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A Chemically-Driven Molecular Information Ratchet

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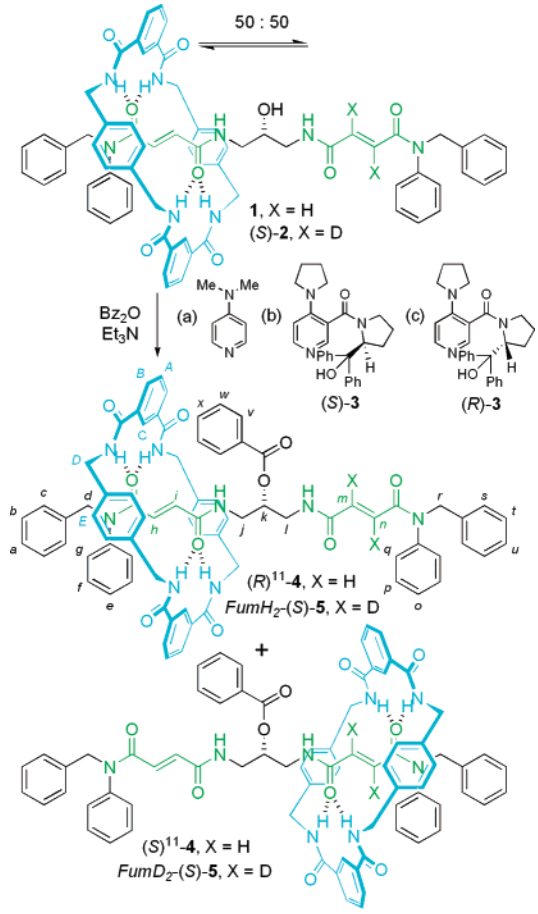
An information ratchet[1] is a basic class of Brownian ratchet mechanism[2] in which a barrier is raised or lowered according to the position of a Brownian particle on a potential energy surface, resulting in the particle distribution being directionally driven away from equilibrium.[3] More than a century of analysis[4] of Maxwell's celebrated "demon" thought experiment[5] (the information ratchet in its most fundamental form) has shown that for the information transfer that triggers the change in barrier height to be useful an energy input is required to avoid falling foul of the Second Law of Thermodynamics.[6] Finding ways of introducing ratchet mechanisms into molecular-level structures is central to the invention of functional synthetic molecular machine systems more complex than simple switches.[3,7] Recently, an information ratchet mechanism was experimentally demonstrated[8] with a rotaxane, using photosensitized energy transfer between the ring and a stilbene unit on the thread as the key step in changing the macrocycle distribution between two thread binding sites ("stations") from the equilibrium value of 65:35 to 45:55 without the binding affinity of the ring for either station ever varying. Here we report on a very different approach to a molecular information ratchet mechanism, in this case fueled solely by chemical energy. The position of the macrocycle in a rotaxane-based molecular shuttle is used to affect the rate at which a bulky ester is introduced between two stations on the thread. Once in place the ester provides a steric barrier trapping the ring on one side or the other. For rotaxane **1**, with two identical stations, the macrocycle distribution changes from 50:50 to 33:67 (Scheme 1); for rotaxane (*R*)-**6**, with nonidentical stations, it can be driven from 74:26 to 63:37 (Scheme 2). The former corresponds to a dynamic kinetic resolution of a rotaxane with 34% ee.

Symmetrical bisfumaramide rotaxane **1** and an isotopomer, (*S*)-**2**, in which one of the fumaramide stations is deuterated to provide an NMR probe of the macrocycle's position, were prepared in 12 and 17 steps, respectively, from (*S*)-3-amino-1,2-propanediol (see Supporting Information). The X-ray crystal structure of **1** (Figure 1) shows four-point hydrogen bonding between the benzylic amide macrocycle and a single fumaramide group on the thread.[9] The interstation spacer was chosen to inhibit both folding and macrocycle-bridging-two-stations motifs[12] so as to favor such macrocycle-to-one-station binding[13] in solution. The short distance between the prochiral hydroxyl and the fumaramide groups ensures that macrocycle occupancy of either station in the rotaxane produces a well-expressed chiral environment at the OH group (Figure 1).

