Switchable Catalysts

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A Rotaxane-Based Switchable Organocatalyst**

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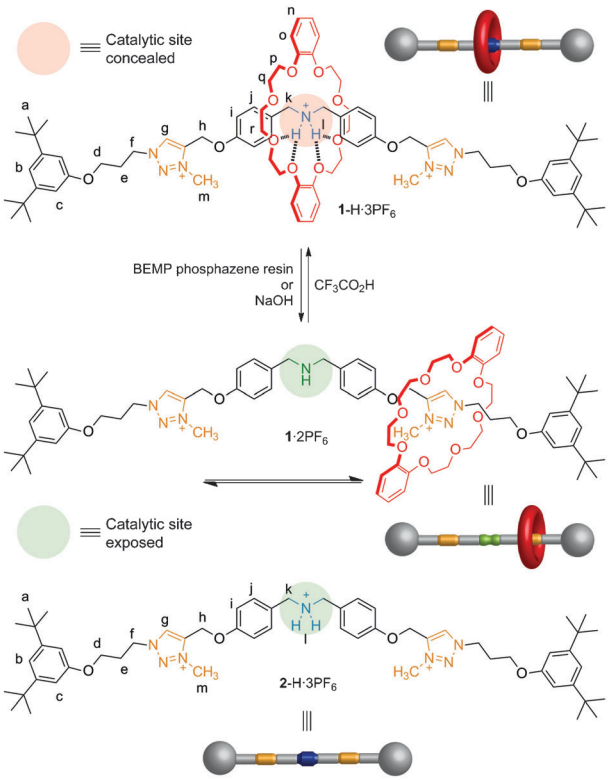
The activity of enzymes is often modulated by cofactors, phosphorylation, allosteric binding, or other trigger-induced effects.[1] Achieving similar control over synthetic catalysts[2] could be useful for influencing both the rate and outcome of chemical transformations, the latter perhaps by switching "on" and "off" different catalysts that promote alternative reactions in the same pot. Rotaxane-based molecular shuttles have previously been used for information storage,[3] mechanical work,[4] gel formation,[5] fluorescence[6] and chiroptical[7] switching, to control binding events[8] and in various controlled-release[9] systems.[10] Herein we show that the well-defined positional changes of the components in a switchable rotaxane can be exploited to conceal and reveal an organocatalytic site.[11]

The design of the system is based on a switchable rotaxane motif[12] developed by Coutrot.[12a–c] The rotaxane (**1**) consists of a dibenzo[24]crown-8 macrocycle and an axle containing both triazolium rings and a dibenzylamine/ammonium moiety[13] (Scheme 1). In principle, a secondary amine/ammonium group is able to carry out iminium catalysis[14] over a wide pH range (that is, irrespective of whether the catalyst is initially in the amine or ammonium ion form). However, when the rotaxane is protonated (**1**-H·3PF$_6$), the ammonium group is a better binding site for the macrocycle than the triazolium rings and so the macrocycle encapsulates the central region of the axle blocking access of reactants to the catalytic center. When the secondary amine of the rotaxane is not protonated (**1**·2PF$_6$), the triazolium groups are the preferred binding sites for the macrocycle and the dibenzylamine group on the axle is exposed and available to perform catalysis.

Rotaxane **1** was prepared using the CuAAC click reaction[15] of an azide-functionalized bulky 3,5-di-*tert*-butylphenyl derivative as the key step to covalently capture a threaded complex of dibenzo[24]crown-8 with a suitable alkyne–ammonium axle (see the Supporting Information).[13] Comparison of the ^{1}H NMR spectra of the protonated and unprotonated thread and rotaxane confirms the different position of the macrocycle on the thread in the two switchable states of the rotaxane in various solvents (CD_3CN (see Figure 1), $CDCl_3$, and CD_2Cl_2). In the ^{1}H NMR spectrum of **1**-H·3PF$_6$ (Figure 1b), there is an upfield shift of the benzylamine aromatic proton signals compared to those in the non-interlocked thread **2**-H·3PF$_6$ (Figure 1a) owing to shielding by the macrocycle ($\Delta\delta H_i = -0.32$ ppm and $\Delta\delta H_j = -0.14$ ppm). The downfield shift and broadening of the benzylic CH_2 groups ($\Delta\delta H_k = 0.45$ ppm) is a result of strong hydrogen bonding between the ammonium group and the crown ether. In contrast, the chemical shifts of the triazolium protons (H_g and H_m) are similar in both the protonated rotaxane (**1**-H·3PF$_6$) and the thread (**2**-H·3PF$_6$).

