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Triphenylphosphonium-Stoppered [2]Rotaxanes

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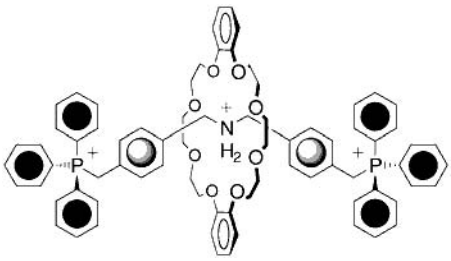
ABSTRACT



The template-directed syntheses of two [2]rotaxanes, one carrying one and the other two triphenylphosphonium stoppers, have been achieved using a threading-followed-by-stoppering approach. Either one or two benzylic bromide functions—located at the *para*-positions of dibenzylammonium-based ions, which become encircled by dibenzo[24]crown-8 macrocycles during the initial thermodynamically controlled phases that mark the recognition events—serve as sites for nucleophilic attack by triphenylphosphine during the subsequent kinetic stages that lead to the formation of the two [2]rotaxanes.

Rotaxanes[1] are molecules that are created when one or more beadlike species become trapped mechanically—usually with some supramolecular assistance[2]—on a dumbbell-shaped entity. Recently, a number of protocols based on self-assembly[3] have been developed[4] for the syntheses of these mechanically interlocked compounds. The most successful protocol has probably been the threading-followed-by-stoppering one.[4a] It involves (Scheme 1) the passage of a rodlike component through the beadlike one at the behest of stabilizing noncovalent bonding interactions. The [2]pseudorotaxane that is generated is then transformed into a [2]rotaxane by a reaction that plants bulky stoppers at the ends of the encircled rod. In recent times, we have developed a variety of approaches that lead to the formation of rotaxanes

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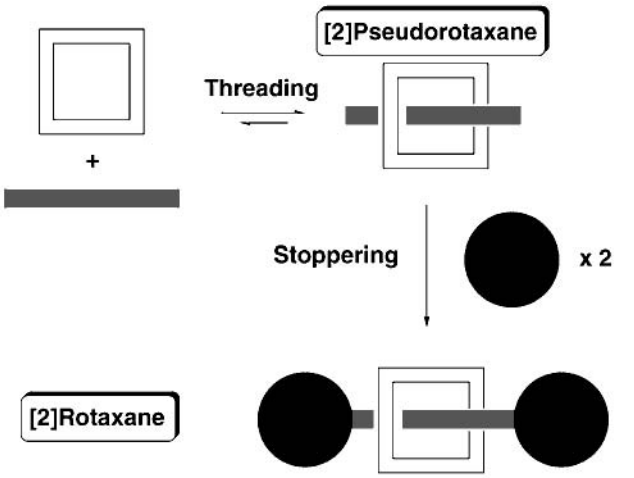
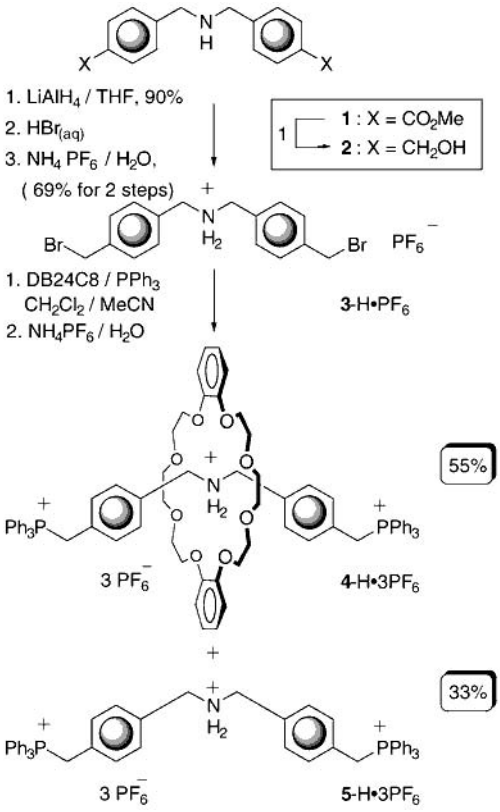
Scheme 1



