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PAPER

Three-state molecular shuttles operated using acid/base stimuli with distinct outputs†

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This paper describes the acid/base-mediated three-state translational isomerization of two [2]rotaxanes, each containing *N*-alkylaniline and *N*,*N*-dialkylamine centers as binding sites for threaded dibenzo[24]crown-8 units. Under neutral conditions, the dialkylamine unit predominantly recognized the crown ether component through cooperative binding of a proton; when both amino units were protonated under acidic conditions, both translational isomers were generated; the addition of a strong base caused aniline–crown ether interactions to dominate. The three states of the [2]rotaxane featuring the 3,5-diphenylaniline terminus in its dumbbell-shaped component were accompanied by distinct absorptive outputs that were detectable using UV spectroscopy.

Introduction

Rotaxane-based molecular shuttles that operate using various stimuli have attracted much attention[1] because such switching systems might aid the development of molecular sensors,[2] functionalized surfaces,[2e,3] nanovalves,[4] molecular devices,[5] actuators,[6] and transporting systems.[7] The dialkylammonium/crown ether recognition pair has been used widely in the synthesis of interlocked molecules[8] that function as acid/base-responsive molecular shuttles.[9–11] Because the strength of the hydrogen bonds between the ammonium (amine) and crown ether components can be regulated by deprotonation (protonation) of the ammonium (amine) center, if the dumbbell-shaped component features another recognition site for the crown ether unit—one that is not affected by acid and base—the system will be capable of exhibiting translational isomerism.

Alternative recognition sites for crown ether units in rotaxane systems have been investigated widely. Loeb reported that the *N*-alkylanilinium cation has an association constant for crown ethers that is similar to that of the dialkylammonium cation.[12] Leigh developed a [2]rotaxane featuring two different dialkylammonium recognition sites in the dumbbell-shaped component; the difference in acidity between the two stations, which differed only in the nature of their substituents, was sufficient to form the basis of a switchable molecular shuttle that operated through changes in the degree of protonation.[13]

The strength of the hydrogen bonding interactions of an ammonium group to a crown ether is based on the number of hydrogen bonds and the acidity of the protons; the degree of protonation of an amine is related to its basicity and the acidity of the proton donor. A diamine featuring amino units having different basicities can exist in three states (amine/amine, ammonium/amine, ammonium/ammonium) depending on the pH. The strength of the hydrogen bonds formed between each of these stations and a crown ether could be controlled by varying the degrees of protonation and deprotonation; when both amino groups are protonated under acidic conditions, the more acidic ammonium center should bind predominantly to the crown ether; under neutral conditions, the more basic amine would be protonated selectively, causing the macrocycle to prefer this recognition site; under basic conditions, the more acidic of the two amino groups might be recognized preferentially (Fig. 1). Here, we report the synthesis of two [2]rotaxanes in which the crown ether unit can be switched between two different amino groups as binding sites under acidic, neutral, and basic conditions. Moreover, UV spectroscopy revealed distinct signals from the [2]rotaxane featuring a 3,5-diphenylaniline terminus upon varying the pH, allowing independent observation of the shuttling process.[14]

Results and discussion

Synthesis of rotaxanes

We chose dialkylamine (ammonium) and aniline (anilinium) units as our two different recognition sites because both protonated forms are suitable recognition sites for crown ethers, but their basicities are quite different (pK_a: $Me_2NH_2^+$, 10.7; $PhNH_3^+$, 4.6). We prepared the [2]rotaxanes **2** and **3** using a previously described method (Scheme 1).[15] The reaction of the aldehyde **1**, DB24C8, and 3,5-dimethylaniline (3,5-diphenylaniline) though thermodynamic covalent chemistry,[16] followed by reduction of the corresponding imine and subsequent spontaneous salt formation in air, gave the