When rotaxane **1**-H·3PF$_6$ was deprotonated with aqueous NaOH or 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) phosphazene resin to give **1**·2PF$_6$,[16] significant changes were observed in the ^{1}H NMR spectrum. At room temperature in CD_3CN, two sets of resonances are present for the triazolium groups and



Scheme 1. Acid–base switching of the position of the macrocycle in rotaxane **1**-H·3PF$_6$/**1**·2PF$_6$.

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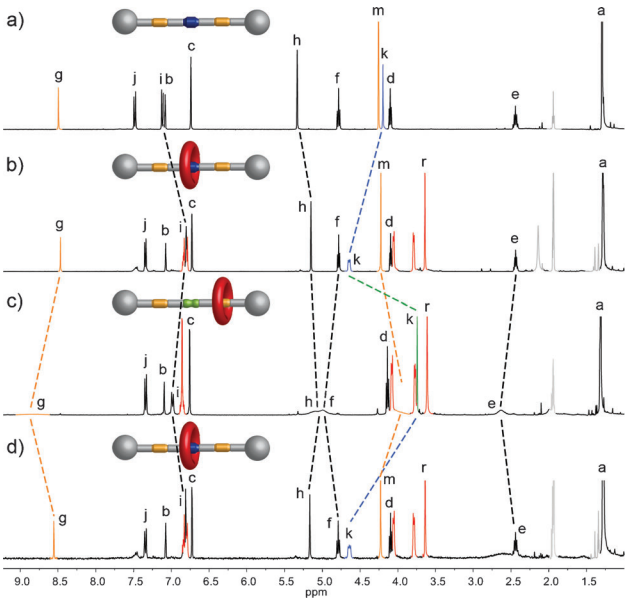
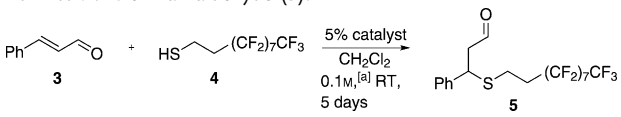


Figure 1. ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) thread **2**·H·3PF_6; b) rotaxane **1**·H·3PF_6; c) rotaxane **1**·2PF_6 (338 K); d) solution from (c) after addition of 1 equivalent of CF_3CO_2H. The lettering and color coding of the signals corresponds to that shown in Scheme 1.

Table 1: Investigation of the catalytic properties of threads **2**·2PF_6 and **2**·H·3PF_6 and rotaxanes **1**·2PF_6 and **1**·H·3PF_6 on the Michael addition of thiol **4** to *trans*-cinnamaldehyde (**3**).[a]



Entry	Catalyst	Yield[b]
1	no catalyst	no reaction
2	dibenzylamine	69%
3	**2**·2PF_6	30%
4	**2**·H·3PF_6	49%
5	**1**·2PF_6	83%
6	**1**·H·3PF_6	no reaction
7	**1**·2PF_6/**1**·H·3PF_6 + 10 min $NaOH_{(aq)}$ wash	66%[c]
8	no catalyst + 10 min $NaOH_{(aq)}$ wash	traces[d]

[a] Reactions were run with 5 mol% catalyst loading at 0.1 M concentration of thiol **4** with 1.5 equiv of aldehyde **3**. [b] Yield of **5** isolated after column chromatography. [c] Yield after 10 min washing with 1 M $NaOH_{(aq)}$ and subsequent 1 h stirring at room temperature. [d] Traces of **5** were detected after the $NaOH_{(aq)}$ wash but, in the absence of an amine, the amount of **5** present did not increase over 5 d of subsequent stirring.

