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Template Synthesis of [2]Rotaxanes with Large Ring Components and Tris(biphenyl)methyl Group as the Blocking Group. The Relationship between the Ring Size and the Stability of the Rotaxanes

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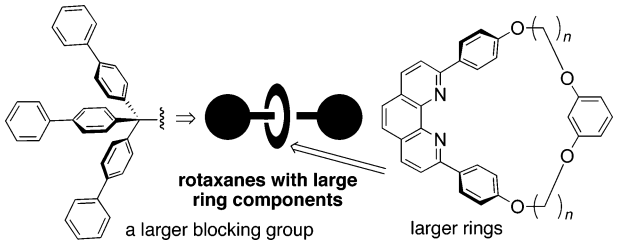

We synthesized a series of macrocyclic phenanthrolines **3a**−**e** and a tris(biphenyl)methyl derivative **4**. [2]Rotaxanes with large ring components (**10a**,**b**) were synthesized by the template method, and the stability of the rotaxanes was examined. The study revealed that the tris(biphenyl)methyl group is an effective blocking group for the rotaxanes with up to a 33-membered ring. Even a rotaxane with a 37-membered macrocyclic phenanthroline (**10b**) could be isolated. The dissociation of **10b** occurred at 60 °C.

[2]Rotaxane is an important class of mechanically interlocked molecules, which is composed of a ring component and an axle component. A number of methodologies have been reported for the efficient synthesis of rotaxanes.[1] Among them, the template method utilizing the transition metal−ligand bond, which was developed in the 1980s,[2] has been widely used.

To prevent the dissociation of a [2]rotaxane, it is necessary to use a sufficiently large blocking group compared to the size of the ring. The stability of [2]rotaxanes with various blocking groups has been studied. Triphenylmethyl group was the blocking group which was used for the synthesis of a rotaxane with a C30 macrocycle.[3] It was observed that the triphenylmethyl group did not pass through a C29 macrocycle at rt, but the dissociation occurred at 120−130 °C.[4−6] When the blocking group was changed to a bis(cyclohexyl)methyl group, a [2]rotaxane with a C28 macrocycle was isolated as a stable compound.[6] When a tris(4-*tert*-butylphenyl)methyl group was introduced as the blocking group, the rotaxane with an up to 33-membered cyclic olefin turned out to be stable.[6] 1,3,5-Tris(*p*-tolyl)phenyl group was used as the blocking group for the "directed" synthesis of a rotaxane with a 26-membered macrocycle.[7] The stability and kinetics of the deslipping reactions of amide rotaxanes[8] and polyether rotaxanes[9] have been studied in depth.

Our recent interest in the chemistry of rotaxanes prompted us to study the synthesis of a rotaxane which has a larger ring component and a larger blocking group by the template method. Though some large blocking groups, such as fullerenes,[10] porphyrins,[11] calixarenes,[12] and dendrimers,[8b,13] have been utilized for the synthesis of the rotaxanes, the chemical stability and/or the availability of these blocking groups would be rather limited. We designed and synthesized a series of 33−53-membered macrocyclic phenanthrolines and a larger stopper (tris(biphenyl)-methyl group) which would be a very stable, large, and versatile blocking group. Herein we report the synthesis and stability of the rotaxanes prepared by the reactions of these components.

Polyether macrocyclic phenanthrolines are widely used components for the template synthesis of rotaxanes.[1] We prepared a variety of macrocyclic phenanthrolines **3** from 2,9-bis(4-hydroxyphenyl)-1,10-phenanthroline **1**[14] and various di-

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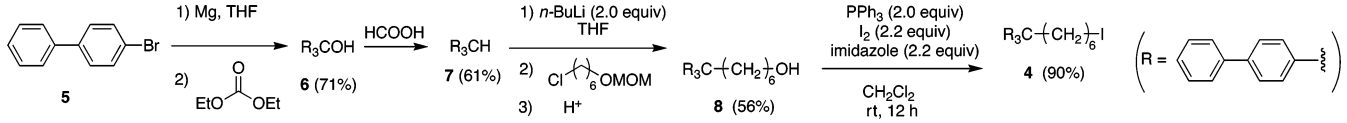
SCHEME 1



