High Yielding and Practical Synthesis of Rotaxanes by Acylative End-Capping Catalyzed by Tributylphosphine

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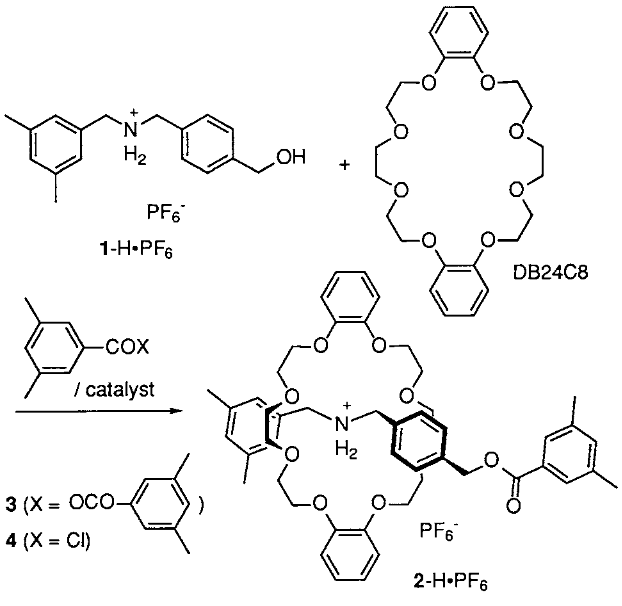
A pseudorotaxane was prepared from dibenzo-24-crown-8 and a dibenzylammonium salt possessing dimethylphenyl and hydroxy groups at the both termini. Acylation of the pseudorotaxane by 3,5-dimethylbenzoic anhydride in the presence of tributylphosphine afforded corresponding rotaxane in 90% yield. Various rotaxanes were readily synthesized in excellent yields by this method.

The formation of inclusion complexes between secondary ammonium salts and crown ethers as the result of attractive hydrogen-bonding interaction has been extensively studied as a powerful strategy that allows flexible design of pseudorotaxanes.[1] However, very limited end-capping of these pseudorotaxanes to form rotaxanes have been reported so far.[2,3] Moreover, the yields were always low until Busch *et al.* reported oxidative coupling of a pseudorotaxane bearing thiol group at the terminus,[2d] although only symmetrical [3]rotaxane can be prepared by this method. One of the difficulties arose from keeping hydrogen-bonding during the end-capping of pseudorotaxanes by covalent bond formation.[4] Although acylation of hydroxy groups by acid chlorides or anhydrides to form esters is one of the most basic and quantitative reactions, this type of reactions, which requires nucleophile or base, has been thought to be incompatible with the end-capping of hydrogen-bonding-based pseudorotaxanes.[2b] Recent development of selective acylation catalyst for ester formation, however, prompted us to use these catalyst systems for rotaxane synthesis.[5] Finally, we have found tributylphosphine is an excellent catalyst for acylation that does not disturb the pseudorotaxane structure. Although some high yield syntheses of a [2]rotaxanes have been reported,[2d,6] this communication provides a novel, highly effective, and general method to prepare [2]rotaxanes consisting of secondary ammonium salts and crown ethers.

We started with a new axle, dibenzylammonium salt **1**-H•PF_6, which has a dimethylphenyl group as a stopper and a hydroxy group as a foothold for end-capping. A CPK model study showed that the dimethylphenyl group is bulky enough to prevent escape of dibenzo-24-crown-8 (DB24C8) from this terminus. While **1**-H•PF_6 is only very slightly soluble in dichloromethane, it became soluble by addition of one equivalent of DB24C8. The ^{1}H-NMR spectrum of the mixture in CD_2Cl_2 showed the new set of signals that correspond to the complex formed. The stability constant K_a of the complex could be estimated to be >1000 L·mol^{-1} in CD_2Cl_2 at 23 °C from the spectra.[7] In the ^{1}H-NMR spectrum of the complex, benzylic protons attached to the ammonium group, which were observed as two singlets in the absence of DB24C8, are shifted down-field and appeared as multiplet signals, whereas the methyl protons are shifted up-field by the shielding effect of benzene ring in DB24C8, suggesting pseudorotaxane formation similarly to other systems.[1b,2b,4]



Scheme 1.

