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# A New Protocol for Rotaxane Synthesis

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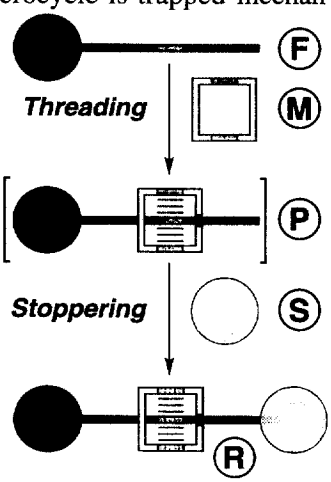
***Abstract***: A novel [2]rotaxane was synthesized when an aniline-bearing [2]pseudorotaxane—generated by the hydrogen bond-driven threading of a dibenzylammonium filament through the cavity of the macrocyclic polyether dibenzo[24]crown-8—was stoppered via reaction with a bulky isocyanate. Complete characterization of the [2]rotaxane was accomplished by NMR spectroscopy, mass spectrometry and X-ray crystallography. 

***Keywords***: Rotaxanes; Self-assembly; Synthetic methods; Template synthesis

Rotaxanes[1] are molecular species created when a bead-like macrocycle is trapped mechanically, i.e., without the assistance of any valence forces, on a dumbbell-shaped entity. Recently, a number of protocols based on self-assembly[2] have been developed[3] for the synthesis of these mechanically-interlocked compounds. The most successful protocol has probably been the threading followed by stoppering approach,[3a] which involves (Scheme 1) the threading of a linear filament (F) through the cavity of a macrocycle (M), by virtue of noncovalent bonds,[4] to generate a pseudorotaxane (P) that is then transformed into a rotaxane (R) by reaction with a bulky stoppering reagent (S). Here, we report a novel variant of this approach, which affords a [2]rotaxane by employing, as the threading motif, the dibenzylammonium–dibenzo[24]crown-8 (DB24C8) interaction[5] and, as the stoppering reaction, urea formation[3d,6] by the addition of anilines to isocyanates. The [2]rotaxane's structure has been verified by NMR spectroscopy, mass spectrometry and X-ray crystallography.




**Scheme 1. Diagram illustrating the synthesis of a [2]rotaxane via threading followed by stoppering. The stabilizing noncovalent bonding interactions that allow the pseudorotaxane's assembly are depicted by groups of lines between the lightly shaded portions of the filament and macroring.**

The protocol[7] employed to prepare rotaxane $\mathbf{1}\cdot O_2CCF_3$ is depicted in Scheme 2. The one-pot reaction presumably commences with the protonation of the more basic[8] dibenzylamine unit of **2**[9] by $CF_3CO_2H$. Thereupon, the dibenzylammonium ion thus created threads through DB24C8's cavity to form the

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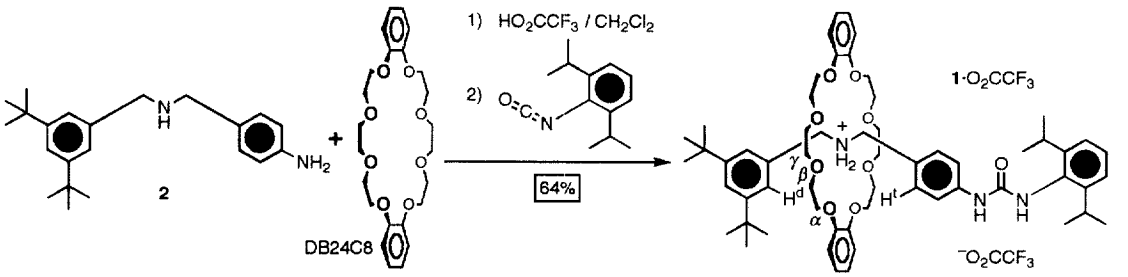


**Scheme 2. Synthetic protocol utilized for the preparation of [2]rotaxane $1 \cdot O_2CCF_3$.**

hydrogen bond-stabilized[5] [2]pseudorotaxane $[DB24C8 \cdot \mathbf{2}–H]^+$, which possesses a 3,5-di-*tert*-butylphenyl (dtbp) moiety that acts as a stopper in the final product $\mathbf{1}^+$. The reaction sequence concludes when this pseudorotaxane's free anilino group is stoppered by nucleophilic addition to 2,6-diisopropylphenyl isocyanate, producing a urea whose appended 2,6-diisopropylphenyl (dipp) unit is bulky enough to prevent dumbbell extrusion from the DB24C8 macroring. The fact that $\mathbf{1}^+$ is stable to column chromatography demonstrates convincingly that both of the terminal stopper groups are large enough to ensure macroring–dumbbell interlocking.

