Unusually Lowered Acidity of Ammonium Group Surrounded by Crown Ether in a Rotaxane System and Its Acylative Neutralization

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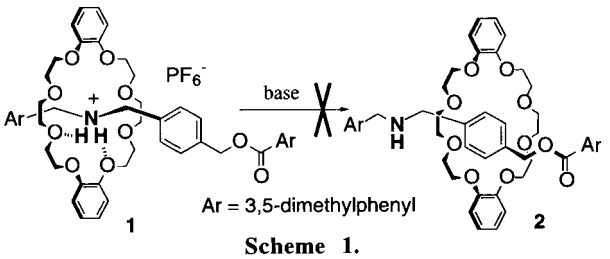
Acidity of a secondary ammonium group in a rotaxane system with a crown ether was unusually lowered. *N*-Acylation of the ammonium group by acid anhydrides or chlorides proceeded slowly in the presence of excess tertiary amine to give the *N*-acylated rotaxanes without salt structure.

Recent enormous development in the directed synthesis of interlocked molecules such as rotaxane and catenane has originated from the utilization of attractive intermolecular interactions.[1] Since this interaction still remains in the interlocked molucules as a strong intramolecular interaction that suppresses free rotation or movement of the components, removal of such interaction from the interlocked molecules has been extensively studied.[2] The conformation change induced by such modification can be used as a basic action of molecular switch.[3]

A rotaxane consisting of crown ether and secondary ammonium salt is one of the most easily accessible rotaxanes.[4] It seems that intramolecular hydrogen-bonding interaction can be easily removed by neutralization of ammonium group. However, such transformation was reported only where the axle had the second interaction site that stabilized the deprotonated form.[5] Neutralization of a simple rotaxane consisting of a crown ether and an ammonium group such as **1**[4i] has been impossible.[6] Neverthless, the acidity of ammonium group in the combination with crown ether has not been evaluated so far.



Scheme 1.

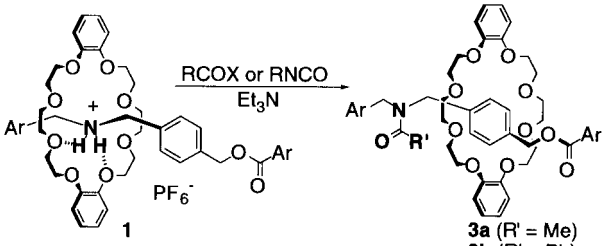
The low acidity of ammonium group in **1** was demonstrated by H-D exchange experiment. Thus, **1** (0.06 mol/L) was treated with D_2O (7 mol/L) in acetonitrile-d_3 at 25 °C to follow H-D exchange reaction. The reaction took place slowly, and the concentration of proton on ammonium group decreased with first order kinetic where half-life period ($\tau_{1/2}$) was 17 min. The rate of H-D exchange was compared with those of other weakly acidic compounds as shown in Table 1. Kinetic acidity of **1** is very low, even lower than that of alcohol and pyrrole. It should be noted that the solvent used in this H-D exchange experiments is very polar, and hydrogen-bonding interaction is exhaustively weakened in such media. Thus, kinetic acidity of **1** in ordinary organic solvent might be far lower.

While the neutralization of **1** is impossible, the free amine-rotaxane **2** can be present as an equilibrium when **1** is treated with base. We attempted to trap **2** by suitable electrophiles. Thus, **1** was treated with 5 folds of triethylamine and 2 folds of acetic anhydride in THF at 40 °C for 24 h. As expected, *N*-acetylated rotaxane **3a** was obtained albeit in low yield (39%).[7] No other product was observed, indicating that the reaction is retarded by the low concentration of **2** in the system. It should be noted that **3a** shows smaller R_f value (0.22) than **1** (R_f 0.54) (on silica gel TLC, eluent: CH_2Cl_2-CH_3CN 10/1 v/v), indicating that **3a** is more polar than **1**, and **1** does not behave as a typical ionic compound. Structure of **3a** obtained by X-ray crystal structure analysis[8] is shown in Figure 1. While the crown ether in **1** is located at the ammonium group,[4,9] acetylation ejected the crown ether to the position at the *p*-phenylene group in **3a**, where no attractive interaction can be seen between the wheel and the axle components in rotaxane.

Table 1. Half-life time ($\tau_{1/2}$) of H-D exchange and *pKa* data.[a]

substrate	$\tau_{1/2}$	*pKa*[b]
Me_2NH_2 Cl	< 1 min	10.8
pseudorotaxane **6**	< 1 min	-
EtOH	< 1 min	15.9
pyrrole	ca. 2 min	17.5
1	17 min	-
acetophenone	>> 24 h	19.2

[a][substrate] = 0.06 mol/L and [D_2O] = 7 mol/L in acetonitrile-d_3 at 25 °C. [b]In water, ref. 10.



Scheme 2.

The reaction condition of the acetylation was optimized. The results are summarized in Table 2. **3a** was obtained in high yield in acetonitrile or DMF. When the reaction was carried out for longer period, **3a** was obtained in 100% yield.