Table 1. Preparation of rotaxane **2**-H•PF_6 by acylation of [DB24C8•**1**-H][PF_6][a]

Catalyst (equivalent)	Time /h	[DB24C8] / [**1**-H•PF_6]	Solvent	Acylation reagent	Yield /%
none	3	3.0	CH_2Cl_2	**3**	0[c]
DMAP(0.5)[b]	3	3.0	CH_2Cl_2	**3**	13
DMAP(0.5)[b]	3	3.0	CH_2Cl_2	**4**	7
TMSOTf (0.1)	3	3.0	CH_2Cl_2	**3**	trace[c]
TMSOTf (0.1)	24	3.0	CH_2Cl_2	**3**	trace[c]
Bu_3P (0.1)	3	3.0	CH_2Cl_2	**4**	10
Bu_3P (0.1)	24	3.0	CH_2Cl_2	**4**	18
Bu_3P (0.1)	3	3.0	CH_2Cl_2	**3**	90
Bu_3P (0.1)	3	1.05	CH_2Cl_2	**3**	89
Bu_3P (0.1)	3	3.0	benzene[d]	**3**	88
Bu_3P (0.1)	3	3.0	dioxane[d]	**3**	74
Bu_3P (0.1)	3	3.0	acetonitrile[d]	**3**	90

[a] The reactions were carried out at room temperature. [**1**-H•PF_6] = 0.5 mol/L. [b] In the presence of 1.5 equivalent of triethylamine. [c] Determined by ^{1}H-NMR spectra of crude product. [d] Heterogeneous.

Acylation of the pseudorotaxane [DB24C8•**1**-H][PF_6] by 3,5-dimethylbenzoic anhydride (**3**) or 3,5-dimethylbenzoyl chloride[8] (**4**) was examined in the absence or the presence of catalysts (Scheme 1). [2]Rotaxane **2**-H•PF_6 was isolated from the reaction mixture by preparative gel permeation chromatography. The rotaxane structure was confirmed by several means including ^{1}H-NMR, FAB-MS, and IR spectra. ^{1}H-NMR signals of **2**-H•PF_6 correspond well to those of [DB24C8•**1**-H][PF_6], except for the benzyl ester protons. Further, **2**-H•PF_6 survived several repetition of chromatographic operation, indicating that the dimethylphenyl stopper is large enough to ensure interlocking.

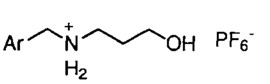
The results of the acylative end-capping are summarized in Table 1. No reaction occurred without catalyst. Although the triethylamine/4-dimethylaminopyridine (DMAP) couple has been frequently used as an activator and a catalyst for acylation, **2**-H•PF$_6$ was obtained in a low yield, probably because triethylamine disturbed hydrogen-bonding. Trimethylsilyl triflate did not work at all.[5c] Tributylphosphine was a very effective catalyst, affording a 90% yield of **2**-H•PF$_6$ when it was used with anhydride **3**.[5b] This yield is unusually high for the preparation of a [2]rotaxane.[6] The less basic phosphine did not disturb the hydrogen-bonding between the ammonium salt and the crown ether.[5a] Being different from the normal acylation system, the acid chloride was less effective than acid anhydride since the basicity of the leaving group played an important role. Little solvent effect was observed in this end-capping reaction (Table 1). It was surprising that the use of highly polar solvent such as acetonitrile did not decrease the yield of **2**-H•PF$_6$ in spite that the hydrogen-bonding interaction must be weakened in polar solvents. Although the system was heterogeneous when benzene, dioxane, or acetonitrile was used as the solvent, **2**-H•PF$_6$ was obtained in high yield in any case. Decrease of the amount of DB24C8 from 3.0 to 1.05 equivalent did not influence the yield of **2**-H•PF$_6$ (from 90 to 89%). The high yield synthesis of **2**-H•PF$_6$ (90%) should be attributed to the combination of large K_a of pseudorotaxane formation, excellent catalytic activity and the low basicity of tributylphosphine.