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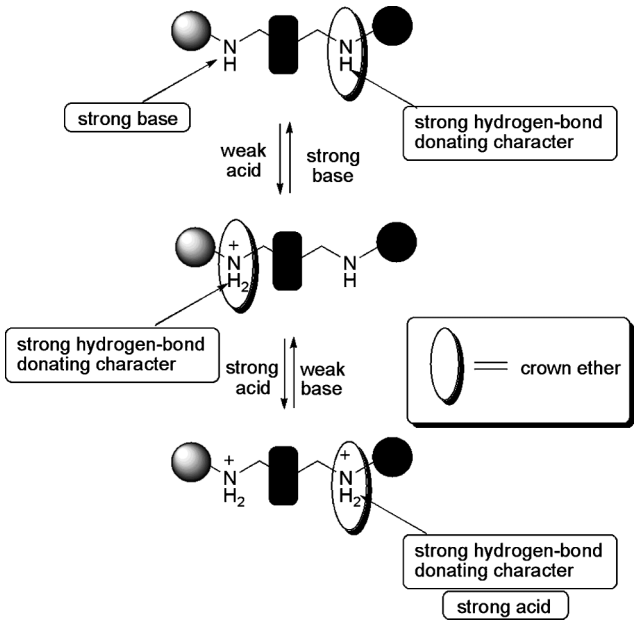
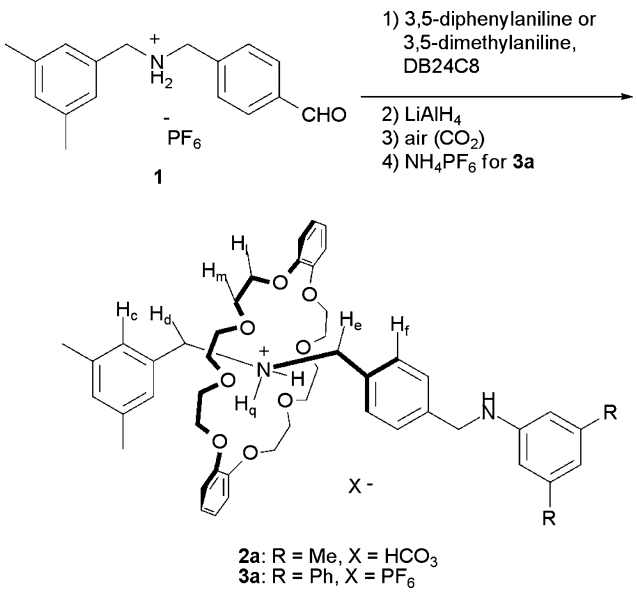


Fig. 1 Three-state acid/base responses of a molecular shuttle incorporating a dumbbell-shaped component featuring two different amino groups.



2a: R = Me, X = HCO_3
3a: R = Ph, X = PF_6

Scheme 1

[2]rotaxane **2a** (**3a**), featuring a dimethylaniline (diphenylaniline) stopper, in good yield. In the case of **3a**, the hexafluorophosphate salt was formed to facilitate isolation.

^{1}H NMR spectroscopy revealed that each of the [2]rotaxanes was isolated in its singly protonated form, with the DB24C8 component bound to the *N*,*N*-dialkylammonium moiety of the dumbbell-shaped component (Fig. 2). The ^{1}H NMR spectrum of **2a** features signals that are characteristic of a crown ether/dibenzylammonium-type rotaxane: a concentration-independent signal for the protons of the NH_2 (H_q) unit at 7.52 ppm and signals for the pairs of benzylic protons (H_e, H_d) at 4.42 and 4.56 ppm. Moreover, a correlation existed between the signals of the DB24C8 unit's protons H_m and H_n and the protons H_c and H_f of the dumbbell-shaped component