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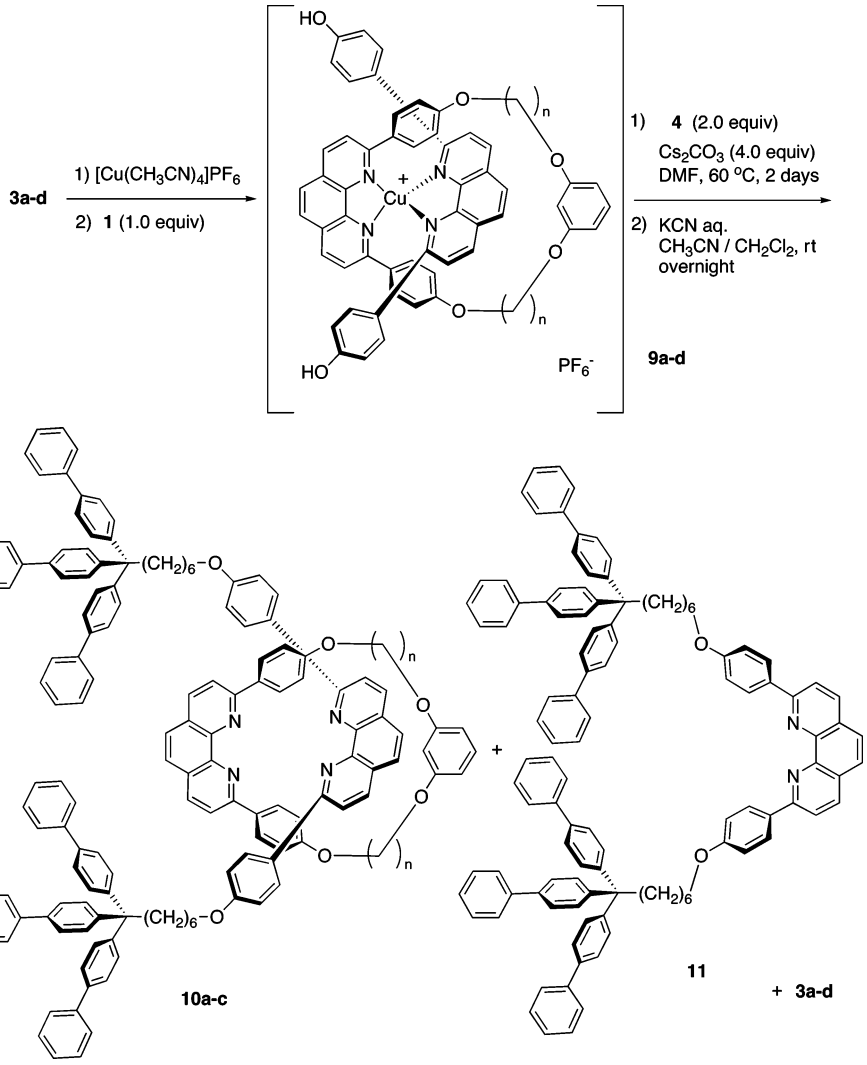
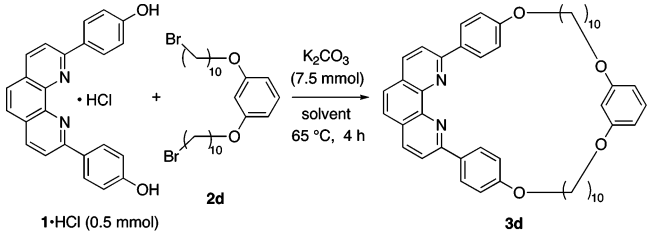


TABLE 1. Examination of the Reaction Conditions for the Macrocyclization of 1 with 2



entry	solvent	concn of **1** (mM)	**2d** (equiv)	yield (%)
1	anhydrous DMSO	20	1.5	5
2	anhydrous DMSO	5	1.5	34
3	anhydrous DMSO	5	1	38[a]
4	99% DMSO−1% H_2O	5	1	43
5	95% DMSO−5% H_2O	5	1	42
6[b]	99% DMSO−1% H_2O	5	1	37

[a] The yield was not reproducible (see text). [b] $CsCO_3$ was used as the base.

bromides derived from resorcinol. We expected that the *meta*-substituted structure would stabilize the cyclic conformation, preventing the "shrinking (narrowing of the cavity)" of the ring.[15] We selected the reaction of **1** with **2d** as the model reaction and examined the optimum condition for the macrocyclization. The results are summarized in Table 1. On the basis of previous studies,[16] we chose anhydrous DMSO as the solvent and carried out the reaction in the presence of an excess of K_2CO_3 and 1.5 equiv of the dibromide **2d** ($n = 10$). When the concentration of **1** was 30 mM, the yield of **3d** was very low, and a large amount of oligomeric products were isolated (entry 1). On the other hand, the yield of **3d** increased to 34% when the reaction was carried out under highly diluted conditions (entry 2). Though 1 equiv of **2d** was sufficient for this reaction, we noticed that the yield of **3** was not reproducible when anhydrous DMSO was used as the solvent (entry 3). Further examination of the reaction conditions revealed that **3** was isolated in a higher and reproducible yield in comparison to