using this particular protocol. Thus, triazole,[4a] pyridinium,[5] urea,[6] carbamate[7] and imine formation[8] all yield [2]rotaxanes from [2]pseudorotaxanes formed[9] between appropriately functionalized dibenzylammonium (DBA^+) cations that spontaneously penetrate the cavity of dibenzo[24]crown-8 (DB24C8). Here, we report an important new stoppering procedure for the synthesis of [2]rotaxanes that relies upon this particular form of supramolecular assistance, prior to the formation of triphenylphosphonium stoppers, when benzylic *p*-bromomethyl groups on the DBA^+ derivatives become the sites for nucleophilic attack by triphenylphosphine. Clearly, if this synthetic goal can be achieved, then the possibility of generating phosphorus ylides and studying their subsequent reactions with aldehydes and ketones becomes a reality.

The synthesis of the [2]rotaxane **4**-H·3PF_6 is outlined in Scheme 2. Bis(4-methoxycarbonylbenzyl)amine[4a] **1** was reduced ($LiAlH_4$/THF), yielding the diol **2** (90%), which was converted (69%) into the protonated dibromide **3**-H·PF_6 with aqueous HBr (48%), followed by counterion exchange (NH_4PF_6/H_2O). It is important for subsequent rotaxane formation that **3**-H·PF_6 binds DB24C8 in a pseudorotaxane fashion. On account of the fact that the free species and the pseudorotaxane are in slow exchange on the ^{1}H NMR time scale, the single-point method[10] was used to establish K_a values of 352 and 1778 M^{-1} for the 1:1 complex formed in CD_3CN and CD_2Cl_2/CD_3CN (1:1), respectively.

Scheme 2



The synthesis[11] of the [2]rotaxane **4**-H·3PF_6 was consequently carried out (Scheme 2) in the mixed solvent by simply adding PPh_3 to a 100 mM solution of **3**-H·PF_6 and DB24C8. After counterion exchange, **4**-H·3PF_6 was isolated in 55% yield, along with 33% of the dumbbell-shaped compound **5**-H·3PF_6. Although **3**-H·PF_6 is insoluble in CH_2Cl_2, when DB24C8 is added to a suspension, the dibromide dissolves slowly, presumably as a result of pseudorotaxane formation. This observation led to the [2]-rotaxane **4**-H·3PF_6 being synthesized in 70% yield in CH_2Cl_2 solution.

During the synthesis of the rotaxane, a white precipitate of the salt **5**-H·3X (X = Br, PF_6) is formed, thus reducing

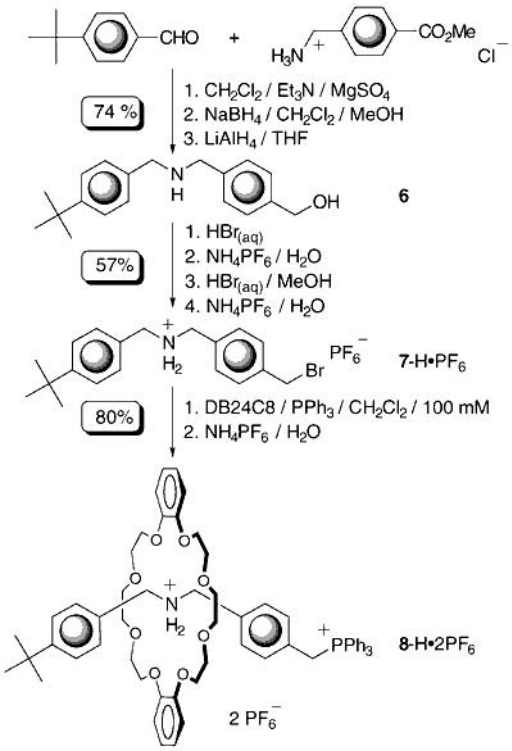
(10) For leading references on this method, see: Adrian, J. C.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 678−680.

