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Synthesis and Molecular Shuttling of [2]Rotaxanes under Mild Conditions

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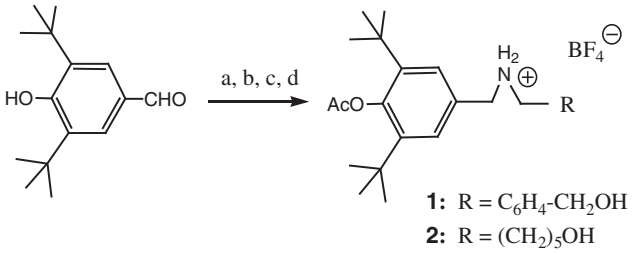
[2]Rotaxanes constructed with an ethereal end-capped axle and a dibenzo-24-crown-8 wheel were synthesized from pseudorotaxanes bearing an alcoholic terminus and diaryldiazomethanes using diphenyl phosphate as a catalyst. The reaction proceeded at room temperature in nonpolar solvents within several hours. The [2]rotaxanes thus obtained behaved as ammonium salts derived from a very strong base such as DBU. Thus, the amine form of the [2]rotaxane reacted with a weak acid, CO_2–H_2O, to give a hydrogencarbonate salt of the [2]rotaxane, which turned back to the amine form after drying followed by evacuation.

Rotaxanes, supramolecules consisting of interlocked dumbbell-shaped and macrocyclic molecules, are examples of molecular machines, in which mechanical motion can be driven photochemically, electrochemically, or chemically (through pH, solvents, and ions).[1] Hence, rotaxanes are expected to act as molecular devices with synchronous shuttling motions. Several approaches have been adopted for the synthesis of rotaxanes from loosely interlocked pseudorotaxanes. Shrinking or clipping the macrocycles and end-capping the axes of pseudorotaxanes are popular synthetic methods.[2] Among these options, the end-capping procedure[3] has the most extensive applicability and has therefore been developed using various types of terminal functional group in the axle molecules. For rotaxanes containing labile functional groups, a possible requirement for advanced functionality, synthesis and molecular shuttling must be performed under mild conditions. Several end-capping methods fulfill such a synthetic demand, including ester formation using 3,5-dimethylbenzoic anhydride–trialkylphosphine,[3a] and oxazole formation using isocyanates.[3b] Further efficient end-capping methods for [2]rotaxanes are still required to expand the synthetic versatility of this technique.

Here, we report the synthesis of [2]rotaxanes by end-capping of pseudo-[2]rotaxanes with an alcoholic terminus using diaryldiazomethane (DDM) with diphenyl phosphate as a catalyst under mild conditions. The resulting [2]rotaxanes with an ether linkage are expected to be tolerant of various agents. We furthermore propose a method for molecular shuttling under mild and green conditions using CO_2–H_2O, which enable use of labile and functional rotaxanes.

Etherification of pseudorotaxanes bearing an alcoholic terminus was performed as a first step using a stoichiometric amount of diphenyl diarylmethyl phosphate (DDP), which is known to be a good alkylating reagent for alcohols.[4] The diarylmethyl group was expected to have sufficient bulk to act as an effective end-cap for rotaxanes constructed with 24-crown-8 rings. DDPs were prepared from DDMs and diphenyl phosphate (DP). As axle molecules, we prepared two secondary ammonium salts bearing benzylic or aliphatic alcohols **1** or **2** as the termini (Scheme 1).



Scheme 1. Synthesis of axle molecules **1** and **2**. a) Ac_2O, cat. H_2SO_4, rt, 2 h (96%), b) RCH_2NH_2, MS-4 Å, $CHCl_3$, rt, 5 h (96%), c) 1.2 equiv $NaBH_4$, MeOH–EtOH, 5 °C, 3 h (90%), d) 1.1 equiv HBF_4, 0 °C, 5 min, ether (100%).