This rotaxane synthesis could be simply carried out on a large scale without any difficulty. Starting from 2.4 g (5.2 mmol) of DB24C8 and 2.0 g (5.0 mmol) of **1**-H•PF$_6$, 3.5 g (81%) of pure **2**-H•PF$_6$ was obtained after recrystallization from ethyl acetate.[9] It is noteworthy that **2**-H•PF$_6$ can be prepared from readily available chemicals without any column chromatography.

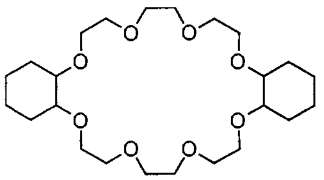
Successful syntheses of various [2]rotaxanes (Table 2) confirmed the generality and versatility of the present method.

Table 2. Synthesis of [2]rotaxanes[a]

$(^tBuCO)_2O$ **5**



6-H•PF$_6$: Ar = 3,5-dimethylphenyl
7-H•PF$_6$: Ar = 9-anthryl



DC24C8

Axle	Rotor	Stopper	Yield[b]/%
1-H•PF$_6$	DB24C8	**3**	90
1-H•PF$_6$	DB24C8	**5**[c]	85
1-H•PF$_6$	DC24C8	**3**	88
6-H•PF$_6$	DB24C8	**3**	78
7-H•PF$_6$	DB24C8	**3**	82

[a] The reactions were carried out at room temperature in CH_2Cl_2 (0.5 mol/L) for 3 h in the presence of 3 equiv. of DB24C8 and 0.1 equiv. of Bu_3P. [b] After isolation by preparative GPC (eluent: $CHCl_3$). Every rotaxane showed satisfactory NMR, IR, FAB-MS, and elemental analysis data. [c] Reaction was carried out for 24 h.

The dibenzylammonium structure was not essential for the high yield. Dicyclohexano-24-crown-8 (DC24C8) can be used without a severe decrease of the yield of rotaxane, indicating that the π-π interaction is not essential for the preparation of the (pseudo)rotaxane because the hydrogen-bonding interaction is much stronger than the π-π interaction. Aliphatic carboxylic acid anhydride is also applicable for the present acylative end-capping, although the reaction is slow with bulky pivalic anhydride.

Thus, the high yield synthesis of [2]rotaxanes by tributylphosphine-catalyzed acylation with acid anhydrides was demonstrated as a general and extremely effective method to prepare [2]rotaxanes consisting of ammonium salts and crown ethers. Since the preparation of this type of axle is quite easy, synthesis of various functionalized rotaxanes by the present method is under active investigation.

References and Notes

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7 K_a was too large to estimate adequately by ^{1}H-NMR spectra.

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9 Typical procedure: To a solution of **1**-H•PF$_6$ (2.0 g, 5.0 mmol) and DB24C8 (2.4 g, 5.2 mmol) in dichloromethane (7 mL) was added **3** (2.1 g, 7.5 mmol) and then tributylphosphine (125 μL, 0.5 mmol). After 3 h, water (25 mL) was added. The reaction mixture was stirred for 1 h, washed with 5% aqueous sodium hydrogencarbonate solution followed by saturated aqueous ammonium hexafluorophosphate solution, dried with anhydrous magnesium sulfate, and evaporated. The crude product was dissolved in a small amount of dichloromethane, and was poured into a large amount of hexane to give crude **2**-H•PF$_6$ as a white precipitate, which was then recrystallized from ethyl acetate to give 3.5 g (81%) of pure **2**-H•PF$_6$ as white crystals. mp 152-153 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (br, 2H), 7.57 (br, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.20 (br, 1H), 6.90-6.75 (m, 11H), 5.26 (s, 2H), 4.65-4.62 (m, 2H), 4.48-4.45 (m, 2H), 4.10 (d, J = 4.2 Hz, 8H), 3.77 (d, J = 4.2Hz, 8H), 3.47 (s, 8H), 2.36 (s, 6H), 2.15 (s, 6H) ppm; IR (neat): 1714 (C=O), 841 (P-F), 557 (P-F) cm^{-1}; FAB-MS (*m*-NBA): *m/z* 836.7 [M^+-PF_6], 388.1 [M^+-PF_6-DB24C8]; Found: C 61.10; H 6.55; N 1.38%. Calcd for $C_{50}H_{62}F_6NO_{10}P$: C 61.16; H 6.36; N 1.43%.