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A rotaxane synthesis based on stilbene photoisomerization. A photoswitchable catch and release process†

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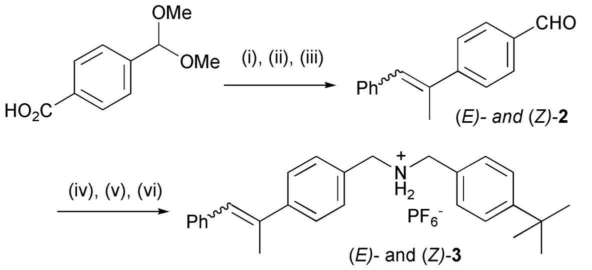
A [2]rotaxane, having (*Z*)-α-methylstilbene as a stopper, is (1) synthesized in good yield by using a (*E*)- to (*Z*)-stilbene photoisomerization process, and (2) dissociated by reverse photoisomerization from (*Z*)- to (*E*)-stilbene.

The design of rotaxanes organized by noncovalent interactions has attracted much attention.[1] Photoresponsive rotaxanes are highly attractive interlocked molecules because of the fact that their properties can be changed in response to photo-irradiation. Photoinduced dynamics and electron transfer between wheel and axle groups in rotaxanes have been previously investigated,[2] and applications of these properties to material science have been developed.[3]

The structure of a rotaxane can be rigidly fixed by the placement of bulky functionality at the axle ends to prevent slippage.[4] In this case, the association–dissociation process between the two components is generally not reversible.[5] An important application of rotaxanes is found in the work of Yui and co-workers,[6] which has led to the development of biodegradable polyrotaxanes for biomedical applications (*e.g.*, drug carriers). In these rotaxanes, degradation processes promote the release of biologically active compounds.

The reversible isomerizations of (*E*) and (*Z*)-stilbene can be promoted by using UV irradiation.[7] The (*E*)-stilbene isomer has a planar conformation whereas its (*Z*)-isomer exists in a conformation in which the two *cis*-benzene rings twisted owing to a repulsive interaction between protons at the 2 and 2′ positions in the planar structure. Owing to this feature, we believed that (*Z*)-stilbenes would serve as effective stoppers in the construction of rigid rotaxanes. Inspection of molecular models of (*Z*)- and (*E*)-α-methylstilbenes as well as dibenzo-24-crown-8 (DB24C8) (Fig. 1) shows that the flat (*E*)-isomer can be easily threaded through the crown. In contrast, the twisted (*Z*)-isomer is sufficiently large to prevent being threaded through DB24C8.[8] Based on these and other considerations, we developed a novel approach to rotaxane synthesis, which relies on the use of (1) hydrogen bonding guided self-assembly between secondary ammonium groups and DB24C8,[9] and (2) photoisomerization of (*Z*)- and (*E*)-α-methylstilbene as a reversible end-closing–end-opening process.

The group that serves as a precursor to the axle in this rotaxane synthetic design is the stilbene containing ammonium salt (*E*)-**3**. The route used to prepare **3** is initiated by methylation of the dimethylacetal of 4-carboxybenzaldehyde, which affords the corresponding methylketone (Scheme 1). Wittig olefination of the ketone followed by deprotection produces a separable mixture of (*E*)- and (*Z*)-stilbene derivatives **2**. Individual treatment of these isomers with 4-*tert*-butylbenzylamine gives the corresponding imines, which are then converted to the corresponding ammonium salts, (*E*)- and (*Z*)-**3**. Reduction and counter ion exchange then generates substances which possess (*E*)- and (*Z*)-α-methylstilbene groupings on one end of the chain and a bulky aryl group[9b] at the other end.



Scheme 1 *Reagents and conditions*: (i) MeLi; (ii) $Ph_3P{=}CHPh$; (iii) H_3O^+; (iv) 4-*tert*-butylbenzylamine; (v) $NaBH_4$; (vi) H_3O^+ then NH_4PF_6.