(11) **Sample Procedure for the Preparation of 4-H·3PF_6 and 5-H·3PF_6.** Triphenylphosphine (297 mg, 1.1×10^{-3} mol) was added to a solution of the bis(bromomethyl) derivative **3**-H·PF_6 (200 mg, 3.8×10^{-4} mol) and DB24C8 (508 mg, 6.6×10^{-4} mol) in $MeCN/CH_2Cl_2$ (3.8 mL, 1:1). The reaction was then left to stir at room temperature overnight. The resulting white precipitate was filtered off and washed with CH_2Cl_2. The organic layer was then removed and the resulting solid redissolved in CH_2Cl_2 and any insoluble material removed by filtration and added to the white solid obtained from the previous filtration after anion exchange. This white solid was shown to be the free dumbbell-shaped compound **5**-H·3PF_6 (179 mg, 33%). Et_2O was then added to the CH_2Cl_2 solution, and the resulting white precipitate was filtered and washed with more Et_2O. This white solid was then dissolved in MeCN, and saturated aqueous NH_4PF_6 was added until no further precipitation was observed. This precipitate was filtered, washed with water, and then dried under vacuum. Further purification was carried out by flash chromatography with CH_2Cl_2/MeOH (100: 0, 99:1, ..., 95:5), resulting in a white solid of **4**-H·3PF_6 (340 mg, 55%). **Rotaxane 4**-H·3PF_6: ^{1}H NMR (400 MHz, CD_3CN) δ = 7.83−7.87 (m, 6H), 7.61−7.66 (m, 12H), 7.45−7.50 (m, 12H), 7.13 (d, J = 8 Hz, 4H), 6.80 (m, 4H), 6.66−6.70 (m, 8H), 4.60 (m, 4H), 4.42 (d, J = 14.8 Hz, 4H), 3.91−3.93 (m, 8H), 3.65−3.66 (m, 8H), 3.51 (s, 8H); ^{13}C NMR (100 MHz, CD_3CN) δ = 147.1, 135.4 (J_{PC} = 3 Hz), 134.1 (J_{PC} = 9.7 Hz), 132.6 (J_{PC} = 3.8 Hz), 131.2 (J_{PC} = 5.4 Hz), 130.2 (J_{PC} = 12.5 Hz), 129.8, 128.0 (J_{PC} = 8.3 Hz), 121.3, 117.4 (J_{PC} = 85.7 Hz), 112.2, 70.6, 70.1, 67.6, 51.9, 29.4 (J_{PC} = 48.5 Hz); ^{31}P NMR (162 MHz, CD_3CN) δ = 22.8 (Ph*P*$^+$), −143.6 (septet, J = 708 Hz, PF_6^-); MS (FAB) 1486 (M − PF_6)$^+$, 1341 (M − 2PF_6)$^+$, 1196 (M − 3PF_6)$^+$. **Dumbbell-Shaped Compound 5-H·3PF_6:** ^{1}H NMR (400 MHz, CD_3CN) δ = 7.84−7.89 (m, 6H), 7.65−7.69 (m, 12H), 7.50−7.56 (m, 12H), 7.29 (d, J = 8 Hz, 4H), 6.99 (dd, J = 2.4, 8 Hz, 4H), 4.65 (d, J = 14.9 Hz, 4H), 4.12 (brs, 4H); ^{13}C NMR (100 MHz, CD_3CN) δ = 135.4 (J_{PC} = 3 Hz), 134.1 (J_{PC} = 9.8 Hz), 131.5 (J_{PC} = 5.4 Hz), 131.1 (J_{PC} = 3.9), 130.9, 130.2 (J_{PC} = 12.5 Hz), 129.0 (J_{PC} = 8.4 Hz), 117.3 (J_{PC} = 85.8 Hz), 50.7, 29.4 (J_{PC} = 48.5 Hz); ^{31}P NMR (162 MHz, CD_3CN) δ = 23.7 (Ph*P*$^+$), −143.6 (septet, J = 708 Hz, PF_6^-); MS (FAB) 1038 (M − PF_6)$^+$, 893 (M − 2PF_6)$^+$.