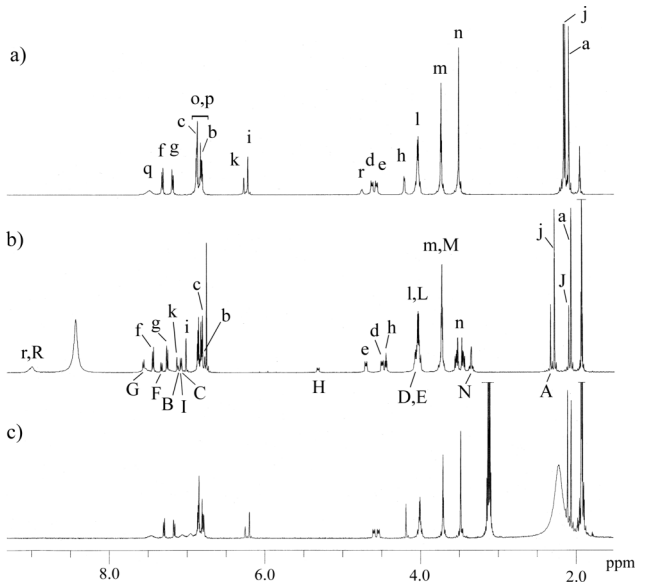


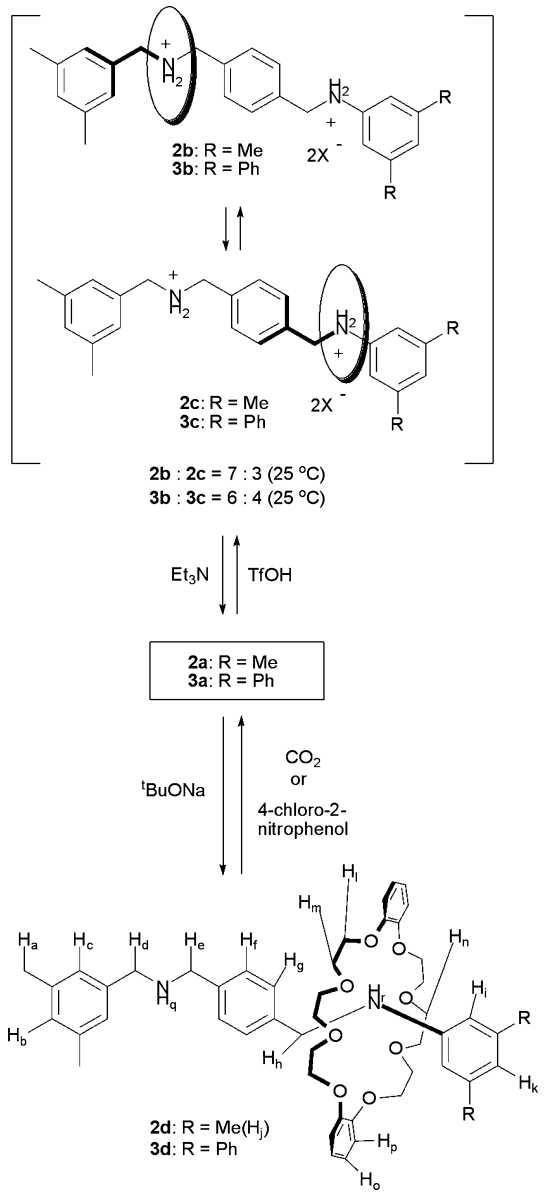
Fig. 2 ^{1}H NMR spectra (500 MHz, CD_3CN) of the [2]rotaxanes **2a–c**. (a) **2a** (X = HCO_3^-); (b) the sample in (a) after the addition of TfOH (5.0 eq.); (c) the sample in (b) after the addition of Et_3N (5.0 eq). Capital letters represent the signals of **2b**; lower-case letters for **2c**.

in the NOESY spectrum of **2a** (ESI†). As expected, only the more basic dialkylamine unit was protonated, forming the *N*,*N*-dialkylammonium cationic center, which acted as the preferred binding site under neutral conditions.[17,18]

Protonation-controlled molecular shuttling

The addition of five equivalents of trifluoromethanesulfonic acid (TfOH) to a solution of **2a** in CD_3CN led to the presence of two sets of signals related to the [2]rotaxane in the ^{1}H NMR spectrum. One new set of signals belonged to the doubly protonated [2]rotaxane **2b**, in which the DB24C8 unit encircles the dialkylammonium center (Fig. 2b and Scheme 2); the other represented its translational isomer **2c**, in which the anilinium center behaves as the recognition site for the DB24C8 unit. The signals for the protons of **2c** are all distinct from those of **2b**. The signals for the benzylic protons H_d and H_e of **2c** are shifted to significantly higher fields relative to those of **2b**, attributable to the loss of the deshielding effects of the DB24C8 unit. In addition, the signal for H_h moved to lower field, a likely result of the deshielding effect of the macrocycle. Shielding effects of the protons of the dimethylbenzyl unit, responsible for the upfield shifts in the signals of the aromatic (H_b and H_c) and methyl (H_a) protons of **2b**, were absent in **2c**. These signals are characteristic of crown ether/anilinium-type rotaxanes.[12]