^{1}H NMR spectroscopy was employed to monitor the complexation of the isomeric ammonium salts to DB24C8. The ^{1}H NMR (1 : 1 $CDCl_3$–CD_3CN) spectrum of a mixture of (*E*)-**3** and DB24C8 revealed the formation of the pseudorotaxane (*E*)-**4**. In contrast, a pseudorotaxane was not produced when (*Z*)-**3** and DB24C8 were mixed. We next explored the proposed photoisomerization approach to the synthesis of rotaxane. UV irradiation of a 1 : 1 $CDCl_3$–CD_3CN solution of (*E*)-**3** (272 mM) and DB24C8 (408 mM), using benzil[7b] (272 mM) as a sensitizer, led to efficient *E* to *Z*-stilbene isomerization of the pseudorotaxane (Scheme 2) and formation of a rotaxane (*Z*)-**4** in a 73% yield (87%: NMR yield) after purification. This substance was stable in d$_6$-DMSO at room temperature in the dark.[10] Rotaxane forming photoisomerization reactions promoted by 9-fluorenone, duroquinone, and pyrene gave the rotaxane in 54% (79%: NMR), 71% (79%: NMR), and 58% (77%: NMR) yields, respectively. The rotaxane was characterized by ^{1}H and ^{13}C NMR, FAB mass, and IR spectrometric methods. As expected,[9] the ^{1}H NMR spectrum of this substance contained proton resonances (assigned using COSY and ROESY methods) with higher field chemical shifts than those of the crown ether and low field chemical shifts for the benzylic protons of the axle. The presence of an intense peak at *m*/*z* 818, corresponding to the loss of the counter ion, in the FAB mass spectrum confirmed the structural assignment of the rotaxane.

^{1}H NMR spectroscopy was used to monitor the progress of the photochemical isomerization reaction resulting in the

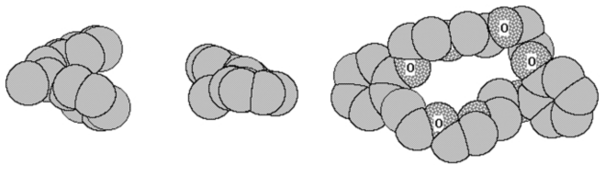
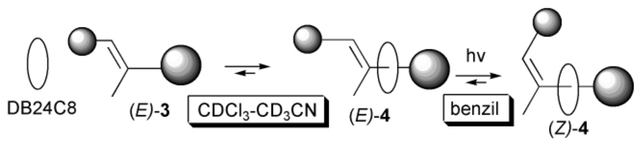


Fig. 1 Space-filling models of (*Z*)-α-methylstilbene (a), (*E*)-α-methylstilbene (b), and dibenzo-24-crown-8 (c).



Scheme 2

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† Electronic supplementary information (ESI) available: NMR spectra. See http://www.rsc.org/suppdata/cc/b3/b306349f/

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formation of the rotaxane. A solution containing equimolar (23 mM) quantities of (*E*)-**3**, DB24C8, and benzil in 1 : 1 $CDCl_3$–CD_3CN was irradiated at 0 °C. The time course of the appearance and disappearance of resonances, assigned to (*Z*)-**4** and (*Z*)-**3**, and those of (*E*)-**4** and (*E*)-**3** was determined by ^1H NMR integration. During the course of the reaction, the signals of the protons of the (*E*)-isomers decreased in intensity concomitant with the increases in the intensities of the resonances associated with the (*Z*)-isomers (Fig. 2). Based on these results, the association constant of pseudorotaxane (*E*)-**4** was determined to be 900 ± 110 M^{-1}.[11,12]