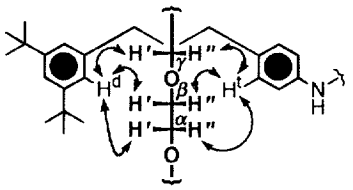

**Figure 1. Diagram highlighting the through-space interactions involving $H^d$ and $H^t$. Each of these protons interacts only with one group of protons on one of the crown ether's diastereotopic faces, i.e., $H^d$ and $H^t$ undergo through-space interactions exclusively with the protons labeled with single- and double-primes, respectively.**

An examination of the $^1$H NMR signals' relative intensities reveals that, in $\mathbf{1}^+$, the macroring and dumbbell components are present in equimolar ratios. The $^1$H NMR spectrum[7] also confirms that these components are compelled to be fastened to one another mechanically. The second order multiplets observed at $\delta$ 4.45–4.49 and 4.68–4.71 are particularly informative in this case; these resonances show[5] that it is the dumbbell's dibenzylammonium moiety that is encircled by the DB24C8 macroring in the interlocked molecular architecture. Conclusive proof that the components are mutually interlocked with one another was provided by a T-ROESY analysis.[10,11] In this experiment, intercomponent ROEs were observed between the $\alpha$-, $\beta$- and $\gamma$-$CH_2$ protons of DB24C8 and the protons $H^d$ and $H^t$ located (vide Scheme 2) on the dtbp and *p*-toluidinyl (ptol) units, respectively. As expected,[3k] DB24C8's $CH_2$ protons become diastereotopic in the [2]rotaxane $\mathbf{1}^+$, meaning that $H^d$ and $H^t$ are involved in through-space interactions only with protons on the nearest faces of the macrocyclic polyether (Figure 1). The FAB mass spectrum of $\mathbf{1} \cdot O_2CCF_3$ shows[7] a base peak, corresponding to the ion $\mathbf{1}^+$, at *m/z* 976, thus confirming the gas phase integrity of its interlocked [2]rotaxane architecture.

The X-ray analysis[12] of a single crystal of the [2]rotaxane $\mathbf{1} \cdot O_2CCF_3$ reveals that there are two crystallographically independent molecules in the asymmetric unit. Apart from the relative orientations of the *i*-Pr and *t*-Bu groups, the dumbbell's conformation is essentially the same in both molecules. However, different geometries are adopted by the DB24C8 macroring in each of the [2]rotaxanes, resulting in slightly modified intramolecular hydrogen bonding interactions. The [2]rotaxane architecture displayed in Figure 2 is stabilized by hydrogen bonds involving both $NH_2^+$ hydrogen atoms and one of the adjacent dtbp–$CH_2$ hydrogen atoms,