The room temperature ^{1}H NMR spectrum of (*S*)-**2** (Figure 2b) confirms that the macrocycle moves rapidly between the two fumaramide groups on the NMR time scale in 1:1 $CDCl_3$−CD_3OD and resides on each station with equal frequency and probability (the shielding of H_h and H_i by the xylylene units of the macrocycle is half that observed[13] in related rotaxanes possessing only one fumaramide unit). Benzoylation (Scheme 1, conditions a) of the free hydroxyl group of **1** or (*S*)-**2** with the achiral acylation catalyst 4-dimethylaminopyridine (DMAP) gave the benzoylated rotaxanes with the macrocycles trapped in equal numbers on either side of the bulky ester barrier (i.e., 50:50 (*R*)/(*S*)-**4**, as evidenced by chiral HPLC, see Supporting Information; and 50:50 *FumH*$_2$-(*S*)-**5**/*FumD*$_2$-(*S*)-**5**,[14] as evidenced by ^{1}H NMR, Figure 2c). However, benzoylation of either **1** or (*S*)-**2** in the presence of chiral catalyst (*S*)-**3**[15] (Scheme 1, conditions b) generated product mixtures with unequal populations of macrocycles on the binding sites: 33:67 (*R*):(*S*)-**4**[11,16] (see Supporting Information) and 33:67 *FumH*$_2$-(*S*)-**5**/*FumD*$_2$-

Scheme 1. Dynamic Kinetic Resolution of a [2]Rotaxane via an Information Ratchet Mechanism[a]



Substrate	Conditions	Product
1	(a)	(*R*)-**4**:(*S*)-**4** 50:50
1	(b)	(*R*)-**4**:(*S*)-**4** 33:67
(*S*)-**2**	(a)	*FumH*$_2$-(*S*)-**5**:*FumD*$_2$-(*S*)-**5** 50:50
(*S*)-**2**	(b)	*FumH*$_2$-(*S*)-**5**:*FumD*$_2$-(*S*)-**5** 33:67
(*S*)-**2**	(c)	*FumH*$_2$-(*S*)-**5**:*FumD*$_2$-(*S*)-**5** 67:33

[a] Reagents and conditions: Bz_2O (2 equiv), Et_3N (2 equiv), DMAP or (*S*)-**3** or (*R*)-**3** (2 equiv), CH_2Cl_2, room temp, 8 h.

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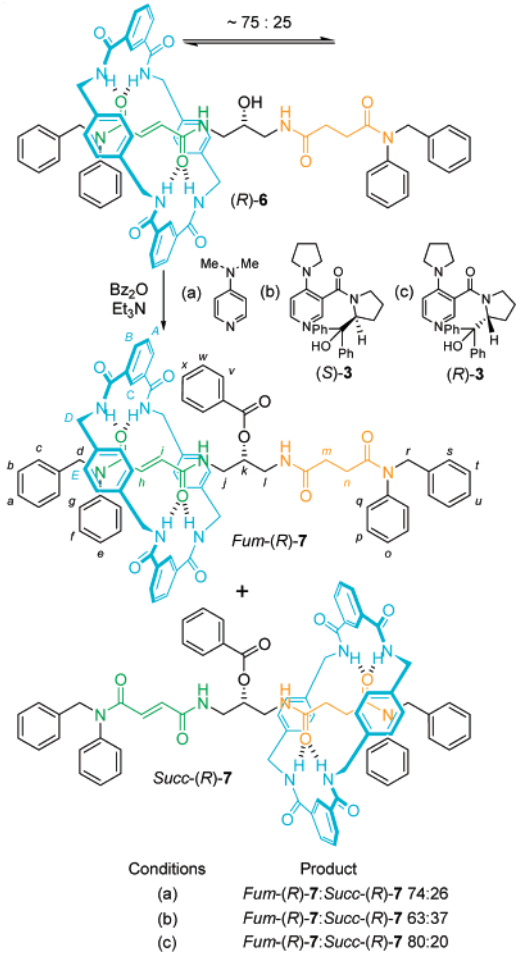
Scheme 2. Ratcheting a Macrocycle Enthalpically Uphill Using a Chemically-Driven Information Ratchet[a]



[a] Reagents and conditions: Bz_2O (2 equiv), Et_3N (2 equiv), DMAP or (*S*)-**3** or (*R*)-**3** (2 equiv), CH_2Cl_2, room temp, 8 h.

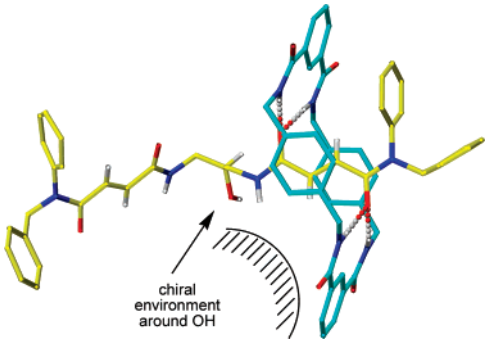


Figure 1. X-ray crystal structure of molecular shuttle **1**.[9] Macrocycle occupancy of either fumaramide unit produces a well-expressed chiral environment at the OH group (in an equal and opposite sense to that generated by macrocycle occupancy of the other fumaramide). The enantiomeric co-conformers[10] are present in equal amounts in the unit cell.

