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# Mild and High-Yielding Syntheses of Diethyl Phosphoramidate-Stoppered [2]Rotaxanes†

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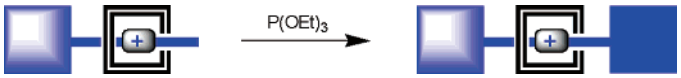
## ABSTRACT




**The mild and efficient reaction between triethyl phosphite and benzylic azides allows us not only to construct rotaxanes in high yield from dibenzo[24]crown-8 (DB24C8) and dibenzylammonium ($DBA^+$)-derived threads but also to incorporate di(*p*-toluidine)[24]crown-8, which binds $DBA^+$ ions much more weakly than does DB24C8, into a corresponding [2]rotaxane.**

Mechanically interlocked molecules continue to attract a great deal of attention because of the growing realization that these materials can be used to develop mesoscale devices[1] and artificial molecular machinery[2] on the nanoscale, and, hence, it remains necessary to devise new synthetic methods for their construction. Rotaxanes,[3] which are a class of mechanically interlocked molecules that comprise one or more macrocyclic units trapped along the rodlike moiety of a dumbbell-shaped component, have been prepared as prototypical molecular switches[4] and linear molecular motors.[2b−d] Among the many synthetic approaches for the construction of rotaxanes,[5] the threading-followed-by-stoppering protocol is one of the most straightforward, especially when combined with the simple recognition motif provided by the dibenzo[24]crown-8 (DB24C8)/dibenzylammonium cation ($DBA^+$) system,[6] which has formed the basis of many diverse interlocked molecular structures.[7] Although the strong noncovalent interactions between DB24C8 and $DBA^+$ allow the near-quantitative formation of pseudorotaxane[8] complexes in relatively nonpolar solvents, there are still only a limited

† In memory of Dr. Norma A. Stoddart.

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(5) Syntheses of molecular rotaxanes can be classified conceptually into three different approaches: (a) The threading-followed-by-stoppering approach relies on the initial formation (by threading) of a pseudorotaxane from bead- and threadlike components, followed by the positioning (stoppering) of bulky end groups to the threadlike component. (b) The slippage approach relies on the passage of a beadlike component over the moderately bulky end groups of a dumbbell-shaped component at elevated temperature. (c) The clipping approach relies on the macrocyclization of the subunits of a beadlike component around the threadlike subunit of the dumbbell-shaped component.

(6) (a) Cantrill, S. J.; Pease, A. R.; Stoddart, J. F. *J. Chem. Soc., Dalton Trans.* **2000**, 3715−3734. (b) Clifford, T.; Abushamleh, A.; Busch, D. H. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4830−4836. (c) Gibson, H. W.; Yamaguchi, N.; Jones, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 3522−3533.

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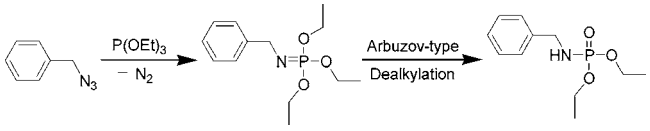
number of chemical reactions that are suitable for generating rotaxanes by the stoppering of these complexes.[9] Reactions that require polar solvents, high temperatures, and strong bases or that produce tight-binding counteranions during the process are undesirable for efficient stoppering reactions of DB24C8/$DBA^+$ systems because such conditions can lead to the dissociation of the pseudorotaxane complexes and, hence, result in poor yields of product rotaxanes.