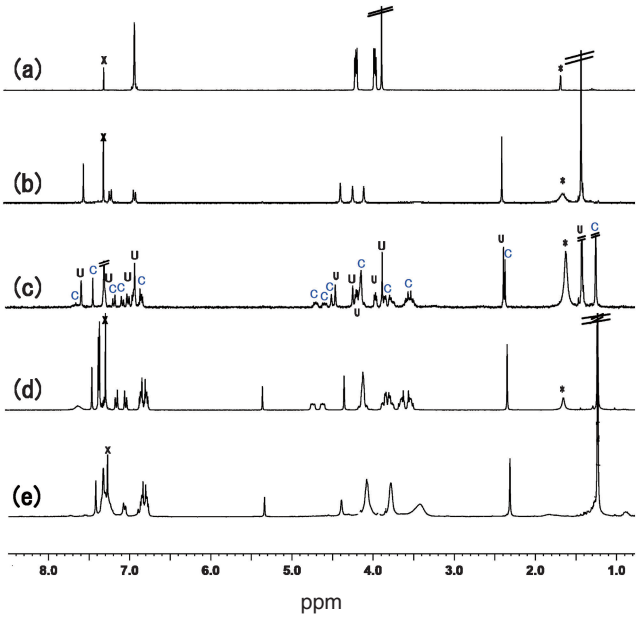
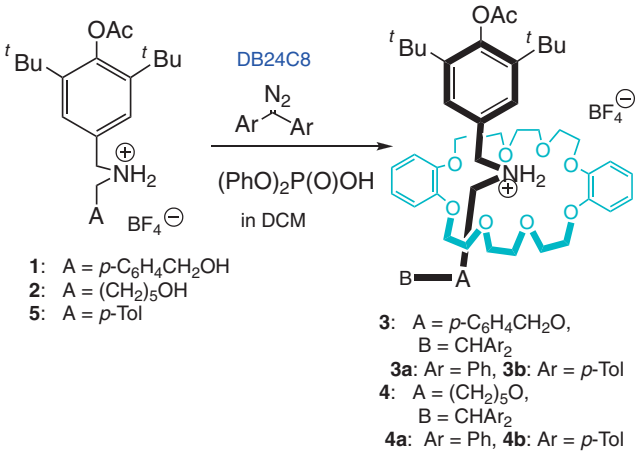


Figure 1. ^{1}H NMR spectra for [2]rotaxane **3a** and related molecules ($CDCl_3$, rt; δ). (a) DB24C8, (b) axle molecule **1**, (c) a mixture of DB24C8 and **1** (ca. 1:1), (d) rotaxane **3a**, and (e) **6a**. Symbols x, ∗, u, and c denote peaks from $CHCl_3$, water, uncomplexed components, and pseudo-[2]rotaxane, respectively. Peaks appeared around 4.6–4.7 ppm in (c) are characteristic for the formation of pseudorotaxane.

Although ammonium salt **1**[BF_4^-] is not particularly soluble in dichloromethane (DCM) or chloroform, addition of dibenzo-24-crown-8-ether (DB24C8) gives a pseudo-[2]rotaxane, which is soluble in both of these solvents. As shown in Figure 1, the equilibrium of association of pseudo-[2]rotaxane leans toward association ($K_a = 300\ M^{-1}$).[5,6]



Scheme 2. Synthesis of [2]rotaxanes **3** and **4**.

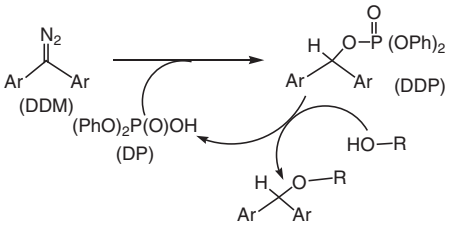
Table 1. Synthesis of rotaxanes **3** and **4** produced via Scheme 2[7]

Run	Axle	DB24C8 /equiv	DDM[a] /equiv	DP /equiv	Time /h	Product yield[b]/%
1	**1**	1.1	2.0 PD	2.0	2.5	**3a**, 63 (54)[c]
2	**1**	1.1	2.0 PD	0.1	2.5	**3a**, 67 (55)
3	**1**	2.0	2.0 PD	0.1	5	**3a**, 78
4	**1**	3.0	2.0 PD	0.1	5	**3a**, 82
5	**1**	2.7	2.0 PD	0.5	4 d[d]	**3a**, 82
6	**1**	1.1	2.0 PD	0.0	5	**3a**, 66
7	**1**	1.1	2.0 TD	0.1	0.5	**3b**, 57 (29)
8	**2**	1.1	2.0 PD	0.1	23	**4a**, 66 (51)
9	**2**	1.1	2.0 PD	0.0	23	**4a**, 65
10	**2**	1.1	2.0 PD	2.0	4	**4a**, 65
11	**2**	1.1	2.0 TD	0.1	1.2	**4b**, 44 (36)

[a]PD: diphenyldiazomethane, TD: di-*p*-tolyldiazomethane. [b]The yields were determined by NMR experiments in $CDCl_3$ using picryl chloride ($\delta = 8.8$) as an internal standard for integration. Isolated yields were shown in parenthesis. [c]Diphenyl diphenylmethyl phosphate reagent was used. [d]Reaction temperature: 2 °C.