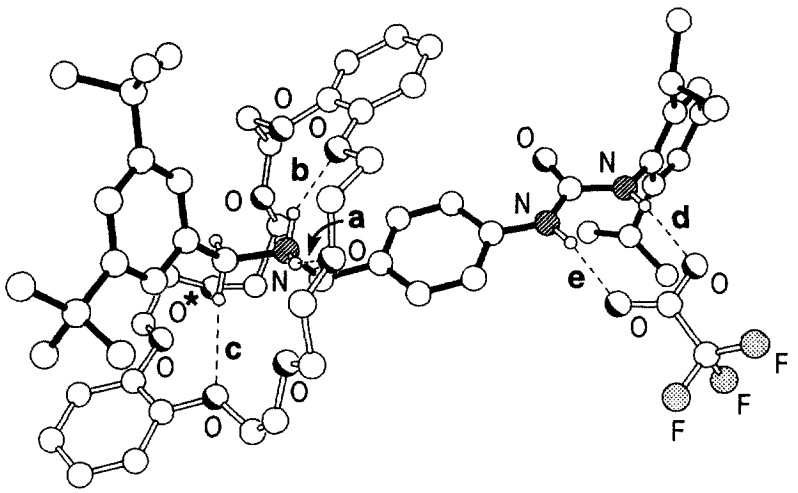


**Figure 2. Molecular structure of one of the pair of independent [2]rotaxanes present in the crystals of $1{\cdot}O_2CCF_3$. Hydrogen bonding distances and angles {[X···O], [H···O] distances (Å), [X–H···O] angles (°)}: (a) 2.85, 2.01, 156; (b) 2.89, 2.16, 137; (c) 3.31, 2.36, 171; (d) 2.89, 2.03, 159; (e) 2.86, 1.98, 164. The other independent molecule has an additional [C–H···O] hydrogen bond (f) which occurs between the asterisk-labeled oxygen atom and one of the ptol–$CH_2$ hydrogen atoms. The hydrogen bonding distances and angles for this second molecule are: (a) 2.91, 2.11, 147; (b) 3.01, 2.23, 145; (c) 3.41, 2.51, 157; (d) 2.76, 1.92, 163; (e) 2.91, 2.02, 168; (f) 3.25, 2.41, 147.**

whereas one of the ptol–$CH_2$ hydrogen atoms is also utilized in its crystallographically independent congener. The $^-O_2CCF_3$ anion forms a pair of hydrogen bonds to the urea unit of each independent rotaxane's cationic dumbbell component. Despite the apparent overlaying of one of the crown ether's catechol rings with the central ptol ring of the dumbbell component in both independent molecules, the interplanar separations are too large to represent any significant stabilizing $\pi$–$\pi$ interactions (the ring centroid···ring centroid distances are 4.48 and 4.54 Å, respectively, in the two molecules). There are no major inter-[2]rotaxane interactions.

In conclusion, we have developed a new one-pot protocol for the synthesis of urea-containing [2]rotaxanes that relies on the stoppering of [2]pseudorotaxanes—generated when an aniline-bearing dibenzylammonium filament threads through the crown ether DB24C8—by bulky isocyanates. It is not unreasonable to conjecture that this protocol can be extended to the synthesis of rotaxanes (i) comprised of more than two components, i.e., [2+$n$]rotaxanes,[3a–c,g,i] or (ii) containing other functional groups formed by nucleophilic addition to isocyanates, e.g., carbamates.[3d] We are also fascinated by the proposition that rotaxanes such as $\mathbf{1}^+$ can function as elementary molecular devices.[13] Experiments are underway in our laboratories to see if $\mathbf{1}^+$ acts as an acid–base controlled molecular switch[3k] wherein the DB24C8 component relocates itself to hydrogen bond with the urea moiety when the dibenzylammonium unit is deprotonated by treatment with base.