the yield of the [2]rotaxane, anticipated on the basis of the high stability of the [2]pseudorotaxane precursor in the reaction solvent. As soon as Ph_3P displaces Br^- ions from **3**-H·PF_6, counterion exchange can take place, resulting in the formation of a tight ion pair between the Br^- and **5**-H^+ ions. The consequence of this competition will be to hinder formation of **4**-H^+ and encourage the production of **5**-H^+.

The synthesis of the [2]rotaxane **8**-H·$2PF_6$ was carried out (Scheme 3) in a manner similar to that described above for

Scheme 3



4-H·$3PF_6$. 4-*tert*-Butylbenzyl-4′-hydroxymethylbenzylamine (**6**) was prepared in 74% overall yield from (i) condensation of 4-*tert*-butylbenzaldehyde with 4-methoxycarbonylbenzylammonium chloride in the presence of anhydrous $MgSO_4$ followed by (ii) reduction of the resulting imine with $NaBH_4$ in MeOH and (iii) reduction of the ester function to a hydroxymethyl group with $LiAlH_4$ in THF. Conversion of **6** to the bromomethyl salt **7**-H·PF_6 required a four-step procedure. Reaction of the alcohol **6** with aqueous 48% HBr resulted in the formation of 4-*tert*-butylbenzyl-4′-hydroxymethylbenzylammonium bromide (**6**-H·Br) as a white precipitate. Following counterion exchange (NH_4PF_6/H_2O) and treatment of this hexafluorophosphate salt with methanolic 48% HBr, 4-*tert*-butylbenzyl-4′-bromomethylbenzylammonium hexafluorophosphate (**7**-H·PF_6) was obtained after yet another counterion exchange with aqueous ammonium hexafluorophosphate. The complexation of **7**-H·PF_6 by DB24C8 was reflected in a K_a value of 400 M^{-1} in CD_3CN, i.e., slightly more than the comparable binding constant for the dibromide **3**-H·PF_6. The template-directed synthesis of the [2]rotaxane **8**-H·$2PF_6$[12] was accomplished in 80% yield by adding Ph_3P to a 100 mM solution of **7**-H·PF_6 and DB24C8 in CH_2Cl_2. Unlike **5**-H·$3PF_6$, the corresponding dumbbell-shaped compound **9**-H·$2PF_6$ did not precipitate out of solution, and therefore was never isolated, from this reaction mixture. However, by simple addition of triphenylphosphine to **7**-H·PF_6 in MeCN, without any DB24C8 present, **9**-H·$2PF_6$ could be obtained easily.

Figure 1 shows the partial ^1H NMR spectra recorded in CD_3CN of both the [2]rotaxane **8**-H·$2PF_6$ and the corresponding free dumbbell-shaped compound **9**-H·$2PF_6$. As expected, the biggest chemical shift differences are the downfield ones of 0.42 and 0.62 ppm for the two sets of C$H_2NH_2^+$ protons on going from **9**-H·$2PF_6$ to **8**-H·$2PF_6$.

There is also a significant upfield shift of 0.25 ppm for the C$H_2PPh_3^+$ protons. The signal for these methylene protons in the [2]rotaxane is particularly sensitive to the environment: δ values of 4.30, 4.64, and 5.03 have been noted in $CDCl_3$, CD_3CN, and CD_3SOCD_3, respectively. Smaller changes in chemical shifts are also observed for the protons on both the *para*-substituted aromatic rings.

