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A Three-Compartment Chemically-Driven Molecular Information Ratchet

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Supporting Information

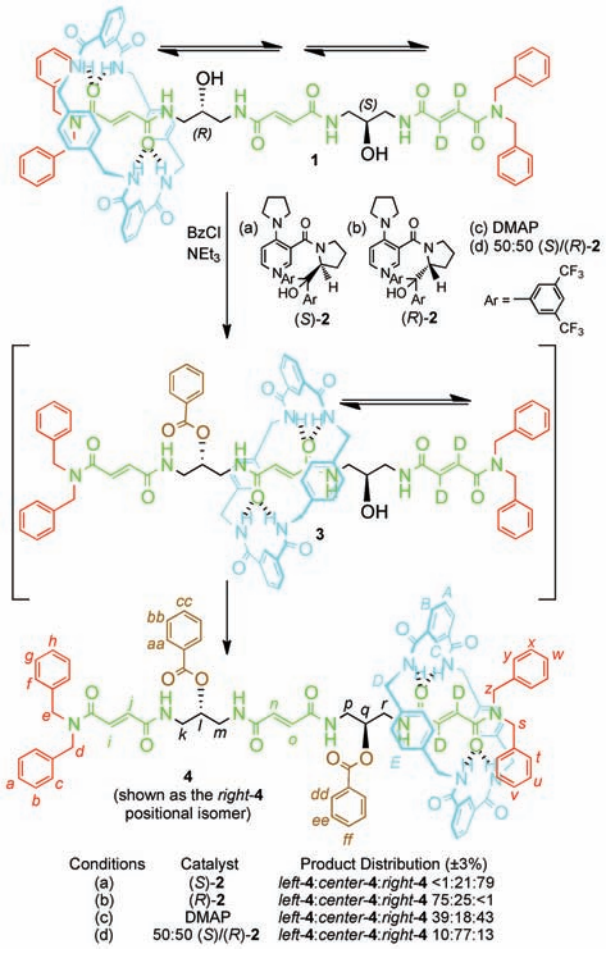
ABSTRACT: We describe a three-compartment rotaxane information ratchet in which the macrocycle can be directionally transported in either direction along an achiral (disregarding isotopic labeling) track. Chiral DMAP-based catalysts promote a benzoylation reaction that ratchets the displacement of the macrocycle, transporting it predominantly to a particular end compartment determined by the handedness of the catalyst.

Synthetic chemists have developed many different types of molecular switches.[1] However, simple positional changes of the components of molecular machines are insufficient for directional transport to occur progressively, or work to be done cumulatively.[1a,2] The advance from switch[1b] to motor[3] requires a ratchet mechanism[1a,2−5] that prevents the work that is done in one step being undone as the machine is reset. Here we describe a rotaxane information ratchet system[4] that is able to directionally transport a macrocycle to either end of an essentially achiral track with three 'compartments'. The two end compartments are identical (and the rotaxane thread has a point of inversion) other than for isotopic labels that are used to distinguish the compartments for analytical purposes,[6] and yet the macrocycle can be efficiently driven to either end of the track (>70:1 between the end compartments, with 21−25% of the rings remaining in the center compartment) by benzoylation reactions in the presence of a chiral catalyst. This is fundamentally different[1a] to rotaxane molecular shuttles[7] that can only switch the ring between *chemically different* binding sites (achieved by changing the relative strengths of the macrocycle-thread interactions at the different sites).

The design of the three-compartment molecular information ratchet (**1**, Scheme 1) is based on a [2]rotaxane in which the distribution of the macrocycle between two compartments can be biased using a chiral-catalyst-promoted acylation reaction.[4b] The interbinding site spacers of **1** were chosen to inhibit axle folding and disfavor the macrocycle binding to more than one fumaramide group at a time.[8] In **1**, the macrocycle is able to shuttle freely between the three compartments separated by the hydroxyl groups. Subsequent benzoylation of the hydroxyl groups provides steric barriers that the macrocycle cannot pass over, trapping the ring in one of three compartments (Scheme 1).

[2]Rotaxane diol **1** was prepared in 13 steps from (*R*)-3-amino-1,2-propanediol (see the Supporting Information).

Scheme 1. Directional Transport of a Macrocycle within a [2]Rotaxane Three-Compartment Chemical Information Ratchet[a]



Conditions	Catalyst	Product Distribution (±3%)
(a)	(*S*)-**2**	*left*-**4**:*center*-**4**:*right*-**4** <1:21:79
(b)	(*R*)-**2**	*left*-**4**:*center*-**4**:*right*-**4** 75:25:<1
(c)	DMAP	*left*-**4**:*center*-**4**:*right*-**4** 39:18:43
(d)	50:50 (*S*)/(*R*)-**2**	*left*-**4**:*center*-**4**:*right*-**4** 10:77:13

[a]Reagents and conditions: BzCl (4 equiv), NEt_3 (4 equiv), (*S*)-**2** or (*R*)-**2** or DMAP or 50:50 (*S*)/(*R*)-**2** mixture (4 equiv), CH_2Cl_2, 10 mM, rt, 2 h.