In this paper, we report a very mild and high-yielding threading-followed-by-stoppering method for the synthesis of rotaxanes. This new stoppering reaction is very efficient: not only could we synthesize [2]rotaxanes using the strong DB24C8/$DBA^+$ recognition system ($K_a$ = 27,000 $M^{-1}$ in $CDCl_3$)[10] in up to 87% yield but we also constructed a [2]-rotaxane in 40% yield based on the very weak noncovalent binding[11] between $DBA^+$ and di(*p*-toluidine)[24]crown-8 (DPT24C8; $K_a$ < 15 $M^{-1}$ in $CDCl_3/CD_3NO_2$ = 2:1 mixture).[12]

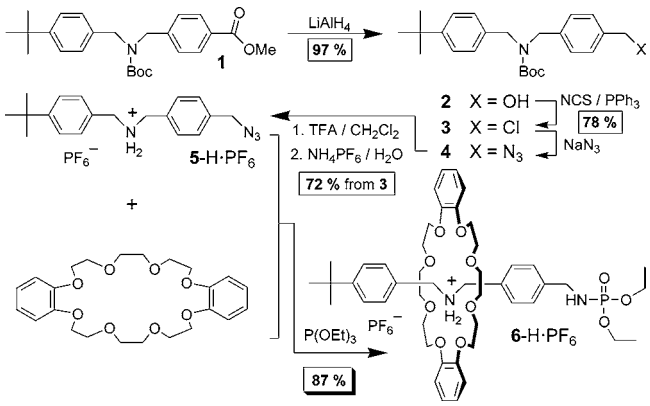
An ideal stoppering reaction for rotaxane synthesis should exhibit a number of features, including high yield, hassle-free purification, and either atom economy[13] or the production of benign byproducts. In the latter case, we believed that the first step of the Staudinger reaction,[14] the conversion of an organic azide to a phosphorimidate by the action of a phosphite, would be an elegant rotaxane stoppering reaction, because it releases only nitrogen gas and the phosphorimidate can undergo a subsequent Arbuzov-type dealkylation reaction[15] to form a stable phosphoramidate at ambient temperature in low-polarity solvents (Scheme 1).

**Scheme 1**




To test our hypothesis, we prepared the azide-functionalized dibenzylammonium hexafluorophosphate salt **5**-H·$PF_6$ by the procedure depicted in Scheme 2. Ester **1**[16] was reduced with $LiAlH_4$ to give the benzylic alcohol **2** whose subsequent

**Scheme 2**




chlorination using $NCS/PPh_3$ afforded the benzylic chloride **3**. Chloride **3** was then converted to azide **4** under Finkelstein conditions.[17] Removal of the Boc protecting group and then subjecting the trifluoroacetate salt to an ion exchange process ($NH_4PF_6/H_2O$) gave the desired azide-functionalized product **5**-H·$PF_6$ in 72% yield in three steps from the benzylic chloride **3**. The reaction between triethyl phosphite and an equimolar mixture of DB24C8 and **5**-H·$PF_6$ in $CH_2Cl_2$ at 100 mM concentration at ambient temperature gave [2]-rotaxane **6**-H·$PF_6$ in up to 87% yield.[18]

The interlocked nature of the [2]rotaxane **6**-H·$PF_6$ was confirmed by $^1H$ NMR spectroscopy (Figure 1a). The characteristic position and shape of the multiplets for the α-, *β*-, and *γ*-$OCH_2$ protons of the DB24C8 unit of **6**-H·$PF_6$, which are centered at *δ* 4.04, 3.75, and 3.55, respectively, are shifted upfield from their values in free DB24C8 (*δ* 4.09, 3.80, and 3.69, respectively; Figure 1b); these shifts are characteristic[19] of a crown ether unit positioned around the $NH_2^+$ center of a dibenzylammonium ion and stabilized by means of [$N^+$−H···O] and [C−H···O] hydrogen bonding

(8) Pseudorotaxanes are supramolecular complexes that resemble rotaxanes by virtue of comprising bead- and threadlike components, but their components are free to dissociate from each other. For examples, see: (a) Asakawa, M.; Ashton, P. R.; Balzani, V.; Boyd, S. E.; Credi, A.; Mattersteig, G.; Menzer, S.; Montalti, M.; Raymo, F. M.; Ruffilli, C.; Stoddart, J. F.; Venturi, M.; Williams, D. J. *Eur. J. Org. Chem.* **1999**, 985−994. (b) Huang, F.; Zakharov, L. N.; Rheingold, A. L.; Jones, J. W.; Gibson, H. W. *Chem. Commun.* **2003**, 2122−2123.