Integration of the signals of the two species revealed a 7 : 3 mixture of **2b** and **2c** in CD_3CN at 25 °C; although we might have expected the DB24C8 unit to preferably encircle the anilinium unit, because its protons are more acidic than those of the dialkylammonium center, we suspect that the total factors, such as π–π stacking of the catechol rings of the DB24C8 unit with the aromatic units neighboring the dialkylammonium center and the differences of steric repulsions between both components, caused the equilibrium to favor **2b**. A mixture of **2a** and trifluoroacetic acid (5 eq.) in $CDCl_3$ afforded a 6 : 4 mixture of **2b** and **2c**.[14]



Scheme 2

The higher ratio of **2c** in $CDCl_3$ might reflect the greater role of hydrogen bonding in this less polar solvent.

Next, we investigated the effect of neutralization of the mixture of the [2]rotaxanes **2b** and **2c** on the relocation of the DB24C8 unit. Fig. 2c displays the ^{1}H NMR spectrum of the mixture of **2a** (10 mM) and TfOH (5 eq.) in CD_3CN after the addition of Et_3N (5 eq.); it reveals that the interconversion was reversible. Indeed, deprotonation of the anilinium units in **2b** and **2c** with Et_3N smoothly regenerated **2a**, with the DB24C8 unit relocated at the original dialkylammonium station.

Deprotonation-controlled molecular shuttling

After treating a solution of the [2]rotaxane **2a** in CD_3CN with a strong base, sodium *tert*-butoxide (^{t}BuONa, 1.2 eq.), and sonicating the mixture for several hours, the resulting ^{1}H NMR spectrum revealed a new set of signals (Fig. 3b and Scheme 2). The changes in chemical shift that occurred upon the addition of

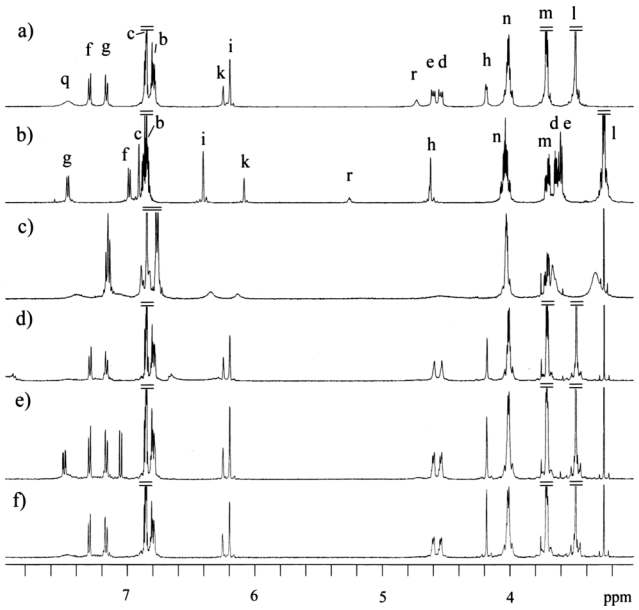


Fig. 3 ^{1}H NMR spectra (500 MHz, CD_3CN) of [2]rotaxanes **2a** and **2d**. (a) **2a** ($X = HCO_3^-$); (b) the sample in (a) after the addition of ^{t}BuONa (1.2 eq.); (c–f) the sample in (b) after the addition of (c) phenol (1.5 eq.), (d) 4-nitrophenol (1.5 eq.), (e) 4-chloro-2-nitrophenol (1.5 eq.), and (f) AcOH (1.5 eq.).

^{t}BuONa were consistent with the formation of a new [2]rotaxane **2d**, featuring two neutral amino groups. The signals of the benzylic protons H_d and H_e of **2d** had shifted significantly to higher fields relative to those of **2a**, attributable to the loss of the deshielding effects associated with the ammonium center and the encircling DB24C8 unit. In addition, the signal for the protons H_h moved to lower field, presumably because of deshielding induced by the encircling crown ether unit. Finally, we observed a correlation between the signals of the DB24C8 protons H_l and the dumbbell-shaped component's protons H_h in the NOESY spectrum of **2a** in the presence of ^{t}BuONa (ESI†), confirming the structure of **2d**.

