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Facile Synthesis of Rotaxanes through Condensation Reactions of DCC-[2]Rotaxanes

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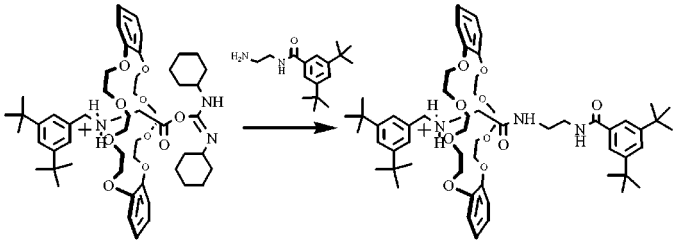
ABSTRACT



In this Letter, we present an easy method for the synthesis of rotaxanes using a novel DCC-[2]rotaxane. The DCC-[2]rotaxane is composed of dibenzo-24-crown-8 ether, an amino acid tether, and di-*tert*-butyl phenyl rings as blocking groups. It is relatively stable and can be purified by column chromatography. A series of model rotaxanes were obtained in good yields by condensing the DCC-[2]rotaxanes with *N*-(2-aminoethyl)-3,5-di-*tert*-butylbenzylamide in acetonitrile and chloroform.

Rotaxanes have progressed from a molecular oddity to a promising new class of nanoscale devices such as molecular shuttles and motors.[1] They can be formed by sliding a ring onto a tether followed by the attachment of large molecules (blocking groups) onto the ends of the tether, which prevent the ring from slipping off. Template-driven rotaxane formation has provided higher yields of rotaxanes by overcoming the generally low yielding step of ring threading.[2] Some of these techniques take advantage of noncovalent interactions between electron-rich crown ethers and ammonium ions to enhance ring threading.[2e,f] Although our method relies on these interactions for threading as well, we use 1,3-dicyclohexylcarbodiimide (DCC) to lock the ring onto a capped-tether. DCC-rotaxanes have been combined with other primary amino blocking groups to give high yields of rotaxanes.[3] DCC-[2]rotaxane **3d** (Scheme 1) was purified by column chromatography and stored prior to being converted into a rotaxane. Thus, this approach will permit labs to have bottles of "instant rotaxanes". This procedure should prove to be general enough so that a wide range of compounds can be easily converted into rotaxanes.

The goals of this project were to demonstrate that noncovalent forces can drive rotaxane formation and to determine whether this threading method controls the yield of rotaxane. A series of rotaxanes were constructed that combined the commonly used crown ether as the ring, a tether containing an ammonium ion with 1−4 methylenes between it and a carboxylic acid, and di-*tert*-butyl phenyl rings as blocking groups.[4] All capped-tethers **1a**−**d** bound DB24C8 in CD_3CN to give pseudorotaxanes **2a**−**d** (Scheme

(1) (a) Ashton, P. R.; Ballardini, R.; Balzani, V.; Credi, A.; Dress, K. R.; Ishow, E.; Kleverlaan, C. J.; Kocian, O.; Preece, J. A.; Spencer, N.; Stoddart, J. F.; Venturi, M.; Wenger, S. *Chem.-Eur. J.* **2000**, *6*, 3558−3574. (b) Raehm, L.; Kern, J. M.; Sauvage, J. P. *Chem.-Eur. J.* **1999**, *5*, 3310−3317. (c) Armaroli, N.; Balzani, V.; Collin, J. P.; Gavina, P.; Sauvage, J. P.; Ventura, B. *J. Am. Chem. Soc.* **1999**, *121*, 4397−4408.

(2) (a) Jeppesen, J. O.; Perkins, J.; Becher, J.; Stoddart, J. F. *Org. Lett.* **2000**, *2*, 3547−3550. (b) Seel, C.; Vogtle, F. *Chem.-Eur. J.* **2000**, *6*, 21−24. (c) Shukla, R.; Deetz, M. J.; Smith, B. D. *Chem. Commun.* **2000**, 2397−2398. (d) Seel, C.; Parham, A. H.; Safarowsky, O.; Hubner, G. M.; Vogtle, F. *J. Org. Chem.* **1999**, *64*, 7236−7242. (e) Kawasaki, H.; Kihara, N.; Takata, T. *Chem. Lett.* **1999**, 1015−1016. (f) Kolchinski, A. G.; Alcock, N. W.; Roesner, R. A.; Busch, D. H. *Chem. Commun.* **1998**, 1437−1438. (f) Martinez-Diaz, M.-V.; Spencer, N.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1904−1907.

(3) We have used various primary amines to make rotaxanes, and these results will be provided in due course.

(4) Raymo, F. M.; Houk, K. N.; Stoddart, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 9318−9322.