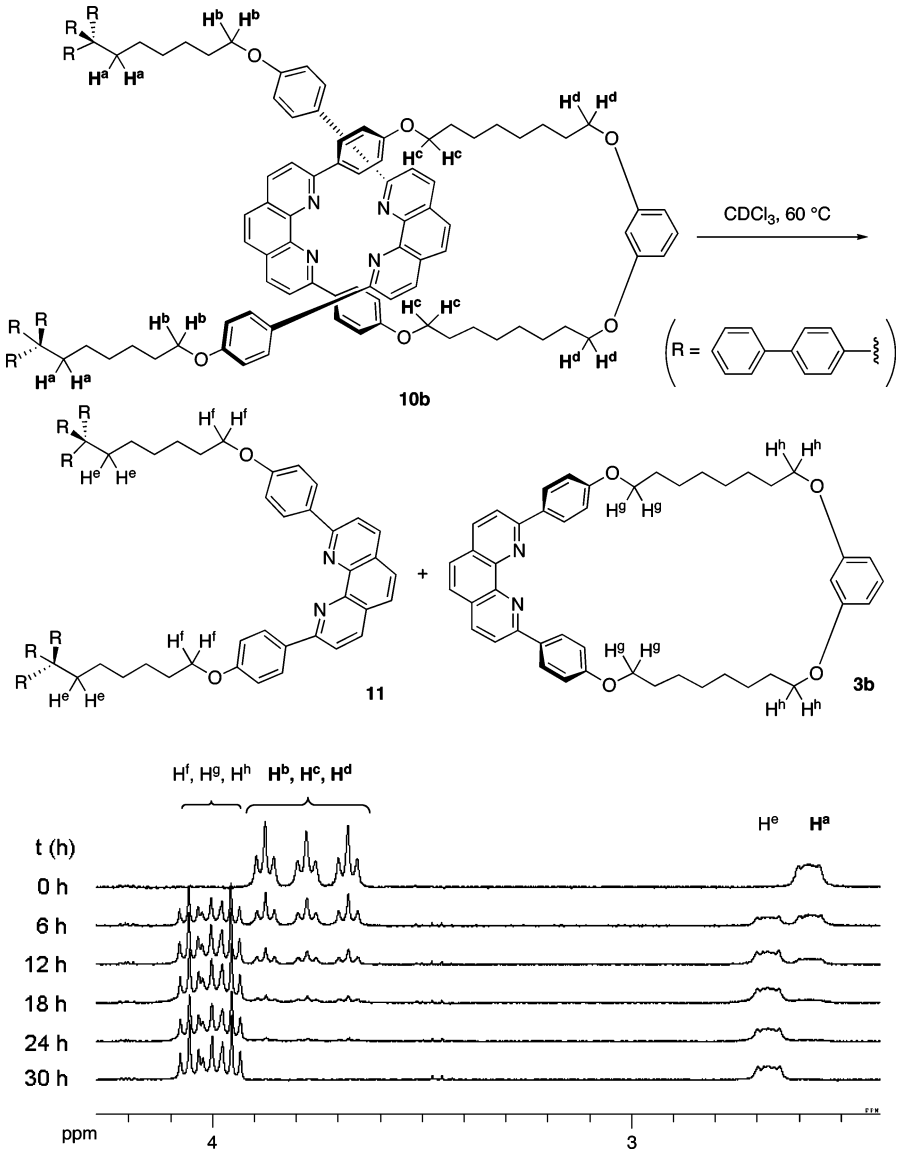
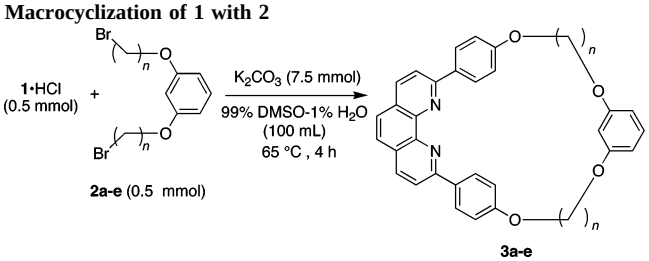


FIGURE 1. Dissociation of **10b** monitored by ^{1}H NMR at 60 °C in $CDCl_3$.