Next, we examined the reversibility of the interconversion between **2a** and **2d**. Because a strong acid also promotes the protonation of the aniline unit, here we used a weak acid to ensure protonation only of the dibenzylammonium center. Fig. 3 displays the ^{1}H NMR spectrum of a mixture of **2a** (10 mM) and ^{t}BuONa (1.2 eq.) in CD_3CN and those obtained after the addition of several acids. Phenol ($pK_a = 9.9$) was not sufficiently acidic; the spectrum recorded after the addition of a small excess of phenol to **2d** in CD_3CN was not identical to that of **2a** (Fig. 3c). Notably, broad signals were present in this ^{1}H NMR spectrum, suggesting that protonation/deprotonation processes and/or interconversion of the translational isomers had rates similar to the NMR spectroscopic time scale at 500 MHz.[19] It appears that when hydrogen bonds exist, a *p*-phenylene group presents quite a steric barrier for the passage of the DB24C8 unit, resulting in slow interconversion of the components of the [2]rotaxane; as such the exchange processes were rapid in the absence of hydrogen bonding.

On the other hand, protonation of **2b** with a small excess of 4-nitrophenol (pK_a = 7.2), 4-chloro-2-nitrophenol (pK_a = 6.4),

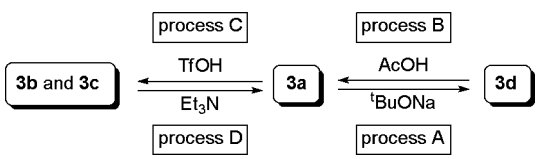
or AcOH (pK_a = 4.8) smoothly regenerated **2a**, with the macrocyclic unit positioned around the dialkylammonium center. Because the pK_a of H_2CO_3 is 6.5, similar to that of 4-chloro-2-nitrophenol, it is likely that we had isolated the [2]rotaxane **2a** in its mono-bicarbonate form after $LiAlH_4$-mediated reduction and exposure to the atmosphere. Although the addition of AcOH might have generated some protonated aniline species (because the pK_a of 4.6 of the anilinium ion is close to that of AcOH), we did not detect any clear signals representing anilinium ions in the resulting ^{1}H NMR spectrum.

Previously, we reported that selective *N*-acylation of the dialkylamine unit in the rotaxane **2a** occurs in the presence of strong bases.[14] We proposed that the strong base (*e.g.*, ^{t}BuONa) deprotonated the dialkylammonium center, causing the DB24C8 unit to interact only weakly with the amino groups; as a result, the more reactive dialkylamine in the deprotonated [2]rotaxane attacked the electrophiles selectively. As a result, the selective *N*-acylation of the [2]rotaxane **2a** led to positioning of the DB24C8 unit around the amino group of the aniline moiety.

Three-state molecular shuttling

Because this system features two reversible switching processes (addition of strong acid followed by weak base; addition of strong base followed by weak acid), we combined them to perform three-state switching through repeated cycling involving sequential addition of TfOH, Et_3N, ^{t}BuONa, and 4-chloro-2-nitrophenol. First, we added TfOH (5 eq.) to protonate the aniline unit; second, we added Et_3N (5 eq.) to neutralize the mixture; third, to deprotonate the dialkylammonium center in the dumbbell-shaped component and the generated $Et_3NH{\cdot}OTf$, we added ^{t}BuONa (7 eq.); finally, we added 4-chloro-2-nitrophenol (7 eq.) to the mixture. Using the same sequence, we required larger excesses of the additives to complete the second three-state switching cycle. We achieved up to four switching cycles, which we monitored using ^{1}H NMR spectroscopy (ESI†).

Using the same approach, we examined the three-state translational isomerization of the [2]rotaxane **3a**, bearing a 3,5-diphenylaniline moiety as a terminus. We performed the reversible transformations from **3a** to a mixture of **3b** and **3c** (process C) and back (process D) and from **3a** to **3d** (process A) and back (process B) using the corresponding acids and bases, with the existence of each state confirmed using ^{1}H NMR spectroscopy (Scheme 3 and the ESI†).



