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The Cyclopentyl Group, As a Small but Bulky Terminal Group, Allows Rapid and Efficient Active Transport

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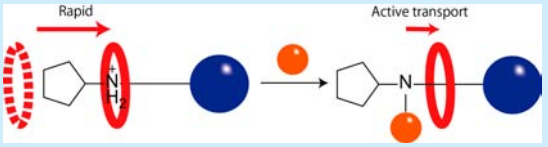
Supporting Information

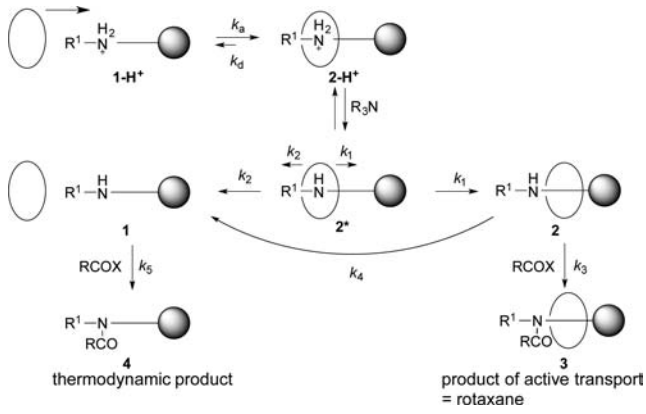
ABSTRACT: Secondary ammonium salts bearing a cyclopentyl terminal group rapidly formed pseudorotaxane with 1.5 equiv of DB24C8. Acylation of the pseudorotaxane with 50 equiv of benzoyl chloride in the presence of 50 equiv of triethylamine in toluene afforded rotaxane, the product of active transport, in 95% yield. The cyclopentyl group is small enough to allow rapid formation of pseudorotaxane, and bulky enough to facilitate the quantitative active transport by steric repulsion.



Since the first examples of artificial active transport systems were reported,[1] various researchers have carried out intensive efforts to achieve rapid and quantitative active transport.[2] In this regard, some rotaxane-based artificial active transport systems have been developed.[3] These systems are advantageous for studying artificial active transport because the active transport of the wheel component (mover) on the axle component (track) can be monitored without dissociating the components. Most artificial active transport systems are driven by the photoisomerization of the N═N or C═C double bond. In these systems, the efficiency of active transport is often far less than 100% because of the photoequilibrium in photoisomerization. Further, photons with an energy of >100 kJ/mol are used for the active transport in which only several kJ/mol is necessary. In contrast, the efficiency of active transport in biological systems, which is driven by the phosphorylation with ATP, is very high with high energy efficiency.[4] Until now, only a few chemically driven artificial active transport systems have been studied.[5]

We have reported a quantitative active transport system driven by acylation, the chemical equivalent of phosphorylation, based on the steric hindrance of the terminal group on the axle component of rotaxane[6] (Scheme 1). This system starts from secondary ammonium salt-type rotaxane **2**-H$^+$ containing a dibenzo-24-crown-8 (DB24C8) unit as the wheel component. Using a cyclohexyl or *tert*-butyl group as the terminal group (R^1) is the key to successful active transport. The unstable rotaxane **2***, which is formed by the neutralization of **2**-H$^+$, dissociates (rate constant k_2) into **1** and DB24C8 because of thermodynamic stability. Because the cavity of DB24C8 is only slightly larger than the cyclohexyl and *tert*-butyl groups,[7] DB24C8 tentatively moves (rate constant k_1) against the terminal group on the axle component to avoid steric hindrance before dissociation (rate constant k_4) into **1** and DB24C8. When the position of DB24C8 in the resulting transient conformer **2** is fixed by the rapid acylation of the amino group (rate constant k_3), rotaxane **3** is obtained. Thus, **4** is a thermodynamic product, while **3** is the product of active transport. Quantitative (>99%) active transport was achieved, indicating that both k_1/k_2 and k_3/k_4 values are fairly larger than unity. The large k_1/k_2 value can be attributed to the bulkiness of R^1. Because k_3 is large under the rapid acylation conditions, k_3/k_4 also becomes large.