TABLE 2. Examination of the Reaction Conditions for the Macrocyclization of 1 with 2



entry	*n*	product	yield (%)
1	6	**3a**	41
2	8	**3b**	42
3	10	**3c**	43
4	12	**3d**	26
5	16	**3e**	37

the result shown in entry 3 by the addition of a small amount of water to the reaction mixture (entry 4). The addition of a larger amount of water had little effect on the yield (entry 5). We assume that the higher solubility of the potassium salt of **1** in a DMSO/water mixture has accelerated the reaction. Though we carried out this reaction in the presence of $CsCO_3$ instead of K_2CO_3, the yield of **3d** did not improve (entry 6).

TABLE 3. Synthesis of Rotaxanes 10 from 3

entry	**3**	ring size	yield of **10** (%)	yield of **11** (%)	recovery of **3** (%)
1	**3a**	33	62 (**10a**)	17	27
2	**3b**	37	34 (**10b**)[a]	45	63
3	**3c**	41	0	62	100
4	**3d**	45	0	69	72

[a] Slow dissociation (deslipping) was observed (see text).

We used this optimized condition for the synthesis of a series of macrocyclic phenanthrolines (**3**), and the results are summarized in Table 2. The effect of the ring size on the yield of **3** was small when the alkyl chain was shorter ($n = 6-10$, entries 1−3), and compounds **3a**−**c** were isolated in ca. 40% yields. On the other hand, the yields of larger macrocyclic phenanthrolines slightly decreased (entries 4 and 5).

We selected a tris(biphenyl)methyl group as a large and stable blocking group, and the synthesis of **4** is summarized in Scheme

1. Thus, tris(biphenyl)carbinol (**6**)[17] was prepared by the reaction of the Grignard reagent prepared from **5** and diethyl carbonate. The procedure[18] reported for the synthesis of triarylmethyl derivatives was followed, and the alcohol **6** was subjected to reduction by formic acid to yield **7**[19] in 61% yield. Compound **7** was further converted to alcohol **8**. Iodination[20] of **8** gave **4** in 90% yield.

To estimate the size of the tris(biphenyl)methyl group, we chose the template method[21] for the synthesis of rotaxanes and examined the relationship between the size of **3** with the yield of the rotaxane **10**. The syntheses of the rotaxanes **10a**,**b** are shown in Scheme 2. Thus, macrocycle **3** and bis(hydroxyphenyl)phenanthroline **1** were reacted with a Cu(I) salt, and the macrocyclic Cu(I) complex **9** was prepared in situ.[22] Compound **9** was reacted with **4** in the presence of Cs_2CO_3, the Cu(I) ion was removed, and the products were isolated. The results are summarized in Table 3.

When the reaction was carried out with **3a** (33-membered ring), the corresponding rotaxane **10a** was isolated in 62% yield, along with a small amount of **11**[23] and the recovered macrocyclic phenanthroline **3** (entry 1). The result indicates that the tris(biphenyl)-methyl group is large enough to prevent the deslipping reaction (dissociation of **10a** into **11** and **3a**). Though the reaction of a larger phenanthroline (**3b**, 37-membered ring) also proceeded, the yield of **10b** was much lower (34%, entry 2). The corresponding rotaxane was not isolated when **3c** (41-membered ring) or **3d** (45-membered ring) was chosen as the cyclic component.[24]

To understand the observed lower yield of **10b**, we further examined the stability of **10b** and found that the dissociation of **10b** occurred at 60 °C. Compound **10b** was dissolved in $CDCl_3$, and the dissociation was monitored by heating the solution at 60 °C. The time course of the dissociation (deslipping) is shown in Figure 1. The kinetics of the deslipping reaction was analyzed at 70−90 °C, and the rate constants and thermodynamic parameters were calculated as follows: $\Delta G^{\ddagger}(353\ \mathrm{K}) = 116$ kJ/mol, $\Delta H^{\ddagger} = 65.0$ kJ/mol, $\Delta S^{\ddagger} = -144$ J/mol.[25] The very high entropic contribution would reflect the rigid structure of the blocking group and the requirement of the particular conformation of **10b** for the progress of the reaction.[8c] The lower yield of **10b** (Table 3, entry 2) would be explained in terms of the partial dissociation of **10b** during the work up and/or purification.[23,26] On the other hand, no dissociation of **10a** was observed when a solution of **10a** in $CDCl_3$ was heated at 60 °C for 30 h. From these results, it is clear that the tris(biphenyl)methyl group would be large enough for the formation of **10a**. On the other hand, the stability of **10b** is rather limited at rt, and the tris(biphenyl)methyl group slowly passes through the 37-membered ring formed by **3b** at elevated temperature (60 °C).