Scheme 3

The transformations of the [2]rotaxane **3** between its three states led to changes in its absorption properties (Fig. 4). For the [2]rotaxane **3a**, we observed a broad band having its maximum (λ_{max}) at approximately 333 nm, representative of a typical 3,5-diphenylaniline unit.[20] Addition of TfOH (10 eq.) decreased the intensity of the band as a result of protonation of the 3,5-diphenylaniline unit; note that the values of ε for

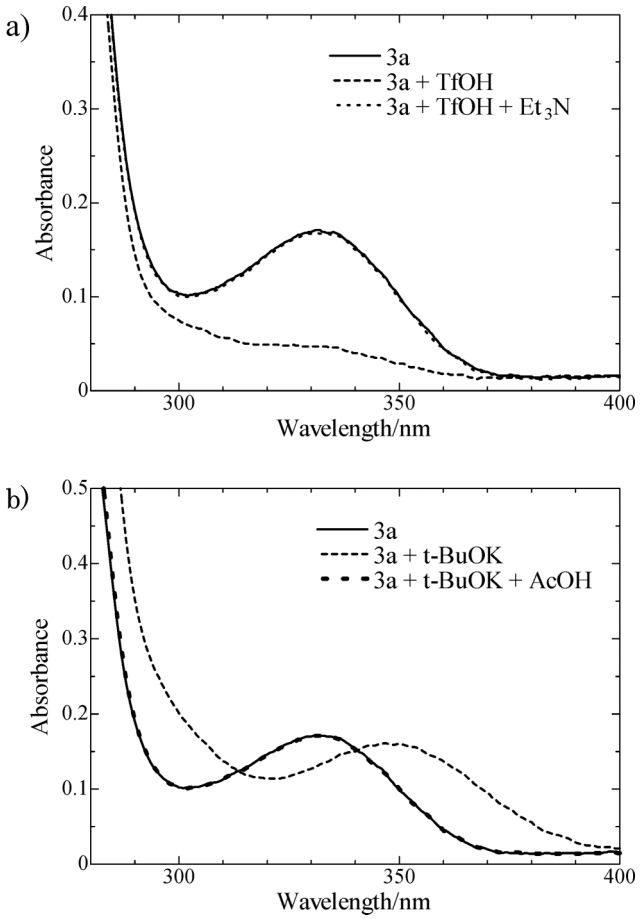
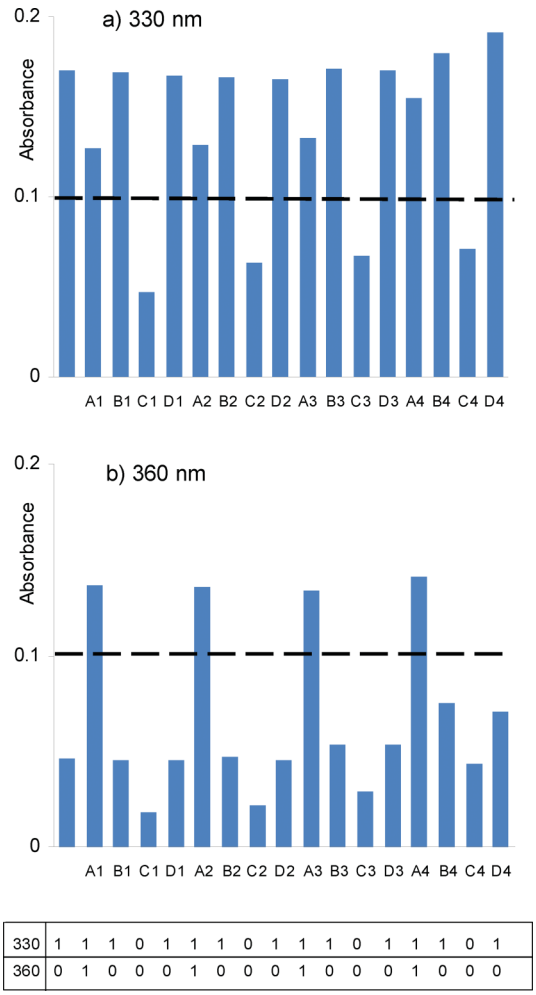