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(11) Chiu, S.-H.; Liao, K.-S.; Su, J.-K. *Tetrahedron Lett.* **2004**, *45*, 213-216.

(12) Because of the low solubility of DBA·$PF_6$ in $CDCl_3$ and its weak interaction with DPT24C8, we provide this upper limit for the association constant by comparing it with that determined ($K_a$ = 15 $M^{-1}$) for the binding of DPT24C8 with a more soluble and more strongly binding salt, bis(4-fluorobenzyl)ammonium hexafluorophosphate. See: Ashton, P. R.; Fyfe, M. C. T.; Hickingbottom, S. K.; Stoddart, J. F.; White, A. J. P.; Williams D. J. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2117−2124 and ref 11.

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(14) Gololobov, Yu. G.; Gusar, N. I.; Chaus, M. P. *Tetrahedron* **1985**, *41*, 793−799.

(15) (a) Balthazor, T. M.; Grabiak, R. C. *J. Org. Chem.* **1980**, *45*, 5425−5426. (b) Taher, A.; Eichenscher, S.; Slawin, A. M. Z.; Tennant, G.; Weaver, G. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1968−1972.

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(17) Biffin, M. E. C.; Miller, J.; Paul, D. B. *The Chemistry of the Azido Group*; Patai, S., Ed.; Interscience: London, 1971; pp 57−190.

(18) Association constant ($K_a$) between **5**-H·$PF_6$ and DB24C8 in $CDCl_3$ was determined by $^1H$ NMR spectroscopy to be 6650 $M^{-1}$ using the single-point method (see: Ashton, P. R.; Chrystal, E. J. T.; Glink, P. T.; Menzer, S.; Schiavo, C.; Spencer, N.; Stoddart, J. F.; Tasker, P. A.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1996**, 2, 709−728 and ref 12). Values of $K_a$ determined in this way are merely "ballpark" figures (see Supporting Information); for a discussion of a method for determining the values more precisely, see: Jones, W. J.; Gibson, H. W. *J. Am. Chem. Soc.* **2003**, *125*, 7001−7004.

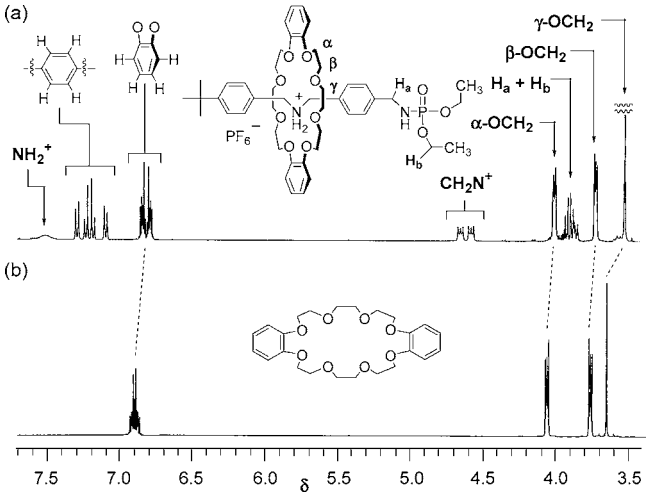
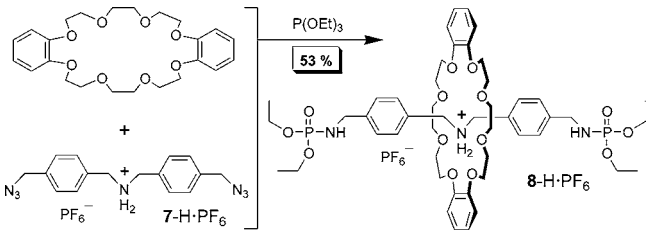