Scheme 1



When the active transport was started from the dissociation state (DB24C8 + **1**-H$^+$), the bulkiness of R^1 suppresses the progress of the first step. When a *tert*-butyl group was used as R^1, the approach of DB24C8 to the ammonium salt moiety over the R^1 group became impossible ($k_a \approx 0$).[7c] DB24C8 could enter the axle over a cyclohexyl group, even though it took a very long time (>100 days) to convert **1**-H$^+$ into **2**-H$^+$.[7a,b] We envisioned that with a small R^1 group, over which the cavity of DB24C8 can pass without significant steric hindrance, **1**-H$^+$ may be rapidly converted into **2**-H$^+$. However, a small R^1 group would also increase k_2 and k_4, thus preventing the active transport. To achieve rapid and efficient active

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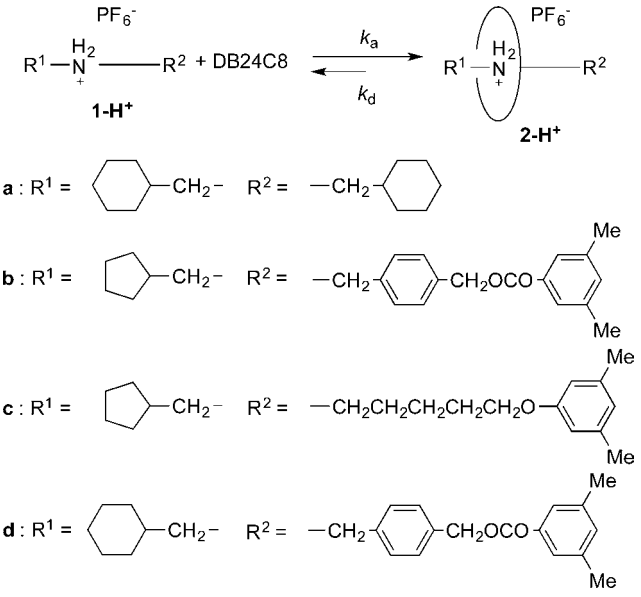
transport from the dissociation state (DB24C8 + **1**-H^+) to **3**, an appropriate R^1 group and reaction conditions should be found by which k_a is enhanced, but both k_2 and k_4 are suppressed. In this study, we demonstrate that the cyclopentyl group is not only a small enough group to allow the rapid formation of **2**-H^+, but also a bulky enough group to enable quantitative active transport.

The effects of R^1 on the rate of association (k_a) and dissociation (k_d) were evaluated. Because the direct measurements of k_2 and k_4 are impossible, k_d was used as the relative index of k_2 and k_4. Secondary ammonium salts **1b**-H^+ and **1c**-H^+ were prepared, and their complexation with DB24C8 was carried out. Association constant K_a and rate constant k_a were measured using the ^{1}H NMR spectra of $[\mathbf{1}\text{-}H^+]_0 = [DB24C8]_0 = 0.01$ M in $CD_3CN/CDCl_3$ (1:3, v/v) at 23 °C,[7a] and the dissociation rate constant k_d was calculated as k_a/K_a.[8] The results are summarized in Table 1.

Table 1. Stability Constant K_a and Rate Constants of Association (k_a) and Dissociation (k_d) of 2-H^+[a]



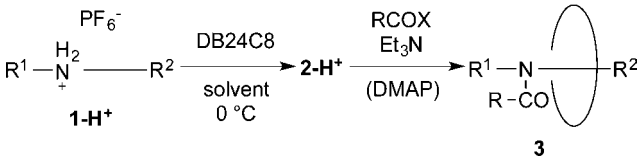
2-H^+	k_a (M^{-1} s^{-1})	k_d (s^{-1})	K_a (M^{-1})
a[b]	4.8×10^{-7}	4.4×10^{-9}	110
b	4.2×10^{-2}	1.1×10^{-4}	400
c	5.0×10^{-2}	1.2×10^{-4}	420

[a]At 23 °C and $[\mathbf{1}\text{-}H^+]_0 = [DB24C8]_0 = 0.01$ M in $CD_3CN/CDCl_3$ (1:3, v/v). [b]Reference 7a. Temperature is 20 °C.