(*S*)-**5** (Figure 2d).[17] Clearly the chiral catalyst, through its *N*-benzoylated reactive intermediate, is able to discriminate between the two enantiomeric co-conformers of **1** which interconvert through the macrocycle shuttling between the fumaramide stations, and acylates the hydroxyl group more rapidly when the macrocycle is on the pro-*S* fumaramide group (and the equivalent $FumD_2$ site in (*S*)-**2**).[18] Use of the antipode catalyst for the benzoylation of (*S*)-**2** (Scheme 1, conditions c), afforded equal and opposite biasing of

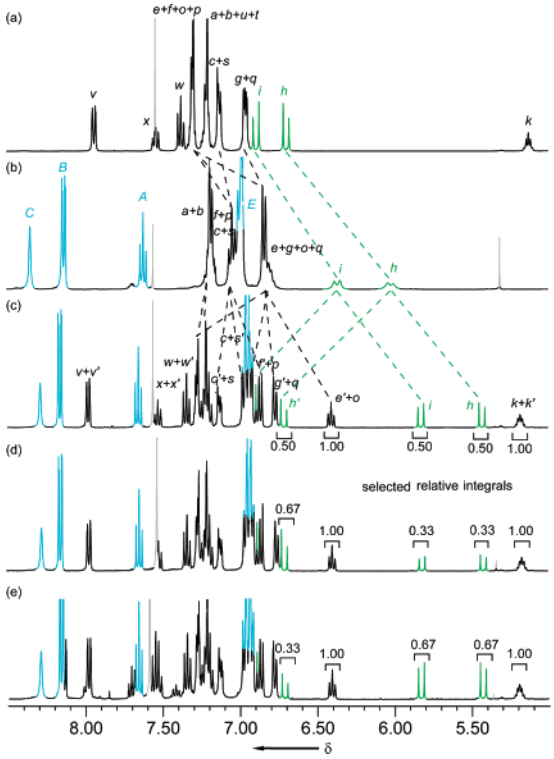


Figure 2. Partial ^{1}H NMR spectra (400 MHz, 1:1 $CDCl_3$−CD_3OD, 300 K) of (a) thread, (b) rotaxane (*S*)-**2**, (c) 50:50 $FumH_2$-(*S*)-**5**/$FumD_2$-(*S*)-**5** produced with DMAP as catalyst (Scheme 1, conditions a), (d) 33:67 $FumH_2$-(*S*)-**5**/$FumD_2$-(*S*)-**5** produced with chiral catalyst (*S*)-**3** (Scheme 1, conditions b) and (e) 67:33 $FumH_2$-(*S*)-**5**/$FumD_2$-(*S*)-**5** produced with chiral catalyst (*R*)-**3** (Scheme 1, conditions c). Residual solvent peaks are shown in gray. For full spectral assignments, see the Supporting Information.

the occupancy of the deuterated and nondeuterated fumaramide stations (Figure 2e).

The difference between the 50:50 (*R*)/(*S*)-**4** mixture and the 33:67 (*R*)/(*S*)-**4** mixture corresponds to a decrease in entropy for the macrocycle distribution, but the enthalpy of macrocycle-thread interactions is unaffected in the symmetrical information ratchet (the fumaramide units are chemically identical in (*R*)- and (*S*)-**4** and essentially the same in (*S*)-**5**). To drive the macrocycle enthalpically uphill it is necessary to use dissimilar stations and transport some of the macrocycles from a stronger binding site to a weaker one. The spatial asymmetry which causes the information ratchet mechanism to operate in Scheme 1 is not exclusively a property of enantiomers or pseudoenantiomers; any shuttle in which the position of the macrocycle enhances asymmetry about a reactive center can, in principle, be used to alter the macrocycle distribution between dynamically exchanging co-conformers.[19]

This was demonstrated (Scheme 2) using nonsymmetrical molecular shuttle (*R*)-**6**,[20] a rotaxane containing one fumaramide group and one succinamide group, a weaker binding station for the benzylic amide macrocycle because it lacks the preorganization of the hydrogen-bonding sites imparted by the trans olefin.[21] The shielding of the fumaramide protons in (*R*)-**6** (Figure 3b) compared to those in the corresponding thread (Figure 3a), suggests that the equilibrium distribution of the macrocycle between the fumaramide and succinamide sites is ~75:25. Consistent with this, benzoylation of (*R*)-**6** in the presence of DMAP (Scheme 2, conditions a) afforded a 74:26 *Fum*-(*R*)-**7**/*Succ*-(*R*)-**7** ratio. Carrying out the reaction in the presence of (*S*)-**3** (Scheme 2, conditions b), however, whose efficacy in catalyzing the rate of benzoylation of **1** and (*S*)-**2** had proven sensitive to the position of the macrocycle, the *Fum*-(*R*)-