**Figure 1.** Partial $^1$H NMR spectra (400 MHz, $CD_3CN$) of (a) [2]-rotaxane **6**-H·$PF_6$ and (b) DB24C8.

interactions. The broad signal at $\delta$ 7.45−7.56 of the protons of the $NH_2^+$ center supports the existence of [$N^+$−H···O] hydrogen bonding between this center and the DB24C8 unit.[20] The characteristic position and shape of the multiplets centered at $\delta$ 4.68 and 4.60 for the protons on the benzylic methylene units adjacent to the $NH_2^+$ centers is further evidence for the crown ether encircling the $DBA^+$ moiety.[9c] When rotaxane **6**-H·$PF_6$ was dissolved in $CD_3SOCD_3$ and monitored by $^1$H NMR spectroscopy, we observed no release of free DB24C8,[21] which suggests that the terminal diethyl phosphoramidate groups of rotaxane **6**-H·$PF_6$ are true stoppers for the DB24C8 macrocycle.[22] High-resolution fast-atom-bombardment (HRFAB) mass spectrometry gave a molecular ion at *m*/*z* 867.4554 (theoretically at *m*/*z* 867.4561), which confirmed the chemical composition of the diethyl phosphoramidate-terminated [2]rotaxane **6**-H·$PF_6$.

Because this monostoppering reaction proceeded so well, we were inspired to test the stoppering of another azide-substituted dialkylammonium ion. The reaction between triethyl phosphite (200 mM), DB24C8 (200 mM), and the known bisazide-functionalized salt **7**-H·$PF_6$ (100 mM) in $CH_2Cl_2$ at ambient temperature gave [2]rotaxane **8**-H·$PF_6$ in 53% yield (Scheme 3).[23] In this case, we grew single crystals suitable for X-ray crystallography by liquid diffusion of isopropyl ether into a $CHCl_3$ solution of **8**-H·$PF_6$.

**Scheme 3**




The solid-state structure of the [2]rotaxane **8**-H·$PF_6$ indicates (Figure 2) that the interlocked molecule possesses

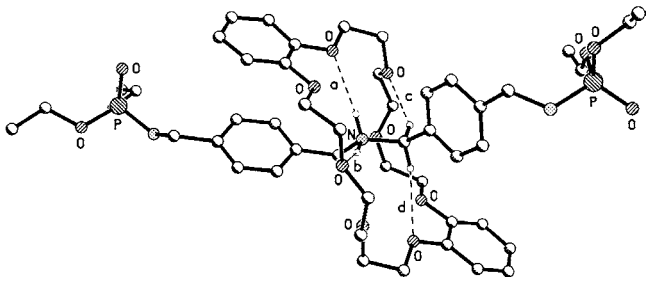


**Figure 2.** Ball-and-stick representation of the solid-state structure of the [2]rotaxane **8**-H·$PF_6$. The hydrogen bonding geometries, X···O, H···O [Å], and X−H···O [deg]: (a) 3.23, 2.36, 162.8; (b) 2.98, 2.11, 161.4; (c) 3.25, 2.41, 144.0; (d) 3.57, 2.62, 168.9.

two phosphoramidate end groups. The DB24C8 component has a conventional Z-shaped conformation with the two catechol rings inclined by ca. 4.7° to one another. The dicationic dumbbell component is tethered to the crown ether by weak N−H···O and C−H···O hydrogen bonds (a−d in Figure 2), a binding that is supplemented by $\pi-\pi$ stacking between one of the catechol rings of the DB24C8 component and the central phenylene ring of the dumbbell component (centroid···centroid distance and mean interplanar separation of 3.84 and 3.55 Å, respectively).

The interlocked nature of the [2]rotaxane **8**-H·$PF_6$ was also corroborated by $^1$H NMR spectroscopy (see Supporting Information). The HRFAB mass spectrum of **8**-H·$PF_6$ displayed a molecular ion at *m*/*z* 976.4484, which confirms that the [2]rotaxane has diethyl phosphoramidate termini.

To determine the generality and efficiency of this synthetic method, we were interested in testing whether we could stopper a very weakly binding crown ether/$DBA^+$-based pseudorotaxane system, i.e., one using DPT24C8 as the macrocycle.[11] The very weak electron-donating ability of the aniline nitrogen atoms of DPT24C8 make the strength of its

(19) Cantrill, S. J.; Fulton, D. A.; Heiss, A. M.; Pease, A. R.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **2000**, *6*, 2274−2287.