Fig. 4 (a) UV absorption spectra of the [2]rotaxanes **3a**, **3a** + TfOH (10 eq.), and **3a** + TfOH (10 eq.) + Et_3N (10 eq.) in CH_3CN–CH_3OH (9 : 1). (b) Absorption spectra of the [2]rotaxanes **3a**, **3a** + ^{t}BuOK (8 eq.), and **3a** + ^{t}BuOK (8 eq.) + AcOH (10 eq.) in CH_3CN–CH_3OH (9 : 1).

the π–π* transitions of aniline and anilinium species in water are 1430 and 160, respectively. Addition of Et_3N led to the recovery of the intensity of this signal. In contrast, the absorption maximum of the [2]rotaxane **3a** in the presence of ^{t}BuOK (1.5 eq.) appeared at 347 nm, presumably because of the interaction between the 3,5-diphenylaniline unit and the DB24C8 unit; this value of λ_{max} is close to those of similar rotaxanes featuring 3,5-diphenylaniline and [24]crown-8 units.[15] Protonation of the dialkylamine with AcOH led to spontaneous switching of the DB24C8 unit back to its original position and regenerated the broad band with its absorption maximum at 333 nm. Remarkably, the acid/base-mediated shuttling of the macrocyclic component could be repeated many times without obvious degradation. The spectral variations resulting from the interconversion of the three states were separately distinguishable by the absorptions at 330 and 360 nm. We can consider the intensities of the absorbances at 330 and 360 nm in the UV spectra as outputs, and the acidic, neutral, and basic conditions as inputs. Fig. 5 displays the operation of the rotaxane-based molecular switch, with detection based on absorbance at 330 or 360 nm (state 1: absorbance > 0.1; state 0: absorbance < 0.1). The three different inputs clearly reflect the operation of a logic gate; indeed, this multistate [2]rotaxane mimics three-input AND and XOR logic gates.[21]



330	1	1	1	0	1	1	1	0	1	1	1	0	1	1	1	0	1
360	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0

Fig. 5 Monitoring the three-state molecular switching of the [2]rotaxane **3** using UV spectroscopy through the absorbance at (a) 330 and (b) 360 nm. Processes A–D are defined in Scheme 3; 1–4 represent cycle numbers. Dashed lines indicate the detection limits. First line: no additive; A1: + ^{t}BuOK (10 eq.); B1: + AcOH (10 eq.); C1: + TfOH (30 eq.); D1: + Et_3N (15 eq.); A2: + ^{t}BuOK (40 eq.); B2: + AcOH (10 eq.); C2: + TfOH (85 eq.); D2: + Et_3N (10 eq.); A3: + ^{t}BuOK (90 eq.); B3: + AcOH (10 eq.); C3: + TfOH (320 eq.); D3: + Et_3N (10 eq.); A4: + ^{t}BuOK (310 eq.); B4: + AcOH (15 eq.); C4: + TfOH (640 eq.); D4: + Et_3N (260 eq.).

Summary

We have examined the acid/base-driven three-state molecular shuttling of a [2]rotaxane comprising DB24C8 as the macrocycle and dialkylamine (ammonium) and aniline (anilinium) units as stations in the dumbbell-shaped component. Under basic conditions, the DB24C8 unit encircled the aniline moiety; under neutral conditions, the macrocycle encircled the dialkylammonium station; under acidic conditions, both protonated amino groups acted as stations. Furthermore, UV spectroscopy revealed different absorption maxima for the three states of the [2]rotaxane possessing a 3,5-diphenylaniline terminus, with the intensity of the absorption of the aniline moiety being affected by the presence of the encircling DB24C8 species and the degree of protonation. The reversible shuttling of the macrocyclic component was, therefore, accompanied by reversible changes in the absorption intensity of the aniline terminus, making it possible for this rotaxane to act as a molecular storage device.

Experimental

General methods

Infrared spectra were recorded using a Shimadzu FTIR-8600PC instrument. ^{1}H NMR spectra were recorded using JEOL AL-300 and LA-500 spectrometers, with TMS as the internal standard. Mass spectra were recorded using a JMS-700T instrument. UV spectra were recorded using a HITACHI U-3900H spectrometer. All reactions were performed under a positive atmosphere of dry N_2, unless otherwise indicated. All solvents were removed through rotary evaporation under reduced pressure. Silica gel column chromatography was performed using Kanto Chemical silica gel 60N. Thin-layer chromatography was performed using Merck Kieselgel 60PF_{254}.