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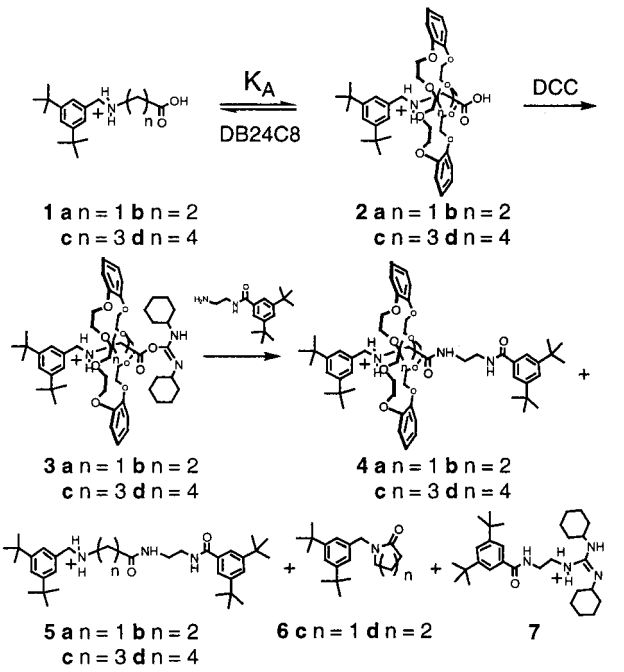
Scheme 1



1). The largest binding energies were observed in the longer capped-tethers (Table 1). It should be noted that a PF_6^- counterion for the ammonium ion was needed for rotaxane formation because it forms a relatively weak contact ion pair in organic solvents. Association constants for the capped-tethers **1a** and **1b** were derived by performing nonlinear least-squares analysis of plots that compare the changes in the chemical shifts of protons of the tethers that occur with increased concentration of DB24C8.[5] For the longer capped-tethers (**1c** and **1d**), the rate of the ring slipping off the tether was reduced enough to provide two sets of easily distinguished proton resonances for each tether (Figure 1B). One set of signals belonged to the pseudorotaxane and the other to the free tether, which provided the relative concentrations of these species. Association constants were determined by simply integrating these signals.[6] The association constants could be composite terms, containing K_As for pseudorotaxanes and various nonthreaded complexes. Indirect evidence for the observed K_As reflecting pseudorotaxane formation (K_A in Scheme 1) includes the fact that complexation between compound **5a** and DB24C8 was not observed in ^{1}H NMR titrations. Furthermore, there is only a small standard deviation in the K_As, which is consistent with a single dominant K_A for each pseudorotaxane.

Table 1. Association Constants for Threading of DB24C8 onto the Various Amino Acids at 298 K and Product Yields (Scheme 1)

c-t[a]	solvent	K_A [b]	**4** (**a**−**d**)	**5** (**a**−**d**)	**6** (**c**−**d**)	**7**
1a	CD_3CN	104	32%	16%	−	52%
	$CDCl_3$	N.M.[c]	30%	66%	−	4%
1b	CD_3CN	70	71%	21%	−	8%
	$CDCl_3$	N.M.	44%	42%	−	14%
1c	CD_3CN	220	22%	N.D.[d]	61%	17%
	$CDCl_3$	N.M.	27%	N.D.	38%	35%
1d	CD_3CN	250	20%	N.D.	46%	34%
	$CDCl_3$	N.M.	35%	N.D.	33%	32%

[a] c−t is capped-tether. [b] Error for **1a** and **1b** < 10%, **1c** and **1d** < 15%. [c] N.M. means association constants were not measured because of the low solubilities of capped-tethers **1a**−**d**. [d] N.D. means not detected.

More direct evidence for threading was obtained by simply synthesizing rotaxanes **4a**−**d** (Table 1). Although rotaxane formation verifies threading, these results do not preclude the existence of nonthreaded complexes. If the K_As do measure the concentration of **2a**−**d**, then the amount of rotaxane formed can be controlled by running the reactants at a known concentration. These studies require that conversion of pseudorotaxanes **2a**−**d** to rotaxanes **4a**−**d** is quantitative. Rotaxane reactions were run in CD_3CN at concentrations that could produce a maximum yield of 70% rotaxane, according to their association constants. Only in the reaction that produced rotaxane **4b** did the yield match the association constant for ring threading. This reaction was repeated several times, producing 50% to 70% of rotaxane. We conclude that the K_As show that the pseudorotaxanes are readily formed.

Rotaxane yields of less than 70% were probably the result of increased steric hindrance at the carboxylate caused by DCC, which hampers the addition of the blocking group. Using the smaller CDI activating group with capped-tethers **1b** and **1c**, however, produced only a very small amount of rotaxanes **4b** and **4c** (<10%), respectively. Most likely DB24C8 slips over the smaller imidazole ring. The reaction rate for the free capped-tether should be faster than the DB24C8-bound tether; thus byproducts **5b** and **6c** were the main products.

