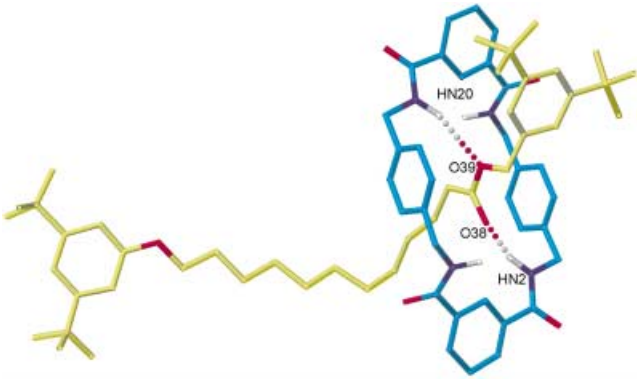


Figure 4. *X*-ray crystal structure of rotaxane **1**. Intramolecular hydrogen-bond lengths (Å) and angles: O38-HN2 1.89, 161.9°; O39-HN20 2.60, 162.2°. Carbon atoms of the macrocycle are shown in blue and those of the thread in yellow; oxygen atoms are red, nitrogen atoms dark blue and amide hydrogen atoms white. Non-amide hydrogen atoms are omitted for clarity. CCDC-127612 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

directional (162.2° is a typical NH···O hydrogen bond angle[30]) to a lone pair of an sp^3-hybridized orbital of an oxygen atom, in what is presumably a very weak interaction.

In conclusion, we have synthesized rotaxane **1**, whose components bear no formal mutual recognition elements through the first example of controlled submolecular translational motion in organic synthesis. In principle, there is no reason why mechanically interlocking auxiliary strategies should not work with other molecular-shuttle systems, including those based on cyclodextrins, which already have US FDA approval for use in the pharmaceutical and food industries. In our laboratories the approach is currently being used to prepare mechanically interlocked analogues of substrates that are unavailable by conventional synthetic methods and to modify the physical and chemical properties of a range of pharmaceuticals, dyes, reagents, catalysts, and components for molecular electronics.

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[13] Within the context of a recent book and paper (V. Balzani, A. Credi, M. Venturi, *Chem. Eur. J.* **2002**, *8*, 5524–5532; V. Balzani, A. Credi, M. Venturi, *Molecular Devices and Machines—A Journey into the Nanoworld*, Wiley-VCH, Weinheim, **2003**) it was proposed that the term "supramolecular" be expanded from Lehn's original definition of "chemistry beyond the molecule" (i.e., assemblies of two or more molecules or ions held together by noncovalent forces) to include large molecules (e.g., dendrimers, rotaxanes, proteins etc.) which feature functional intramolecular interactions or photophysics. In our view such a revision is unwarranted. When scientific language evolves it needs to retain a precise definition to remain useful (e.g., "acid" to "Lewis acid" or "Brønsted acid"). Consider as a contrary example the term "self-assembly", which has acquired such an imprecise meaning over recent years that it now conveys virtually nothing as a descriptor. In its currently accepted definition, "supramolecular"—by analogy to the term "molecular"—refers to how the atoms in a structure are held together, not their photophysical properties. It distinguishes molecules from clusters of molecules, for example pseudorotaxanes (host–guest complexes in which the components are free to exchange between bound and unbound species) and rotaxanes (molecules in which the components cannot exchange with outside systems without breaking covalent bonds). It does not matter that their properties can be similar or that bond energies sometimes make it difficult to distinguish between molecular and supramolecular species, just as the timescale-dependent inversion of asymmetric nitrogen atoms does not confer on the term "chirality" any less clear a meaning. Language—especially scientific language—needs to be precise; subject areas, for example, "supramolecular chemistry" or "organometallic catalysis", on the other hand, should be as broad and inclusive as possible, and have always happily encompassed chemistry not technically suggested by their titles (J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, Wiley-VCH, Weinheim, **1995**, p. 90).

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