When diol **1** was treated with benzoyl chloride and triethylamine in the presence of chiral acylation catalyst (*S*)-**2**[9] (Scheme 1, conditions a), the macrocycle was predominantly

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trapped in the right-hand[10] compartment (<1:21:79 *left*-**4**/*center*-**4**/*right*-**4**) via monobenzolyated intermediates such as **3**. Use of the antipode catalyst, (*R*)-**2**, led to an equal and opposite distribution, showing that the direction of net transport depends on the handedness of the chiral catalyst (Scheme 1, conditions b). Benzoylation of **1** with the achiral acylation catalyst 4-dimethylaminopyridine (DMAP) yielded the benzoylated rotaxane with the macrocycle trapped preferentially in the two end compartments (Scheme 1, conditions c), the sites thermodynamically favored by the macrocycle in **1**. Given that the achiral catalyst favors the end compartments, it is perhaps somewhat counterintuitive that the use of racemic **2** (Scheme 1, conditions d) favors the center compartment.

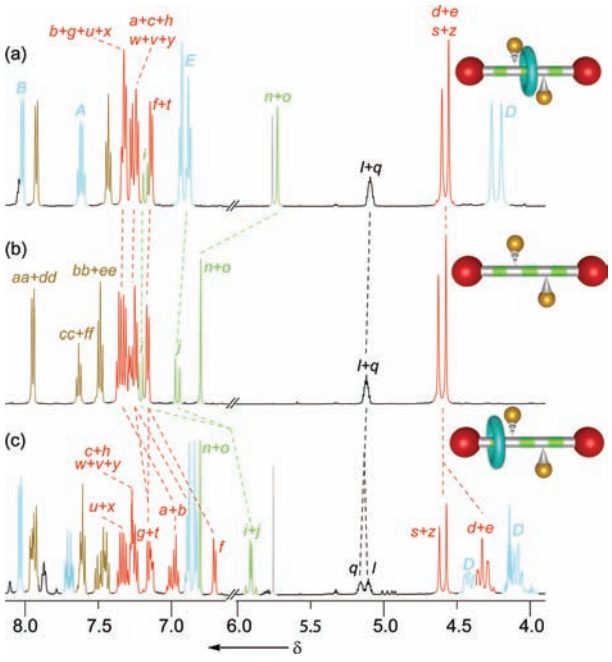
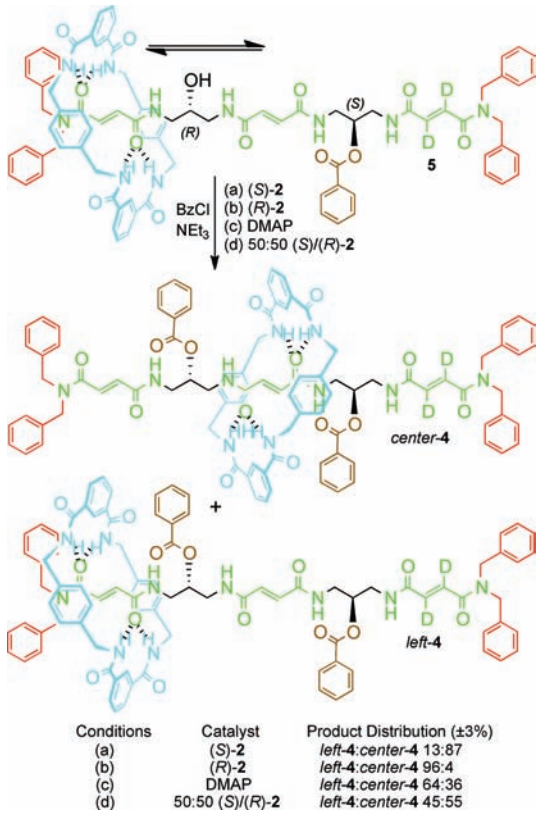


Figure 1. Partial ^{1}H NMR spectra (500 MHz, DMSO, 300 K) of (a) *center*-**4**, (b) thread, (c) *left*-**4**. Residual solvent peaks are shown in gray. The lettering corresponds to the proton labeling shown in Scheme 1. For full spectral assignments see the Supporting Information.

Each of the isomers of **4** were isolated and characterized unambiguously by ^{1}H NMR spectroscopy and high-resolution mass spectrometry. As expected, the ^{1}H NMR spectrum of *center*-**4** is highly symmetrical (Figure 1a), while *left*-**4** and *right*-**4** have identical ^{1}H NMR spectra apart from the influence of one of the fumaric groups being deuterated (the spectrum of *left*-**4** is shown in Figure 1c).[6] The relative shielding of protons by the aromatic rings of the macrocycle enables the position of the ring in each rotaxane to be deduced by comparing the chemical shift in the rotaxane to the equivalent signal in the dibenzoylated thread (Figure 1b). The relative amounts of the different products in the crude ratcheting reaction mixtures were determined by ^{1}H NMR (see Supporting Information, Section 6).