We were somewhat surprised that reactions using the longer capped-tethers (**1c** and **1d**), which should reduce the steric hindrance at the carboxylate, did not produce higher yields of rotaxanes. One possible explanation for the low yields of rotaxanes is that an intramolecular salt bridge exists between the carbonyl oxygen atom of the acid and the N-H of the ammonium ion of these tethers when they exist as the pseudorotaxanes **2c**−**d**. An H-bonded ring may force DB24C8 to reside close to the carboxylic moiety, thereby increasing the steric hindrance at this site and hampering acylisourea formation.

The other major products of the reactions were the expected blocked tethers **5a**,**b** or lactams **6c**,**d** and a single impurity that forms in all rotaxane reactions. This impurity must come from the blocking group because it is not observed in ^{1}H NMR spectra of various DCC-[2]rotaxanes. Mass and NMR spectral analyses showed that the impurity

(5) The following binding equation was used to calculate the association constants for capped-tethers **1a** and **1b**, $\Delta\delta = \Delta\delta_{obs} - \Delta\delta_0 = K_A[C]\,\Delta\delta_{max}/(1 + K_A[C])$, where the difference in the chemical shift ($\Delta\delta$) of a capped-tether proton in the presence of DB24C8 ($\Delta\delta_{obs}$) and in its absence ($\Delta\delta_0$) depends on the concentration of DB24C8 (C), the chemical shift of the proton when it is completely bound to DB24C8 ($\Delta\delta_{max}$), and the association constant of this complex (K_A).

(6) Stephen, J. L.; Wisner, J. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2838−2840.

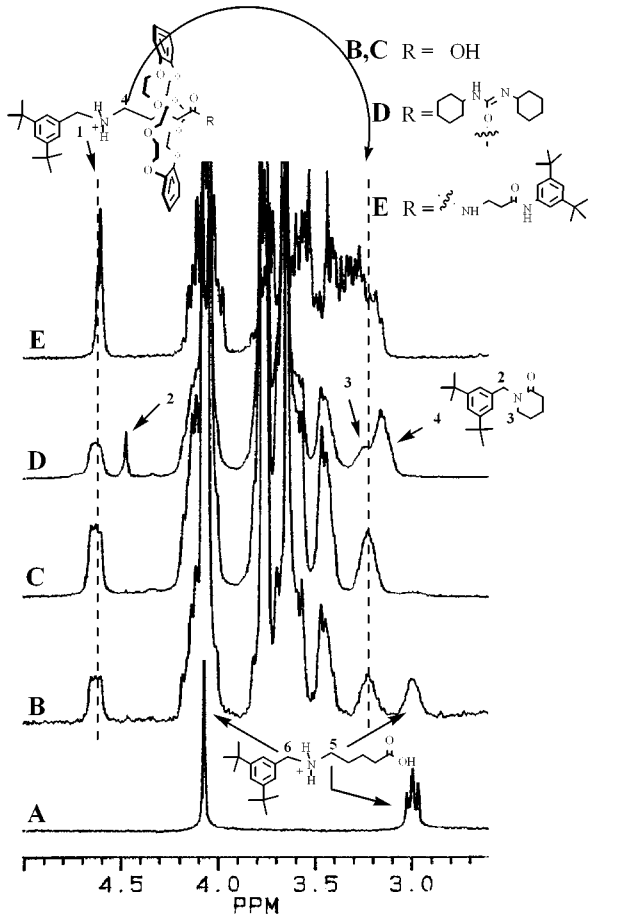


Figure 1. The following representative ^{1}H NMR spectra for the formation of rotaxane **4d** in CD_3CN at room temperature are given: (A) tether **1d**, (B) tether **1d** 50% bound with DB24C8, (C) tether **1d** 100% bound with DB24C8, giving **2d**, (D) addition of DCC to **2d**, giving a mixture of DCC-[2]rotaxane **3d** and lactam **6d**, and (E) the purified rotaxane **4d**. The numbers identify protons that clearly indicate which species are formed.

is consistent with the dicyclohexyl guanidinium derivative **7**. This compound could be formed by the amine of the blocking group attacking the diimide carbon atom of the DCC-[2]rotaxanes. Addition of the blocking group to DCC does not produce compound **7**. Thus, the increased steric congestion at the carboxylic moiety of DCC-[2]rotaxane **3a**−**d** caused by the ring makes this reaction possible.

Performing the reactions in chloroform produced yields of rotaxanes similar to those seen in acetonitrile (Table 1). Association constants for pseudorotaxane formation were not measured in $CDCl_3$ because of the low solubility of the capped-tethers. Once the capped-tethers interact with DB24C8 in chloroform, they dissolved, allowing rotaxane formation to proceed.