Stoddart et al. reported that the cyclopentyl group is too small to act as the terminal group of rotaxane.[7a] Credi et al. used the cyclopentyl group in a unidirectional transport system as the terminal group that is slightly bulkier than the phenyl group.[3c] Thus, the formation of **2**-H^+ from **1b**-H^+ or **1c**-H^+ with DB24C8 approached equilibrium within 1.5 h because the cyclopentyl group is smaller than the cyclohexyl group. Due to the same reason, the k_d values for **2b**-H^+ and **2c**-H^+ are 10^4 times larger than that for **2a**-H^+. In general, a bulkier terminal group is necessary for the quantitative active transport because active transport occurs because of the steric repulsion of the terminal group.

The active transport was studied in chloroform. Either **1b**-H^+ or **1c**-H^+ was mixed with DB24C8 in chloroform. The ammonium salts were scarcely soluble in chloroform, while pseudorotaxane **2**-H^+ was soluble in chloroform. Therefore, the acylation reaction was carried out after the system became homogeneous. The results are summarized in Table 2.

Table 2. Acylative Active Transport Using a Cyclopentyl Group As the Terminal Group[a]



entry	1	RCOX (equiv)	Et_3N (equiv)	DMAP (equiv)	solvent	DB24C8 (equiv)	yield of **3** (%)
1	b	Boc_2O (50)	50	1	$CHCl_3$	2.0	0
2	b	BzCl (50)	50	1	$CHCl_3$	2.0	78
3	c	BzCl (50)	50	1	$CHCl_3$	2.0	74
4	c	BzCl (50)	50	1	$CHCl_3$	2.0	38
5	c	BzCl (50)	30	1	$CHCl_3$	2.0	57
6	c	BzCl (50)	50	5	$CHCl_3$	2.0	61
7	b	BzCl (50)	50	0	$CHCl_3$	2.0	63
8	c	BzCl (50)	50	0	$CHCl_3$	2.0	60
9	b	BzCl (50)	50	0	toluene	2.0	38
10	c	BzCl (50)	50	0	toluene	2.0	72
11	c	BzCl (50)	50	0	$CHCl_3$	1.5	77
12	c	BzCl (50)	50	0	toluene	1.5	95

[a]Reactions were carried out at 0 °C for 40 min. A mixture of DB24C8 and **1**-H^+ was stirred until the system became homogeneous before the addition of RCOX followed by Et_3N.

We have previously reported that an active transport with 74% efficiency occurred when **2d**-H^+ bearing the cyclohexyl terminal group was treated with 50 equiv of di-*tert*-butyl dicarbonate (Boc_2O) in the presence of 50 equiv of Et_3N and 1 equiv of DMAP.[6] Therefore, **2b**-H^+ prepared from **1b**-H^+ with 2 equiv of DB24C8 was subjected to the same reaction conditions (entry 1). However, no rotaxane **3b**, the product of active transport, was obtained; however, **4b**, the thermodynamic product, was obtained quantitatively. To enhance k_3, a more electrophilic acylation agent, benzoyl chloride, was used (entry 2). As expected, the product of active transport **3b** was obtained in 78% yield. This result shows that k_2 and k_4 are small enough even with the cyclopentyl group as the terminal group, and the efficiency of active transport can be controlled by k_3. **1c**-H^+ also afforded the product of active transport **3c** in 74% yield under the same reaction conditions (entry 3). The efficiency of active transport decreased with the decrease in the amount of acylation agent or Et_3N (entries 4 and 5). Although k_3 may increase with the amount of DMAP, the efficiency of active transport decreased (entry 6). Excess DMAP would inhibit the pseudorotaxane formation. Surprisingly, the decrease in the efficiency of active transport was not significant even