In summary, we synthesized a series of cyclic phenanthrolines **3a**−**e** and a tris(biphenyl)methyl derivative **4**. Larger rotaxanes **10a**,**b** were synthesized by the template method, and the stability of the rotaxanes was examined. The study revealed the size of the tris(biphenyl)methyl group, which is an effective blocking group for the rotaxanes with up to a 33-membered ring. We also succeeded in the synthesis and isolation of a larger rotaxane with a 37-membered ring which dissociated at elevated temperature. The synthesis of larger blocking groups, which would be suitable for the synthesis of much larger rotaxanes, is ongoing.

Experimental Section

A Representative Procedure for the Synthesis of Rotaxanes. Synthesis of 10a. To a solution of $Cu(CH_3CN)_4PF_6$ (37 mg, 0.1 mmol) in dry CH_2Cl_2 (5 mL) was added **3a** (0.1 mmol) at rt. After 5 min, the solution was added to a suspension of **1** (36 mg, 0.1 mmol) in dry CH_3CN (5 mL), and the mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure, and to the residue were added iodide **4** (127 mg, 0.2 mmol), dry DMF (2 mL), and Cs_2CO_3 (130 mg, 0.4 mmol). The reaction mixture was kept stirring at 60 °C for 2 days, and the solvent was removed in vacuo. To the residue were added CH_3CN (10 mL), CH_2Cl_2 (5 mL), H_2O (5 mL), and KCN (33 mg, 0.5 mmol). The mixture was stirred at rt for 14 h. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography using hexane/CH_2Cl_2 (1/1, v/v) as the eluent to give **10a** (131 mg, 62%) and **11**[25] (25 mg, 17%). Compound **3a**[25] was also recovered (17 mg, 27%). Compound **10a**: colorless amorphous, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 10.5 Hz, 4H), 8.38 (d, J = 8.38 Hz, 4H), 8.16 (d, J = 9.0 Hz, 2H), 8.12 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz), 7.55 (d, J = 7.2 Hz, 12H), 7.48 (d, J = 8.4 Hz, 12H), 7.40−7.24 (m, 30H), 7.11 (t, J = 8.1 Hz, 1H), 7.04 (d, J = 8.7 Hz, 4H), 6.91 (s, 1H), 6.47 (d, J = 8.1 Hz, 2H), 3.97−3.81 (m, 8H), 3.74 (t, J = 7.2 Hz, 4H), 2.67−2.52 (m, 4H), 1.79−1.56 (m, 12H), 1.50−1.09 (m, 20H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4, 160.4, 160.2, 156.4, 156.2, 146.5, 146.1, 145.9, 140.5, 138.4, 136.6, 132.0, 131.8, 129.8, 129.6, 128.9, 128.6, 127.4, 127.0, 126.9, 126.4, 125.5, 125.4, 119.3, 114.7, 114.6, 106.8, 101.4, 67.9, 67.7, 56.0, 40.3, 30.3, 29.5, 29.0, 26.1, 25.9, 25.8, 25.6; IR (KBr) 2938, 2870, 2363, 1604, 1586, 1491, 1473, 1288, 1252, 1179, 1151, 1020, 835 cm^{-1}. Anal. Calcd for $C_{152}H_{134}N_4O_6$: C, 86.41; H, 6.39; N, 2.65. Found: C, 86.39; H, 6.49; N, 2.63.

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Supporting Information Available: Detailed experimental procedures and spectral data of **2e**, **3a**−**e**, **4**, **8**, **9a**, **10a**,**b**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The rigid phenanthroline moiety prevents the alkyl groups of the ring component to come closer, so that the cavity of the macrocycle would not become narrow. We expected a similar effect by introducing the resorcinol moiety.

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(22) Though we confirmed the formation of **9** by the NMR analysis of the crude mixture, we could not isolate **9** in pure form. See Supporting Information for the NMR spectra of **9a**.

(23) The formation of **11** might occur if the conformation of **9** was not suitable for the formation of the rotaxane when the C−O bond forming reaction proceeded. Incomplete formation of **9** might also result in the formation of **11**.

(24) Attempted detection of the rotaxane in the crude mixture by GPC or NMR analysis failed. Since the formation of the rotaxane from **9e** was less likely, the reaction was not carried out.

(25) See Supporting Information.

(26) The calculated $t_{1/2}$ for the reaction of **10b** at 27 °C was ca. 200 h. Considering the time required for the decomplexation and purification, we assume that the partial dissociation took place. In solid state, **10b** could be stored in a freezer (−20 °C) for a couple of months without dissociation.