(20) For representative examples of NMR spectra of rotaxanes and pseudorotaxanes, see refs 7d, 9b, and 19.

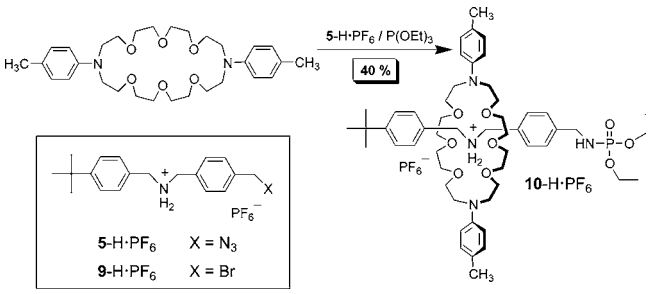
(21) In related pseudorotaxane systems, the use of DMSO as a solvent disrupts hydrogen bonding to such an extent that no complex forms; thus, dissolving a rotaxane of this type in DMSO is a good test for the degree of interlocking of the components. For example, see: Chiu, S.-H.; Rowan, S. J.; Cantrill, S. J.; Glink, P. T.; Garrell, R. L.; Stoddart, J. F. *Org. Lett.* **2000**, *2*, 3631−3634.

(22) The *p*-*tert*-butylbenzyl group is a true stopper for DB24C8 rings, but the *p*-isopropylbenzyl group is a slippage stopper; see: Ashton, P. R.; Baxter, I.; Fyfe, M. C. T.; Raymo, F. M.; Spencer, N.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 2297−2307. The diethyl phosphoramidate group is larger sterically than an isopropyl group when inspected using CPK molecular models.

(23) In addition to requiring two stoppering reactions instead of one, the moderate yield of this reaction, relative to that of the monostoppering reaction, is possibly the result of the relatively weak binding between **7**-H·$PF_6$ and DB24C8 ($K_a$ = 4000 $M^{-1}$ in $CDCl_3$); see: Ashton, P.; Glink, P. T.; Stoddart, J. F.; Tasker, P. A.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1996**, *2*, 729−736.

binding to **5**-H·$PF_6$ in $CH_2Cl_2$ about 2 orders of magnitude weaker than that between DB24C8 and **5**-H·$PF_6$ in the same solvent.[24] Unlike the virtually quantitative formation of the pseudorotaxane between an equimolar mixture (100 mM) of DB24C8 and $DBA^+$ in $CHCl_3$ at ambient temperature, only about half of the DPT24C8 and $DBA^+$ species exist in the pseudorotaxane form under these conditions. We found it difficult to form rotaxanes with this system; indeed, we failed to isolate rotaxane-like products when using two different stoppering methods: the 1,3-dipolar cycloaddition reaction of the azido groups of **5**-H·$PF_6$ with di-*tert*-butyl acetylenedicarboxylate to generate substituted 1,2,3-triazoles as stoppers[14b,24] and the quaternization of triphenylphosphine with the benzylic bromide **9**-H·$PF_6$ (Scheme 4) to form