^{13}C NMR spectra of all four phosphorus-containing compounds show strong P−C couplings, ranging from 85 Hz for the phosphorus coupling to the *ipso* carbons on the phenyl rings to 3 Hz for the coupling of the phosphorus over five bonds through to the "internal" quaternary carbon atoms on the benzylic rings. Assignments of the resonances in the ^{13}C NMR spectra were based on HMQC experiments, as well as on comparisons with known compounds.[13] The Ph_3P^+ signals in the ^{31}P NMR spectra[14] of both dumbbell-shaped compounds, and their related rotaxanes, reveal shifts of around 1 ppm when rotaxane formation occurs.

In conclusion, we have demonstrated a novel approach to the synthesis[2] of rotaxanes that relies upon the supramolecular assistance inherent in the recognition[4] between a secondary dialkylammonium center and the cavity of a crown ether. The new [2]rotaxanes **4**-H·$3PF_6$ and **8**-H·$2PF_6$ have the potential to undergo further covalent modifications on

(12) **Data for Rotaxane 8-H·2PF$_6$:** ^1H NMR (400 MHz, CD_3CN) δ = 7.83−7.87 (m, 3H), 7.61−7.66 (m, 6H), 7.43−7.49 (m, 6H,), 7.23 (s, 4H), 7.15 (d, J = 8 Hz, 2H), 6.82 (m, 4H), 6.73 (m, 4H), 6.64 (dd, J = 2.4, 8 Hz, 2H), 4.72 (m, 2H), 4.49 (m, 2H), 4.39 (d, J = 14.8 Hz, 2H), 3.94−4.00 (m, 8H), 3.59−3.75 (m, 8H), 3.45−3.55 (s, 8H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, CD_3CN) δ = 152.3, 147.3, 135.3 (J_{PC} = 3 Hz), 134.1 (J_{PC} = 9.7 Hz), 133.0 (J_{PC} = 3.8 Hz), 131.0 (J_{PC} = 5.3 Hz), 130.2 (J_{PC} = 12.5 Hz), 129.8, 129.2, 128.7, 127.6 (J_{PC} = 8.3 Hz), 125.6, 121.3, 117.1 (J_{PC} = 85.7 Hz), 112.3, 70.6, 70.1, 67.8, 52.2, 51.7, 34.2, 30.5, 29.4 (J_{PC} = 48.2 Hz); ^{31}P NMR (162 MHz, CD_3CN) δ = 22.6 (Ph*P*$^+$), −143.6 (septet, J = 708 Hz, PF_6^-); MS (FAB) 1122 $(M - PF_6)^+$, 977 $(M - 2PF_6)^+$. **Data for Dumbbell-Shaped Compound 9-H·2PF$_6$:** ^1H NMR (400 MHz, CD_3CN) δ = 7.86−7.89 (m, 3H), 7.66−7.71 (m, 6H), 7.52−7.57 (m, 6H), 7.47 (AB, J = 8 Hz), 7.42 (AB, J = 8 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 6.97 (m, 2H), 4.64 (d, J = 14.8 Hz, 2H), 4.10 (m, 2H), 4.07 (m, 2H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, CD_3CN) δ = 152.4, 135.3 (J_{PC} = 3 Hz), 134.1 (J_{PC} = 9.7 Hz), 131.9 (J_{PC} = 3.8 Hz), 131.3 (J_{PC} = 5.3 Hz), 130.8, 130.2 (J_{PC} = 12.5 Hz), 129.9, 128.4 (J_{PC} = 8.3 Hz), 128.0, 125.9, 117.2 (J_{PC} = 85.7 Hz), 50.2, 49.7, 34.3, 30.5, 29.4 (J_{PC} = 48.8 Hz); ^{31}P NMR (162 MHz, CD_3CN) δ = 23.6 (Ph*P*$^+$), −143.6 (septet, J = 708 Hz, PF_6^-); MS (FAB) 528 $(M - 2PF_6)^+$.