The rotaxanes were constructed using a one-pot synthetic route. As an example, rotaxane **4d** was obtained using capped-tether **1d**, which was obtained from a reductive amination reaction of 3,5-di-*tert*-butylbenzaldehyde and 5-amino valeric acid. To enhance pseudorotaxane formation with DB24C8, the Cl^- counterion was exchanged with PF_6^- by extracting the chloride salt of **1d** (150 mg, 0.42 mmol) with diethyl ether and water containing 1.7 equiv of ammonium hexafluorophosphate. Once the **1d**-PF_6^- salt was collected and dried, pseudorotaxane **2d** was created in $CDCl_3$ (3 mL) by adding DB24C8 (190 mg, 0.84 mmol) to the solution under argon. Formation of the pseudorotaxane and DCC-[2]rotaxane were verified by observing changes in the chemical shifts of protons of tether **1d** in ^{1}H NMR spectra (Figure 1).

Pseudorotaxanes formed quickly, and after approximately 20 min, DCC-[2]rotaxane **3d** was obtained by adding DCC (100 mg, 0.50 mmol) to the solution. After 10 min, *N*-(2-aminoethyl)-3,5-di-*tert*-butylbenzylamide (230 mg, 0.84 mmol) was added, and the reaction was stirred under argon at room temperature for 10 h. Reaction components were filtered and purified on silica using $CHCl_3$/MeOH as the eluent to give a 73% yield of rotaxane **4d**.[7] This reaction was run in $CDCl_3$ with approximately 100% bound tether; therefore, the yields do not match the ones reported in Table 1. We should also note that the yields reported in Table 1 were obtained from reactions that were run on a ca. 0.05 mmol scale.

We have demonstrated that rotaxanes can be easily synthesized in good yields using a DCC-activated rotaxane in CH_3CN or $CHCl_3$ (or their deuterated counterparts). DCC-[2]rotaxane **3d** is stable to purification by HPLC and column chromatography on silica. Gibson et al. have also isolated a sterically hindered acylisourea via column chromatography.[8] These compounds underwent rearrangement to the nitrogen-substituted cyclohexyl urea upon heating.

Dried DCC-[2]rotaxane **3d** was stored in a freezer for 1 week. After this time, there was no change in its ^{1}H NMR spectrum and it still formed rotaxane **4d**. We are currently trying to improve rotaxane yield by forcing the amine of the blocking group to react only with the carbonyl carbon of the DCC-[2]rotaxane by employing Lewis acid catalysts. Another possible route involves using large mixed anhydrides to activate the carboxylic acids.

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Supporting Information Available: Synthetic procedures and characterizations of 3,5-di-*tert*-butylbenzyl alcohol, 3,5-di-*tert*-butylbenzaldehyde, *N*-(2-aminoethyl)-3,5-di-*tert*-butylbenzylamide, and *N*-3,5-di-*tert*-butylbenzyl-5-amino-valeric acid. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The rotaxane exists as a mixture of conformers at ambient temperatures due to the ring sliding on the tether. It is not very soluble in high boiling solvents such as d_6-DMSO. ^{1}H NMR ($CDCl_3$) δ 7.70−7.52 (3H, m), 7.31−7.20 (3H, m), 6.88 (8H, m), 6.66 (1H, s), 6.40 (1H, s), 4.63 (1H, s), 4.23−4.20 (4H, m), 4.07−4.00 (4H, m), 3.80−3.70 (12H, m), 3.60−3.50 (8H, m), 3.43 (2H, br s), 3.33 (4H, br s), 3.08 (2H, br s), 1.98 (2H, br s), 1.66 (4H, br s), 1.30 (18H, s), 1.21 (18H, s); ^{13}C NMR (CD_3OD) δ 175.3, 171.7, 170.7, 153.1, 152.3, 152.2, 148.8, 148.0, 134.7, 133.8, 132.9, 127.0, 126.5, 125.2, 124.0, 122.5, 122.4, 133.7, 79.3, 71.6, 71.1, 69.1, 55.1, 53.6, 52.2, 51.0, 43.1, 41.1, 39.9, 39.7, 35.9, 35.5, 34.7, 33.5, 32.9, 31.8, 26.8, 26.3, 26.0, 25.8, 23.4. ESI MS *m*/*z* $[M + H]^+$.Anal. Calcd for $C_{61}H_{92}N_3O_{10}$: 1026.68 Found: 1026.71.

(8) Nagvekar, D. S.; Delaviz, Y.; Prasad, A.; Merola, J. S.; Marand, H.; Gibson, H. W. *J. Org. Chem.* **1996**, *61*, 1211−1218.