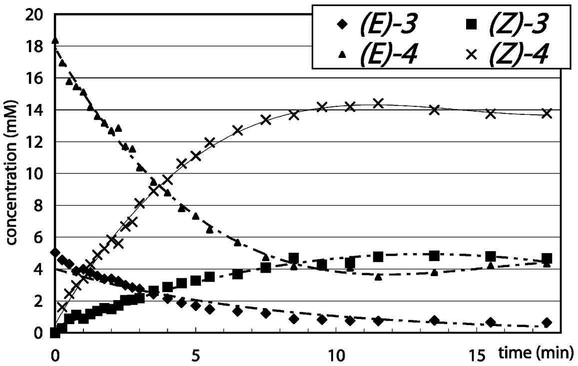
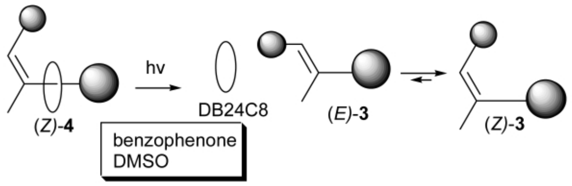


Fig. 2 Plots of concentrations of (*E*)-**3**, (*Z*)-**3**, (*E*)-**4** and (*Z*)-**4** *vs.* time during irradiation of a 1 : 1 $CDCl_3$–CD_3CN solution of (*E*)-**3** and DB24C8 in the presence of benzil at 0 °C. The photoreaction was carried out in an NMR tube under nitrogen with light from a super-high pressure mercury lamp (Ushio USH-250W).

We next examined the *endo*-opening reaction of rotaxane (*Z*)-**4**. Irradiation of a solution of (*Z*)-**4** and benzophenone[7b] in d_6-DMSO led to the production of (*E*)-**3**, (*Z*)-**3**, and DB24C8. ^1H NMR monitoring of this process revealed that photodegradation of (*Z*)-**4** fits a first-order curve, and that photodegradation of (*Z*)-**4** leads to (*E*)-**3** and this is followed by the conversion of (*E*)-**3** to (*Z*)-**3** (Fig. 3).[12]



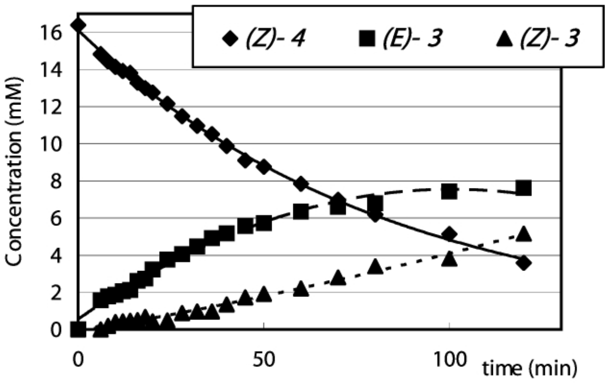


Fig. 3 Plots of concentrations of (*E*)-**3**, (*Z*)-**3**, and (*Z*)-**4** *vs.* time during irradiation of a d_6-DMSO solution of (*Z*)-**4** in the presence of benzophenone at room temperature. The photoreaction was carried out in an NMR tube under nitrogen with light from a super-high pressure mercury lamp (Ushio USH-250W).

The observations described above show that (*E*,*Z*)-photoisomerization of the stilbene component of the pseudorotaxane can be used to form a rotaxane. This approach avoids use of bulky functionality that is more typically employed to cap the ends of the axle grouping. In addition, the results demonstrate that stilbene photoisomerization can also be used to promote degradation of the rotaxane.

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10 The rotaxane is not stable at high temperature in d_6-DMSO owing to the disruption of hydrogen bonding interactions. The first-order rate constant for dissociation was found to be $5.8 \times 10^{-7}\ s^{-1}$ in d_6-DMSO at 90 °C ($t_{1/2}$ of 332 h).

11 Resonances for an unidentified compound were observed in the ^1H NMR spectrum after prolonged irradiation. The association constant was measured at 25 °C.

12 See electronic supplementary information.