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without DMAP (entries 7 and 8). Therefore, further study was carried out in the absence of DMAP to simplify the reaction system. When toluene was used as the solvent, the efficiency of active transport decreased in the case of **1b**-H^+ (entry 9), but increased in the case of **1c**-H^+ (entry 10). The solubility of **1**-H^+ and **2**-H^+ in toluene affected the efficiency of active transport. Further, [DB24C8]/[**1**-H^+] strongly affected the efficiency of active transport. When the amount of DB24C8 was reduced to 1.5 equiv, the efficiency of active transport increased to 77% in chloroform and reached 95% in toluene. Thus, rapid and almost quantitative active transport was achieved using the cyclopentyl group as the terminal group under facile acylation conditions. The efficiency of active transport decreased to 43% when isocyanate was used as the acylation agent. No active transport was observed when acetic anhydride was used as the acylation agent because of its low electrophilicity. When highly electrophilic trifluoroacetic anhydride was used as the acylation agent, the efficiency of active transport significantly increased to 88%.

Figure 1 shows the change in the ^{1}H NMR spectra during the active transport from **1c**-H^+ to **3c**. When DB24C8 was added

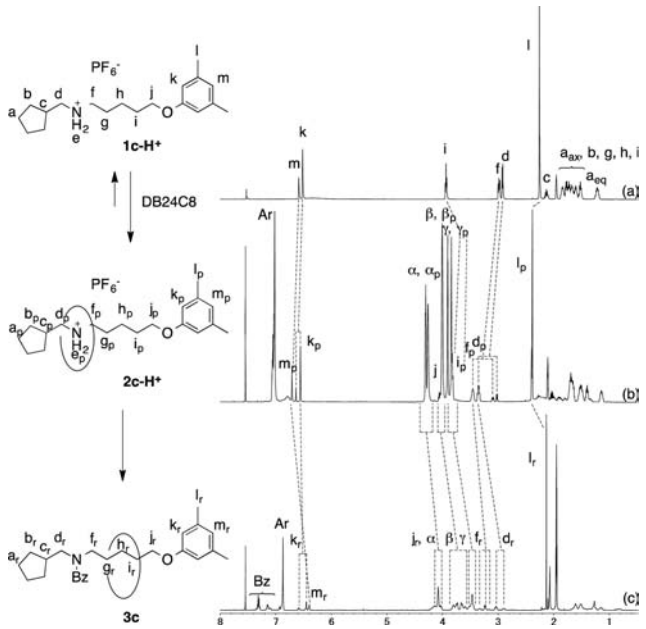
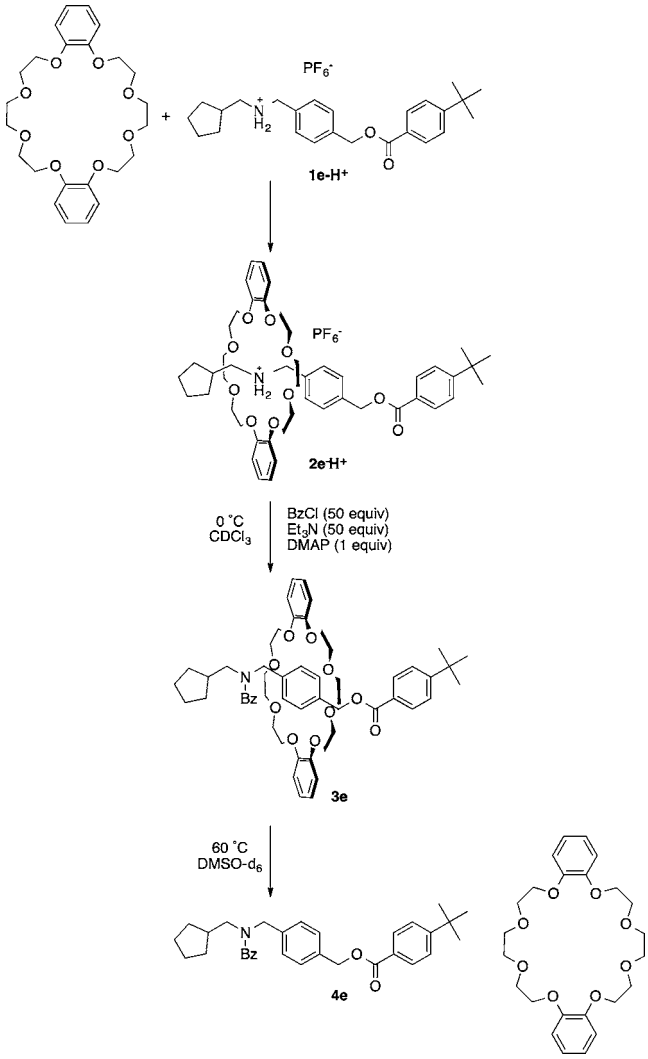