neighboring protons (H_e, H_f, H_g, H_h, H_m) in **1**·2PF_6, indicating that shuttling of the macrocycle between the two triazolium stations is slow on the NMR timescale. At 338 K, the two sets of resonances coalesce and the remaining peaks sharpen (Figure 1c).[17] Most significantly, the benzylic protons are shifted upfield ($\Delta\delta H_k = -0.88$ ppm) and the triazole protons downfield ($\Delta\delta H_g \approx 0.37$ ppm), confirming that the macrocycle resides over the triazolium groups in **1**·2PF_6 (Figure 1c). Upon reprotonation of the secondary amine group with CF_3CO_2H (Scheme 1), the ^{1}H NMR shifts indicate that the macrocycle returns to its original position over the ammonium site (Figure 1d).

Having demonstrated acid–base control over the position of the ring on the axle in **1**, and confirmed the positional integrity of the components in the two different states, we investigated the efficacy of the rotaxane as a switchable organocatalyst. The Michael addition of an aliphatic thiol, such as **4**,[18] to *trans*-cinnamaldehyde (**3**) is typical[19] of a class of reactions accelerated by iminium organocatalysis[14] (Table 1). We first confirmed that the reaction between **3** and **4** does not proceed to a perceptible extent in the absence of a secondary amine catalyst (Table 1, entry 1) and then carried out a series of experiments involving different potential reaction-promoting species (Table 1).

Dibenzylamine and the thread (in both protonated and deprotonated forms, **2**·H·3PF_6 and **2**·2PF_6, respectively) catalyzed the Michael addition of **4** to **3** over 5 days at room temperature in CH_2Cl_2 (Table 1, entries 2–4). The deprotonated form of the rotaxane (**1**·2PF_6) catalyzed the reaction equally effectively (Table 1, entry 5). However, use of the protonated form of the rotaxane, **1**·H·3PF_6, resulted in the starting materials being recovered unchanged after 5 days (Table 1, entry 6).

The most convenient way of switching the rotaxane catalyst "on" (**1**·2PF_6) from its protonated "off" state (**1**·H·3PF_6) is to simply wash a solution of the rotaxane in dichloromethane with 1M aqueous NaOH.[16] Interestingly, when a mixture initially containing **3**, **4**, and **1**·H·3PF_6 (or **1**·2PF_6) was washed with 1M aqueous NaOH, the reaction reached complete conversion to **5** within 1 h (Table 1, entry 7), instead of a reaction time of 5 days when starting with pristine **1**·2PF_6 (that is, with no NaOH wash; Table 1, entry 5). We presume that the rate enhancement is due to deprotonation of thiol **4** by NaOH, making it more nucleophilic. However, treatment with NaOH is not sufficient in itself to allow the reaction to occur efficiently in the absence of an amine catalyst (Table 1, entry 8).

Finally, it proved possible to control the progress of the Michael addition by in situ switching of the rotaxane organocatalyst (Figure 2; see the Supporting Information for experimental details). After 48 h of stirring **3** and **4** in the presence of 5 mol% rotaxane in its inactive, protonated, state (**1**·H·3PF_6), no conversion to product **5** was observed (Figure 2c). Upon brief washing with 1M aqueous NaOH, the rotaxane catalyst was switched "on", resulting in virtually complete conversion of **4** to **5** within 1 h at room temperature (Figure 2d).

In conclusion, we have developed a switchable organocatalyst based on a rotaxane architecture. The catalyst can be switched "on" or "off" by addition of acid or base, which acts to move the rotaxane ring to either conceal or reveal the catalytic site. The system can effectively control the rate of Michael addition of an aliphatic thiol to *trans*-cinnamaldehyde, either by adding the catalyst in its active form or by in situ switching. Organocatalysts are often considered to be the small-molecule counterparts of enzymes.[14] The ability to regulate their activity through external stimuli brings the analogy closer still.