A DCM solution of diphenyl diphenylmethyl phosphate (2 equiv) was added to a mixture of ammonium salt **1** (1 equiv) and DB24C8 (1.1 equiv) in DCM at room temperature in the absence of light. The deep yellow color that emerged from the phosphate agent disappeared within 5 h. The solvent was removed in vacuo, and the residue was subjected to silica gel chromatography. The fraction eluted with DCM contained rotaxane **3a** (Scheme 2). Further purification was performed with gel-permeation chromatography (GPC) by circulating elution of chloroform to give **3a** as a white crystalline solid in 54% yield (Run 1 in Table 1). The ESI mass spectrum of **3a** showed a peak at m/z 1012 (100%, $C_{62}H_{78}O_{11}N^+$), corresponding to the cationic portion of the [2]rotaxane.

Our end-capping agent DDP was found to be capable of alkylating pseudorotaxanes bearing an alcoholic terminus to give [2]rotaxanes and liberate DP, which in turn could react with DDM to rapidly restore DDP. Therefore, a mixture of 1 equiv of DDM and a catalytic amount of DP was sufficient for alkylation of pseudo-[2]rotaxane alcohols (Scheme 3).



Scheme 3.

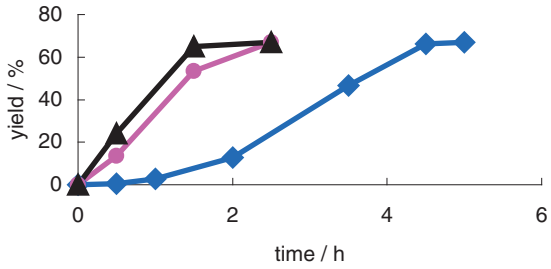


Figure 2. NMR yields of [2]rotaxane **3a** vs. reaction time with (0.1 equiv: ●; 1.0 equiv: ▲) and without (◆) diphenylphosphate (1.1 equiv DB24C8, 2.0 equiv diphenyldiazomethane, rt, in $CDCl_3$).

Thus, the catalytic use of DP was effective in the synthesis of **1a** without deterioration of the yield, as shown in Table 1 (Run 2), and Figure 2. Prior preparation of a moisture-sensitive DDP agent is not necessary. The addition of 0.1 equiv of DP to a mixture of ammonium salt, crown ether, and DDM in DCM at room temperature in dark conditions gave [2]rotaxanes in good yields. Increasing the amount of DB24C8 (1.1, 2.0, and 3.0 equiv) gradually increased the yield of [2]rotaxane (67%, 78%, and 82%, respectively; Runs 2–4). The reaction was performed at a lower temperature (2 °C; Run 5) without decrease of yield; however, a longer reaction time was necessary (4 days). Interestingly, the etherification with DDM proceeded without the DP catalyst (Run 6, Figure 2), although it required a longer reaction time than the reaction using the catalyst.[8]

The use of di-*p*-tolyldiazomethane instead of diphenyldiazomethane as an end-capping agent for pseudo-[2]rotaxanes was also effective. Accordingly, **3b** was obtained from **1** in a yield of 57% (Run 7). The reaction of **1a** with di-*p*-tolyldiazomethane was more rapid than that with diphenyldiazomethane. In the case of ammonium salt **2**, which had a simple aliphatic alcohol at the end, the end-capping reaction proceeded more slowly and with a slightly lower yield than for **1** (Table 1, Runs 8–11). The association constant for the pseudo-[2]rotaxane **2**–DB24C8 in $CDCl_3$ ($200\ M^{-1}$)[5,6] was lower than that for **1**–DB24C8.

The ethereal end-cap in rotaxanes **3** and **4** showed tolerance of various reagents. For example, **3a** survived under the following conditions: 3 M HCl in CH_3OH–H_2O, 50 °C, 5 h; 1 M KOH in CH_3OH–H_2O, 50 °C, 10 h.