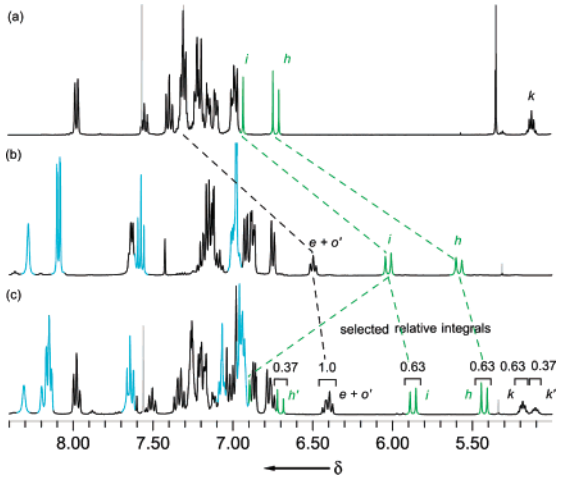


Figure 3. Partial ^{1}H NMR spectra (400 MHz, 1:1 $CDCl_3$−CD_3OD, 300 K) of (a) thread, (b) rotaxane (*R*)-**6**, (c) mixture of *Fum*-(*R*)-**7** and *Succ*-(*R*)-**7** produced with (*S*)-**3** (Scheme 2, conditions b). Residual solvent peaks are shown in gray. For full spectral assignments of purified samples of *Fum*-(*R*)-**7** and *Succ*-(*R*)-**7**, see the Supporting Information.

7/*Succ*-(*R*)-**7** ratio was reduced to 63:37 (Figure 3c).[22] In other words, approximately 15% of the net number of macrocycles that were positioned on the fumaramide site in (*R*)-**6** at equilibrium were transported enthalpically uphill to the succinamide unit by the chemically driven information ratchet. Unlike an energy ratchet mechanism performing a similar task,[2a] at no stage does a thermodynamic driving force exist for the *Fum*/*Succ* ring ratio to be decreased. It happens solely through the kinetics of the chemical reaction selectively trapping the macrocycle in a thermodynamically unfavorable position. Conversely, use of the "mismatched" enantiomer of catalyst **3** with (*R*)-**6** (Scheme 2, conditions c) results in an *increase* in the macrocycle occupancy of the fumaramide station (from 74% to 80%).

In conclusion we have demonstrated a functioning molecular information ratchet mechanism fueled by the energy that comes from an acylation reaction that is sensitive to the position of a dynamically exchanging substrate. The ratchet is exemplified by driving the macrocycle distribution away from its equilibrium position in both symmetrical and unsymmetrical rotaxane-based molecular shuttles. The former corresponds to a dynamic kinetic resolution of the rotaxane, the latter to driving macrocycles enthalpically uphill; in both cases the change occurs without the binding affinity of the macrocycle for the different regions of the thread ever varying and the net direction of the ring movement is determined by the handedness of the catalyst used. Such a mechanism could be used as the "engine" for an autonomous molecular motor which moves a substrate directionally as long as a chemical fuel is available.

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Supporting Information Available: 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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(11) In assigning (*R*)- and (*S*)-**4** we follow the conventions [(a) Schill, G. *Catenanes, Rotaxanes, and Knots*; Academic Press: New York, 1971. (b) Safarowsky, O.; Windisch, B.; Mohry, A.; Vögtle, F. *J. Prakt. Chem.* **2000**, *342*, 437−444] that (i) covalent bonding takes precedence over mechanical bonding and (ii) the region of the thread to which a macrocycle is localized is higher priority than one that it is not.
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(16) Absolute configurations assigned by analogy to the *FumH*$_2$:*FumD*$_2$ ratio found for (*S*)-**5**.
(17) For asymmetric synthesis of a rotaxane (4.4% ee), see: Makita, Y.; Kihara, N.; Nakakoji, N.; Takata, T.; Inagaki, S.; Yamamoto, C.; Okamoto, Y. *Chem. Lett.* **2007**, *36*, 162−163.
(18) Variation of catalyst loading and lowering the temperature did not alter the selectivity of the process while necessitating longer reaction times.
(19) Note that the consumption of a chemical fuel is required to drive the macrocycle distribution away from its equilibrium value. Treatment of **4**, (*S*)-**5**, or (*R*)-**7** solely with a reversible chiral transesterifcation catalyst would not lead to a decrease in the entropy of the macrocycle distribution.
(20) For the synthesis of (*R*)-**6**, see Supporting Information.
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(22) For diastereomeric co-conformers such as *Fum*-(*R*)-**6** and *Succ*-(*R*)-**6**, the position-discriminating reagent or catalyst does not necessarily have to be chiral. However, the steric and chemical space around the hydroxyl group in the two macrocycle translational co-conformers of (*R*)-**6** is obviously very similar to that of **1**. Since (*S*)-**3** discriminates well between the macrocycle positions in **1**, and with the desired directional bias, it was also expected to do so for (*R*)-**6**.

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