Figure 1. ^{1}H-NMR spectra (500 MHz, $CDCl_3/CD_3CN$ (1:3, v/v)) of (a) **1c**-H^+, (b) a mixture of **1c**-H^+ and DB24C8, and (c) **3c**.

to the **1c**-H^+ solution, a new set of signals corresponding to **2c**-H^+ appeared. The peaks of protons d_p and f_p appeared at lower field as compared to the peaks for protons d and f because of the anisotropic effect of the crown ether.[9] In the ^{1}H NMR spectrum of **3c**, the peaks of the protons d_r and f_r appeared at higher field than did the peaks of protons d_p and f_p because of the absence of the crown ether. Instead, the peak of l_r appeared at higher field than that of I_p owing to the shielding effect of the aromatic rings of DB24C8.

As an application of the cyclopentyl-terminal-group-based rapid active transport system, a simple two-step unidirectional transport system was developed (Scheme 2). Secondary ammonium salt **1e**-H^+ with a cyclopentyl group at the *left* end and a *tert*-butyl group at the *right* end of the track was synthesized. When **1e**-H^+ was mixed with DB24C8, the mover was set on the track from the *left* side because the *tert*-butyl

Scheme 2



group is too bulky to allow threading.[7c] Benzoylation of the resulting pseudorotaxane **2e**-H^+ furnished the product of active transport **3e** in 68% yield. During this process, the DB24C8 mover was transferred to the *right* side again. On heating the DMSO-d_6 solution of **3e** at 60 °C, the DB24C8 in **3e** dethreaded from the track to afford **4e** in 75% yield. Because the benzoyl group is too bulky for DB24C8 to overcome, DB24C8 passed over the *tert*-butyl group at the *right* end. Thus, the DB24C8 was moved over the **1e**-H^+ track unidirectionally from the *left* end to the *right* end.

We demonstrated that the cyclopentyl group can be used as a terminal group that allows the *rapid* and quantitative active transport of the DB24C8 mover on a secondary ammonium salt track. The cyclopentyl group is small enough to make DB24C8 pass over it rapidly. The cyclopentyl group is also sufficiently bulky enough to cause the DB24C8 in the neutralized rotaxane to move away from the cyclopentyl group; facile acylation of the secondary amino group facilitates the quantitative active transport by fixation of the transient rotaxane structure. The development of a multistep active transport system using the cyclopentyl group as the terminal group of the rotaxane is in progress.

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■ ASSOCIATED CONTENT

Supporting Information

The experimental procedures, ^{1}H NMR spectra, and high resolution MS. 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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(8) A reviewer has suggested that the K_a, k_a, and k_d values should all be measured in solvents used in the active transport. Unfortunately, owing to the fact that **1b**-H^+ and **1c**-H^+ are only slightly soluble in chloroform and toluene, it is impossible to determine k_a and k_d values in these solvents. Further, because of the very limited solubility of pseudorotaxanes **2b**-H^+ and **2c**-H^+ in toluene, it is also impossible to determine the K_a values in toluene.

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