**Scheme 4**




triphenylphosphonium ions as stoppers.[9c,21,25] Apart from the low concentrations of the respective pseudorotaxanes, it may be possible that the weakly nucleophilic substituted nitrogen atoms of the aniline units of the crown ether complicate these stoppering reactions by reacting with either the electrophilic benzylic bromide unit of **9**-H·$PF_6$ or with di-*tert*-butyl acetylenedicarboxylate, which results in complicated mixtures of products. In contrast, the reaction between triethyl phosphite (100 mM), DPT24C8 (200 mM), and **5**-H·$PF_6$ (100 mM) in $CH_2Cl_2$ at ambient temperature gave the corresponding [2]rotaxane **10**-H·$PF_6$ in 40% yield (Scheme 4). When we treated the thread **5**-H·$PF_6$ with triethyl phosphite in the absence of a crown ether, we obtained a complicated mixture of products from which we could not isolate the corresponding dumbbell-shaped phosphoramidate. Thus, the shielding of the ammonium centers by the crown ethers seems to be an important factor in the success of the reaction. In the presence of the weaker-binding crown ethers, the reaction mixture contains a relatively higher concentration of free **5**-H·$PF_6$ (ca. 20% is uncomplexed initially under our reaction conditions) than it does in the reactions using the stronger-binding macrocycle (>96% of **5**-H·$PF_6$ is complexed initially under the conditions in Scheme 2); this higher amount of free thread has a greater chance of being consumed by the side reactions during the rotaxane formation reaction, and, therefore, the product is formed in a lower yield.

Again, the interlocked nature of the components of this product can be deduced from its $^1$H NMR spectrum. The multiplets centered at $\delta$ 4.66 and 4.60 for the protons of the benzylic methylene groups adjacent to the $NH_2^+$ centers confirm the presence of the DPT24C8 moiety around the $NH_2^+$ center of the dumbbell unit in [2]rotaxane **10**-H·$PF_6$, as does the fact that the "tight" multiplet ($\delta$ 3.48−3.62) for the methylene protons within the $NCH_2CH_2O$ and $OCH_2$-$CH_2O$ units of the uncomplexed DPT24C8 is dispersed over a wide range of chemical shifts ($\delta$ 2.90−3.68), with each pair of methylene protons becoming constitutionally heterotopic, in the [2]rotaxane (Figure 3). Furthermore, the

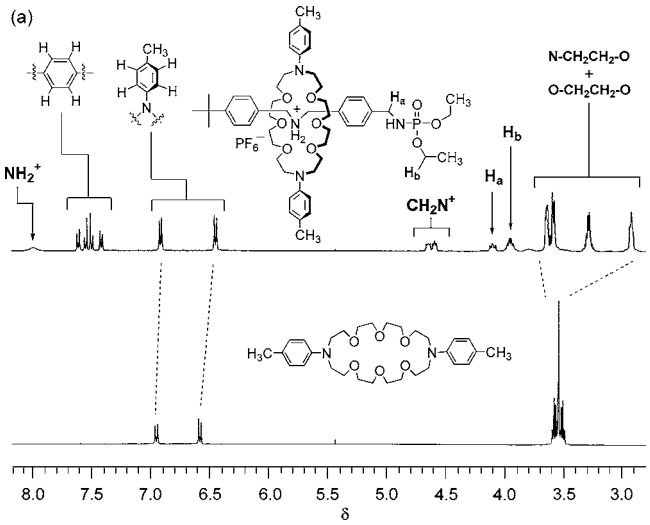



**Figure 3.** Partial $^1$H NMR spectra (400 MHz, $CD_3CN$) of (a) the [2]rotaxane **10**-H·$PF_6$ and (b) DPT24C8.

identification of a signal at *m*/*z* 949.6 for the [**10**-H]$^+$ ion in the FAB mass spectrum supports the presence of the diethyl phosphoramidate-stoppered [2]rotaxane **10**-H·$PF_6$.

We have developed a high-yielding, efficient, and mild synthetic method for the synthesis of rotaxanes. The reaction between triethyl phosphite and benzylic azides allows us not only to construct rotaxanes in high yields from DB24C8 and $DBA^+$-derived threads but also to incorporate DPT24C8, which binds $DBA^+$ ions much weaker than does DB24C8, into a corresponding [2]rotaxane.

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**Supporting Information Available:** Synthetic and spectroscopic data for the new compounds and a discussion on the merits of the single-point method for determining association constants. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) We determined the association constant ($K_a$) between **5**-H·$PF_6$ and DPT24C8 at room temperature in $CD_2Cl_2$ to be 38 $M^{-1}$, i.e., 175-times smaller than that between **5**-H·$PF_6$ and DB24C8 ($K_a$ = 6650 $M^{-1}$).

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