The mechanism of the directional transport process was probed by investigating the reaction of putative intermediates in the ratcheting reaction, such as the mono-OH rotaxane **5** (Scheme 2, see Supporting Information for the synthesis of **5**).

Scheme 2. Benzoylation of [2]Rotaxane 5 at a Single Site[a]



[a]Reagents and conditions: BzCl (2 equiv), NEt_3 (2 equiv), (*S*)-**2** or (*R*)-**2** or DMAP or 50:50 (*S*)/(*R*)-**2** mixture (2 equiv), CH_2Cl_2, 10 mM, rt, 2 h.

Benzoylation of **5** in the presence of DMAP resulted in a 64:36 *left*-**4**/*center*-**4** ratio (Scheme 2, conditions c), again demonstrating that the macrocycle has a thermodynamic preference for the end compartments; this bias must be overcome during the ratcheting process using the chiral catalyst to directionally transport the macrocycle. Use of (*S*)-**2** and (*R*)-**2** in the benzoylation of **5** gave *left*-/*center*-product ratios that were oppositely biased but not equal (13:87 and 96:4 *left*-**4**/*center*-**4**, respectively, Scheme 2, conditions a and b), highlighting that the macrocycle distribution is the result of a directional, kinetic, bias being applied by the chiral catalyst reaction conditions to the thermodynamic preference for the end compartments. The bias is added to ('matched') in the case of catalysis by (*R*)-**2**, resulting in very effective macrocycle transport, or is opposed ('mis-matched'), in the case of catalysis by (*S*)-**2**, resulting in transport that is less effective.

With the use of a 50:50 (racemic) mixture of (*S*)-**2**/(*R*)-**2** in the benzoylation reaction of **5**, it is possible to overcome the thermodynamic preference of the macrocycle for the end compartments and afford a 45:55 mixture of *left*-**4**/*center*-**4** (Scheme 2, conditions d).

Further insight into the mechanism of directional transport can be gained by treating the double benzoylation of **1** as a hidden Markov process,[11] in which **1** is converted in a stepwise fashion into the kinetically trapped products, passing through a set of four singly benzoylated intermediates (see the Supporting Information, Section 7). Although the individual steps of the process cannot be observed, analysis of the benzoylation products of **5** allows the probabilities of the various transitions

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from **1**, via intermediates, to be determined, and thus, an understanding of how the product distribution is built up: With a chiral catalyst, the first benzoylation reaction of **1** occurs preferentially far from the macrocycle—this can be deduced from little macrocycle being trapped in one of the end compartments (Scheme 1, conditions a and b). This is probably due to the steric requirements of the bulky chiral catalyst, since using DMAP itself the macrocycle ends up trapped to a significant extent in both end compartments (Scheme 1, conditions c). Directional transport with the individual chiral catalysts ((*S*)-**2** or (*R*)-**2**) is a result of two ratcheting[1a,2−4] steps. There is selectivity in which hydroxyl group of **1** is first to be benzoylated (which occurs without trapping the ring in the end compartment, as discussed above), as the macrocycle spends significant time in each compartment and can influence the rate of reaction of the chiral reactive intermediates with the different hydroxyl groups on the thread.[12] The second benzoylation reaction then discriminates between the center and the remaining accessible end compartment according to the match between the position of the macrocycle, the stereochemistry of the hydroxyl group and the handedness of the catalyst. The result is highly efficient transport of the macrocycle in **1** to an end compartment determined by the handedness of the chiral catalyst.

In conclusion, we have described a rotaxane in which the position of the macrocycle can influence the rate of benzoylation of hydroxyl groups on the thread with chiral reactive intermediates, resulting in acylation taking place preferentially to one side of the macrocycle. Ratcheted directional transport of the ring results. The macrocycle ends up predominantly on only one of two chemically equivalent binding sites located at opposite ends of a three-compartment thread. Such an outcome (and process) is intrinsically different[1a] to that of switching the thermodynamically preferred position of a ring between two chemically different binding sites in rotaxane molecular shuttles.[7] Understanding the behavior of the ratcheting system in terms of contributions from different processes provides insight into the statistical nature of molecular machines. These findings should prove useful in designing systems in which macrocycles can be transported directionally and progressively through an increasing number of compartments. Such systems are phenomenologically related to the mechanisms used by ion pumps[13] and other molecular motors in biology.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectroscopic data for the rotaxanes, their precursors, and the operation of the molecular information ratchets. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) The designations of 'right-hand', 'left-hand', and 'center' compartments refer to the orientation of the rotaxanes shown in Schemes 1 and 2. *Left*-**4** and *right*-**4** are enantiomers (disregarding the deuterium labels), and diastereomers of *center*-**4**.

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(12) Although the hydroxyl groups on the thread are enantiomeric, the chirality of each is likely to be poorly expressed (the enantiomers only differ in structure eight bonds from the chiral center) other than when the macrocycle is on an adjacent fumaramide residue. The benzoylation reactions do not alter the absolute configuration of the asymmetric carbon atoms.

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