Rotaxane 2a. A suspension of the ammonium salt **1** (1.00 g, 2.50 mmol), DB24C8 (2.25 g, 5.01 mmol), and 3,5-dimethylaniline (0.34 g, 2.76 mmol) in dichloromethane (10 ml) and acetonitrile (10 ml) was stirred at rt for 1.5 days. Evaporation of the solvent gave the corresponding crude imine, which was dissolved in THF (40 ml) and added to a suspension of $LiAlH_4$ (0.36 g, 14.7 mmol) in THF (20 ml) at 0 °C. The resulting mixture was stirred at rt for 2 h and then treated with water, stirred under air, and filtered. The filtrate was concentrated and the residue purified chromatographically (SiO_2; $CHCl_3$/MeOH, 10 : 1) to yield crude **2a**, which was washed with hexane and dried to afford **2a** (1.42 g, 61% from **1**) as a solid. IR (KBr) ν_{max} 3146, 3020, 2916, 1599, 1503, 1450, 1251, 1210, 1120, 1056, 952, 840, 749 cm^{-1}. ^{1}H NMR (500 MHz, CD_3CN) δ 2.07 (s, 6H), 2.12 (s, 6H), 3.45–3.54 (m, 8H), 3.67–3.76 (m, 8H), 3.97–4.06 (m, 8H), 4.19 (d, J = 5.2 Hz, 2H), 4.52–4.56 (m, 2H), 4.58–4.64 (m, 2H), 4.71–4.77 (m, 1H), 6.20 (br s, 2H), 6.25 (br s, 1H), 6.77–6.90 (m, 11H), 7.14–7.18 (m, 2H), 7.28–7.32 (m, 2H), 7.38–7.57 (br s, 2H). ^{13}C NMR (125 MHz, CD_3CN) δ 26.8, 31.2, 34.6, 52.2, 52.4, 68.2, 70.2, 70.6, 112.7, 121.8, 125.5, 126.3, 127.3, 127.9, 128.3, 128.7, 129.0, 129.1, 129.3, 130.5, 137.6, 137.7, 143.0, 147.5, 152.5. HR MS (FAB) calcd for $C_{49}H_{63}N_2O_8^+$ [M – HCO_3]$^+$: m/z 807.4569; found: m/z 807.4584.

Rotaxane 3a. Following the procedure outlined above, but using 3,5-diphenylaniline as the amine, we obtained **3a** as a solid in 60% yield. IR (neat) ν_{max} 3444, 3151, 3059, 2931, 1597, 1504, 1454, 1254, 1215, 1122, 1057, 953, 845, 756, 559. ^{1}H NMR (500 MHz, CD_3CN) δ 2.00 (s, 3H), 2.14 (s, 3H), 3.36–3.38 (m, 8H), 3.57–3.62 (m, 8H), 3.84–3.96 (m, 8H), 4.40 (d, J = 6.4 Hz, 2H), 4.48–4.51 (m, 2H), 4.54–4.58 (m, 2H), 5.29 (br t, J = 6.4 Hz, 2H), 6.71–6.77 (m, 4H), 6.80–7.69 (m, 20H), 7.11 (t, J = 1.5 Hz, 1H), 7.23–7.36 (m, 6H), 7.36–7.45 (m, 4H), 7.59–7.64 (m, 4H). ^{13}C NMR (125 MHz, CD_3CN) δ 21.18, 47.40, 53.18, 53.34, 68.96, 71.00, 71.43, 111.75, 113.51, 115.46, 122.27, 127.83, 127.95, 128.42, 128.47, 129.81, 130.76, 131.09, 131.54, 132.86, 139.15, 142.34, 142.47, 143.28, 148.50, 150.13. Anal. calcd for $C_{59}H_{67}F_6N_2O_8P$: C, 65.79; H, 6.27; N, 2.60%; found: C, 65.59; H, 6.40; N, 2.52%. MS (FAB) calcd for $C_{59}H_{67}N_2O_8^+$ [M – PF_6]$^+$: m/z 931.5; found: m/z 931.5.

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