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(14) All ^{31}P NMR spectra were measured in CD_3CN at room temperature and referenced to external PPh_3 in $CDCl_3$ (δ = −5.31). See: Davies, J. A.; Dutremez, S.; Pinkerton, A. A. *Inorg. Chem.* **1991**, *30*, 2380−2387.

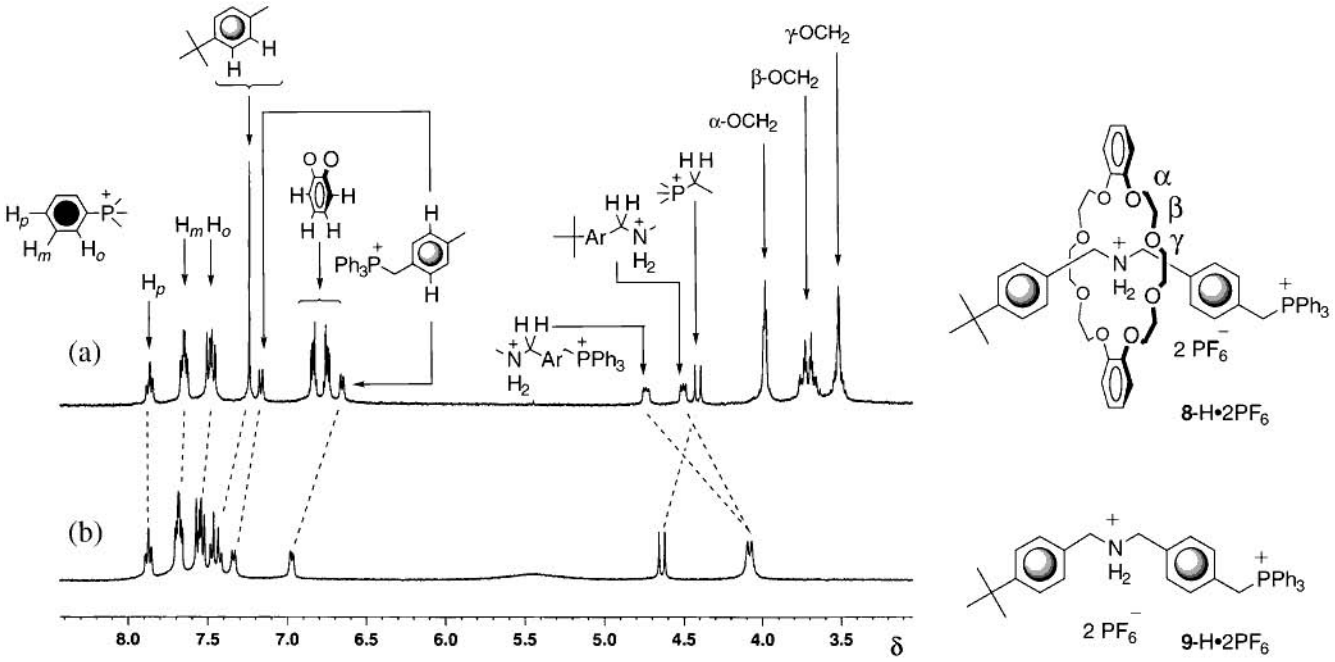

Figure 1. Partial ^{1}H NMR (400 MHz, CD_3CN) spectra of (a) the [2]rotaxane **8**-H·2PF$_6$ and of (b) the free dumbbell compound **9**-H·2PF$_6$

account of the obvious reactivities associated with the benzylic centers adjacent to their triphenylphosphonium stoppers. We are now in a position to study the reactivity of the ylide centers generated, in these new rotaxanes, upon the addition of base. In principle, we now have ways of converting rotaxanes into other, more intricate, interlocked molecular compounds. Work is currently in progress to unleash this potential.

Acknowledgment. We thank UCLA for generous financial support.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **4**-H·3PF$_6$, **5**-H·3PF$_6$, **8**-H·2PF$_6$, and **9**-H·2PF$_6$. This material is available free of charge via the Internet at http://pubs.acs.org.

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