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[7] Experimental procedure: Solid DB24C8 (1.41 g, 3.15 mmol) was added to a stirred solution of **2** (0.34 g, 1.05 mmol) in anhydrous $CH_2Cl_2$ (5 mL). After addition of $HO_2CCF_3$ (81 μL, 1.05 mmol) and 5 min stirring, the solution was treated with a single portion of 2,6-diisopropylphenyl isocyanate (1.13 mL, 5.25 mmol). The reaction mixture was stirred for a further 5 d at 25 °C, then the solvents were removed in vacuo. The remainder was purified by column chromatography ($SiO_2$; gradient elution from 99:1 to 9:1 $CH_2Cl_2$–MeOH) to furnish **1**·$O_2CCF_3$ (0.73 g, 64%) as an off-white powder. M.p. 117–119 °C; $^1$H NMR (400 MHz, $CD_2Cl_2$, 27 °C): $\delta$ 1.19 (s, 30H; $(CH_3)_2CH/(CH_3)_3C$), 3.32 (sept, *J* 7.0 Hz, 2H; $(CH_3)_2CH$), 3.42–3.47 (m, 4H; γ-*H'*), 3.52–3.58 (m, 4H; γ-*H''*), 3.67–3.73 (m, 4H; β-*H'*), 3.78–3.85 (m, 4H; β-*H''*), 4.07–4.17 (m, 8H; α-*H'*/α-*H''*), 4.45–4.49 (m, 2H; ptol–$CH_2$), 4.68–4.71 (m, 2H; dtbp–$CH_2$), 6.79–6.94 (m, 8H; *o*-$O_2C_6H_4$), 7.10 (d, *J* 8.5 Hz, 2H; $H^i$), 7.14 (d, *J* 7.5 Hz, 2H; *o*-*i*-Pr–dipp*H*), 7.21–7.26 (m, 1H; *m*-*i*-Pr–dipp*H*), 7.28 (d, *J* 1.5 Hz, 2H; $H^d$), 7.35 (t, *J* 1.5 Hz, 1H; *o*-(*t*-Bu)$_2$–dtbp*H*), 7.44 (d, *J* 8.5 Hz, 2H; *o*-NH–ptol*H*), 7.53 (br s, 2H; $NH_2^+$), 8.97 (s, 1H; dipp–N*H*), 10.16 (s, 1H; ptol–N*H*); $^{13}$C NMR (100 MHz, $CDCl_3$, 27 °C): $\delta$ 23.5, 24.4, 28.6, 31.5, 34.9, 52.9, 53.1, 68.1, 70.2, 70.5, 112.8, 118.4, 122.0, 122.4, 122.9, 123.3, 123.7, 127.1, 129.7, 131.6, 133.2, 143.2, 147.4, 147.6, 151.4, 155.7; FABMS: *m/z* 976 (100%) $[M - O_2CCF_3]^+$; $C_{61}H_{82}F_3N_3O_{11}$ (1090.3): calcd C 67.20, H 7.58, N 3.85; found C 66.68, H 7.55, N 3.58.

[8] p$K_a$s: $R_2NH_2^+$ 11, $ArNH_3^+$ 3–5 (March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, **1992**; p. 251).

[9] 4-Aminobenzyl-3,5-di-*tert*-butylbenzylamine (**2**) was prepared by $NaBH_4$ reduction of the imine generated by the condensation of 4-azidobenzylamine (McFadden, H. G.; Phillips, J. N. *Z. Naturforsch., C: Biosci.* **1990**, *45*, 196–206) and 3,5-di-*tert*-butylbenzaldehyde (Newman, M. S.; Lee, L. F. *J. Org. Chem.* **1972**, *37*, 4468–4469).

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[11] A spin lock mixing time of 300 ms was used. The $^1$H NMR assignments displayed in [7] were made using this T-ROESY analysis, in tandem with $^1$H–$^1$H COSY and $^1$H–$^{13}$C HMQC experiments.

[12] X-Ray quality single crystals were obtained when a $CH_2Cl_2$ solution of **1**·$O_2CCF_3$ was layered with $C_6H_{14}$s. Crystal data for **1**·$O_2CCF_3$: $C_{59}H_{82}N_3O_9{\cdot}O_2CCF_3{\cdot}1.3CH_2Cl_2$, $M$ = 1200.7, monoclinic, $P2_1/c$ (no. 14), $a$ = 21.583(2), $b$ = 39.539(5), $c$ = 15.511(2) Å, $\beta$ = 96.17(1)°, $V$ = 13160(2) Å$^3$, $Z$ = 8 (there are two crystallographically independent molecules in the asymmetric unit), $D_c$ = 1.212 g cm$^{-3}$, $\mu$(Cu-Kα) = 16.6 cm$^{-1}$, $F(000)$ = 5109, $T$ = 203 K; clear rhombs, 0.83 × 0.33 × 0.30 mm, Siemens P4 rotating anode diffractometer, ω-scans, 16269 independent reflections. The structure was solved by direct methods and all the major occupancy non-hydrogen atoms of the cations and anions were refined anisotropically (the non-hydrogen atoms of the solvent molecules isotropically) using full matrix least-squares based on $F^2$ to give $R_1$ = 0.129, $wR_2$ = 0.334 for 7255 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 110°$] and 1482 parameters.

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