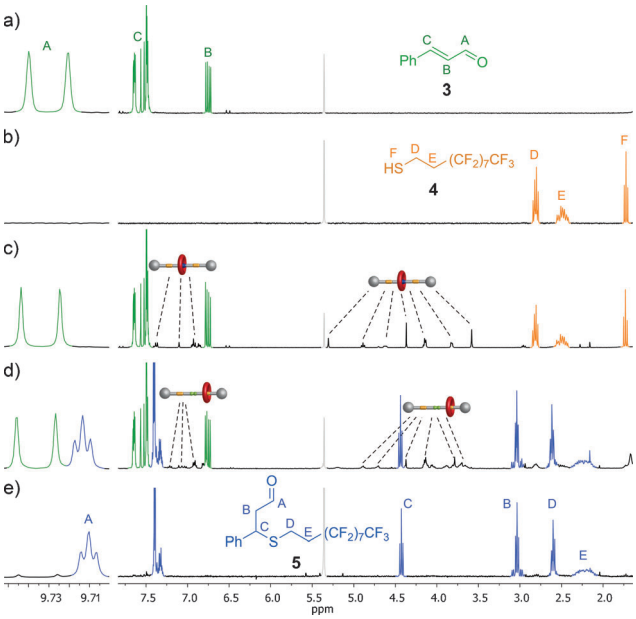


Figure 2. ^{1}H NMR spectra (400 MHz, CD_2Cl_2, RT) of a) *trans*-cinnamaldehyde (**3**); b) thiol **4**; c) reaction mixture of **3** and **4** after 48 h stirring in the presence of 5 mol% **1**-H·3PF_6; d) reaction mixture from (c) 1 h after deprotonation of **1**-H·3PF_6 with a 10 min wash with 1 M $NaOH_{(aq)}$ (residual of **3** is the result of 1.5 equivalents being used to ensure complete consumption of **4**); e) **5**. The signals indicated with dashed lines correspond to the rotaxane catalyst (in its active or inactive forms). The aldehyde signals above $\delta = 9.70$ ppm are shown at 70% relative intensity and on an expanded chemical shift axis (×25) in comparison with the signals below $\delta = 7.75$ ppm.

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[16] Ammonium groups in crown ether-based rotaxanes are often difficult to deprotonate (see: K. Nakazono, T. Takata, *Chem. Eur. J.* **2010**, *16*, 13783 – 13794). In CD_2Cl_2 solution, in which the macrocycle – thread hydrogen bonding is particularly strong, **1**-H·3PF_6 is not deprotonated by K_2CO_3 (solid or aqueous solution), although it can be smoothly converted to **1**·2PF_6 by washing with 1 M $NaOH_{(aq)}$.

[17] No further changes in chemical shift are observed for the signals of the dibenzylamine motif or the macrocycle at higher temperatures.

[18] Fluorinated thiol **4** was chosen for the catalysis experiments as it is odorless, nonvolatile, and has a simple ^{1}H NMR spectrum with signals in a different region to **3**.

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Communications

Switchable Catalysts

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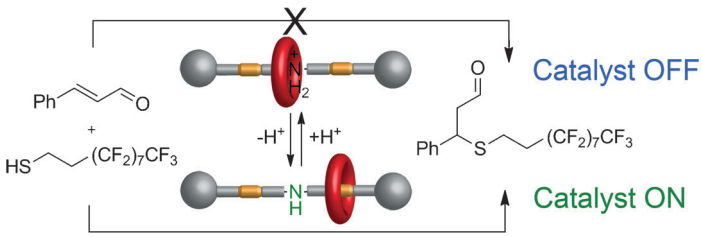
A Rotaxane-Based Switchable Organocatalyst



Switch it on! The activity of an organocatalytic group incorporated within a rotaxane architecture can be controlled by switching the position of the macrocycle. The system was used to mediate the progress of the Michael addition of an aliphatic thiol to *trans*-cinnamaldehyde.