At the next step, we examined the basicity of **3a** in order to determine the appropriate acids and bases for molecular shuttling. Using the linear dependences of chemical shifts for NCH_2 in ^1H NMR spectra vs. the amine/ammonium ratio, several NMR experiments in CD_3CN were performed by mixing a pK_a-unknown ammonium salt with amines of known pK_a.

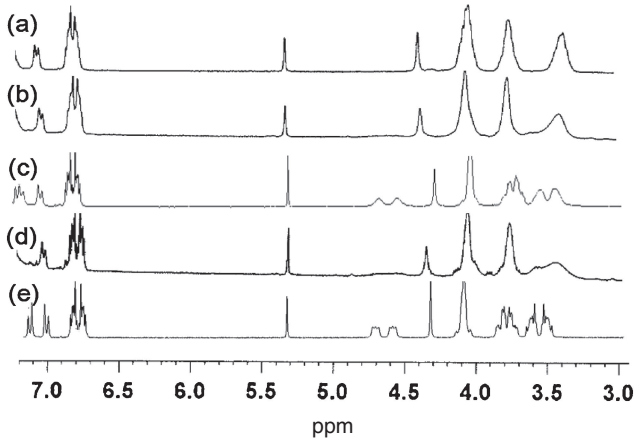
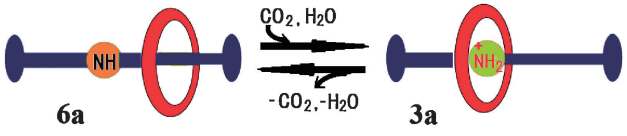


Figure 3. ^{1}H NMR spectra. To the rotaxane **6a** in $CDCl_3$ (a) was added CO_2 gas by bubbling for 2 min (b). No changes observed until the addition of one drop of water and CO_2 gas was again passed through the solution for 1 min to give the ammonium salt (c). The ammonium salt was converted to amine **6a** when the solution was dried with Na_2SO_4 and slightly evacuated with an aspirator for 1 min (d). As a reference, **3a** $[BF_4]$ is shown in (e).

Thus, the pK_{aH} of *N*-*p*-tolylmethyl-(4-acetoxy-3,5-di-*tert*-butylphenyl)methylammonium **5**[BF_4^-], a model for a free axle molecule **1**, was estimated to be 0.3 + pK_{aH} of dibenzylamine (pK_{aH} = 8.52 in H_2O) in CD_3CN, which is normal as a secondary amine. However, the pK_{aH} of [2]rotaxane **3a** was estimated to be 0.6 + pK_{aH} of DBU (pK_{aH} = 12 in H_2O, 24.34 in CH_3CN)[9] in CD_3CN. This can be attributed to the strong N^+–H–O (crown ether) interaction in the rotaxanes, which prevents **3a** from releasing a proton and weakens the acidity by a factor of about 10^4 compared with the free axle molecule **1**. A free rotaxane–amine **6a**[10] was obtained when a benzene solution of **3a** was treated with an aqueous solution of KOH at room temperature. The ^{1}H NMR spectrum of **6a** did not have the characteristic NCH_2 signals that appeared at around 4.7 ppm for **3a** (Figure 1e).

For molecular shuttling of [2]rotaxanes, strong acids such as CF_3CO_2H are usually adopted to convert the amine form into the ammonium form.[1,2,11] However, our finding indicates that the conversion from the [2]rotaxane–amine to the ammonium salt can be done with weak acids such as carbonic acid (pK_a = 6.4). In fact, when CO_2 gas was bubbled into a wet $CDCl_3$ solution of [2]rotaxane–amine **6a**, ammonium salt **3a** [X = $HOCO_2^-$] was obtained (Figure 3). The [2]rotaxane hydrogencarbonate salt **3a** [X = $HOCO_2^-$] transformed again into the amine form by evacuation or by bubbling of Ar gas into the dry solution (Figure 3d). Thus, the molecular shuttling of [2]rotaxanes was performed for the first time under mild conditions that are desired for the handling of labile and functional [2]rotaxanes (Scheme 4).

In summary, our procedure for end-capping of a pseudo-[2]rotaxanes can be carried out without the use of bases, inorganic salts, polar solvents, or heat. The ethereal end-capped product is tolerant of various reagents, which expands the synthetic potential of this route. A convenient and mild method for molecular shuttling in [2]rotaxanes was also demonstrated.



Scheme 4.

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