The versatility of this reaction as a novel modification of hydrogen-bonding promoted rotaxanes was demonstrated with various electrophiles. Benzoyl chloride and benzyloxycarbonyl chloride also gave **3b** and **3c** in 95 and 75% yield, respectively. Phenyl isocyanate gave urea-type of rotaxane **3d** in 71% yield.

Synthesis of [3]rotaxane was carried out as a simple application. Thus, **1** was treated with bifunctional acid chloride **4** in

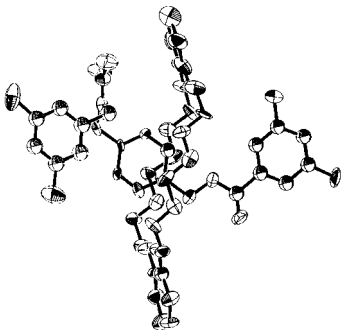
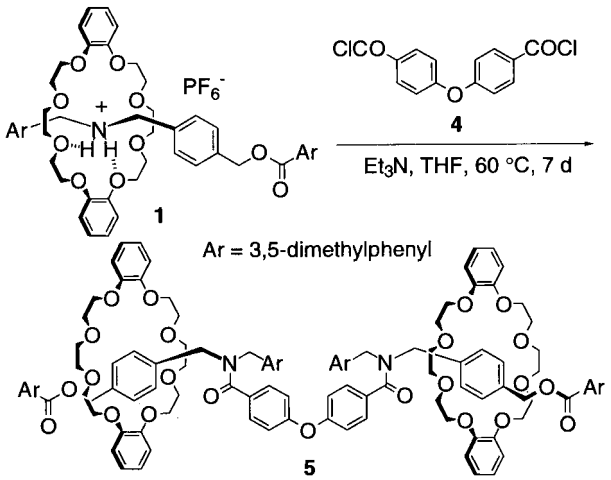


Figure 1. ORTEP drawing (side-view) of **3**. All hydrogens are omitted for clarity.

Table 2. *N*-Acetylation of [2]rotaxane **1**.[a]

electrophile	solvent	time / h	yield[b] / %
Ac_2O	THF	24	39
Ac_2O	chloroform	24	48
Ac_2O	acetonitrile	24	82
Ac_2O	DMF	24	94
Ac_2O	acetonitrile	96	100
PhCOCl	THF	24	95
BnOCOCl	DMF-toluene	72	75
PhNCO	THF	24	71

[a]The reaction was carried out at 40 °C in the presence of two folds of electrophile and five folds of triethylamine. [**1**] = 0.1 mol/L. [b]Isolated. Every rotaxane showed satisfactory NMR, IR, and FAB-MS data.



Scheme 3.

the presence of excess triethylamine to give desired [3]rotaxane **5** in 42% yield.

In conclusion, ammonium group in **1** has unusually low acidity although it can be successfully acylated to give non-ionic rotaxane. One can expect similar behavior to the rotaxanes consisting of crown ether and ammonium salt. Because of the versatility of the present method, modification of rotaxanes to functionalized supramolecules is under active investigation.

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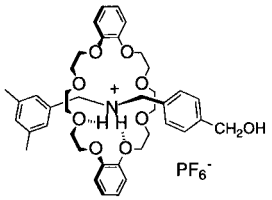
6 We tried to neutralize **1** by the treatment with potassium carbonate, triethylamine, and DBU, although all attempts were unsuccessful. Reflux with calcium hydride also gave no amine. Other crown ether-based rotaxanes[4e,f] behaved similarly. Pseudorotaxane **6** was, however, rapidly neutralized by the action of these bases.



6

7 White crystals. mp 157-158 ˚C (dichloromethane-acetonitrile); ^{1}H NMR (400 MHz, DMSO-d_6, 90 °C): δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.97 (s, 2H), 7.12 (s, 1H), 6.95-6.85 (m, 10H), 6.81 (s, 1H), 6.71 (s, 2H), 5.91 (s, 2H), 4.30 (s, 2H), 4.24 (s, 2H), 4.10-3.95 (m, 8H), 3.70-3.50 (m, 8H), 3.30-3.20 (m, 4H), 3.05-2.90 (m, 4H), 2.22 (s, 6H), 2.18 (s, 6H), 1.98 (s, 3H) ppm, each peak split to two peaks at room temperature because of slow *s-cis* - *s-trans* equilibrium of amide group; IR (KBr): 1712 (ester), 1643 (amide) cm^{-1}; FAB-MS (*m*-NBA): *m/z* 878 [M$^+$]; Found: C, 71.02; H, 7.35; N, 1.60%. Calcd for $C_{52}H_{63}NO_{11}$: C, 71.13; H, 7.23; N, 1.60%.

8 Crystal data for **3**: $C_{52}H_{63}O_{11}N$, FW = 878.07, orthorhombic, *Pccn*, *a* = 18.952(7), *b* = 30.982(10), *c* = 16.529(7) Å, *V* = 9705(5) Å^3, *Z* = 8, μ(MoK$_\alpha$) = 0.83 cm^{-1}, *Dcalc* = 1.202 g/cm^3, *R* = 0.087, *Rw* = 0.114 (516 variables on 1415, >3σ).

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