# SPEED-CONTROLLED MOLECULAR SHUTTLES

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Received August 6, 2002
Accepted September 20, 2002

Five potential molecular shuttles based on degenerate [2]rotaxanes – wherein the ring component is a bis-1,4-phenylene[34]crown-10 and the dumbbell components are terminated by tetraarylmethane (slippage) stoppers and contain two identical bipyridinium recognition sites and a central 1,3-phenylene unit carrying a $CH_2OR$ (R = Me, Et, Ph, i-Pr, and *t*-Bu) substituent on its C-5 position – have been prepared by acylating the parent hydroxymethyl derivative with the appropriate reagents. Dynamic $^1H$ NMR spectroscopy, carried out on these five potential molecular shuttles in $CD_3CN$ solutions, has revealed average Gibbs energy barriers to shuttling of 11.5, 12.0, 14.6, and 14.8 kcal $mol^{-1}$ for the [2]rotaxanes where R = Me, Et, i-Pr, and Ph, respectively. For the [2]rotaxane where R = *t*-Bu, the Gibbs energy barrier to shuttling must exceed 17.2 kcal $mol^{-1}$.

**Keywords**: Dynamic NMR spectroscopy; Molecular recognition; Molecular shuttle; Post-assembly covalent modification; Rotaxanes; Molecular machines; Crown ethers; Bipyridinium salts.

Molecular compounds, comprised of mechanically interlocked components, can now be assembled[1–4] efficiently using template-directed protocols[5] that rely upon supramolecular assistance to covalent synthesis[3]. Since the weak noncovalent bonding interactions that orchestrate the synthesis of such compounds – *e.g.*, catenanes and rotaxanes[6] – containing mechanical bonds live on between the components inside the molecules thereafter, they can be activated such that their components move with respect to each other in either a linear fashion – *e.g.*, the ring component along the rod of the dumbbell component of a [2]rotaxane as in a molecular shuttle[7] – or a rotary manner – *e.g.*, one ring in a [2]catenane circumrotating through the other ring as in a bistable switch[8]. Moreover, these molecules can be activated[9–11] by switching the recognition elements on and off between the components chemically, electrically, and optically such that they perform motions – *e.g.*, shuttling actions or muscle-like elongations and

contractions – reminiscent of the moving parts in macroscopic machines. Such motor-molecules and molecular machines hold considerable promise[12] for the fabrication of sensors, actuators, amplifiers and switches at the nanoscale level.

Although the vast majority of research to date has been carried out in the context[7–11] of solution-phase mechanical processes, we have demonstrated[13] recently that relative mechanical movements between the components in interlocked molecules can be stimulated electrically within the setting of a solid-state device. Not only has reversible, electronically driven switching been observed[14] in devices incorporating a bistable [2]catenane, but a crosspoint random access memory circuit and a simple logic circuit have been fabricated[15] using an amphiphilic, bistable [2]rotaxane. These experiments can be considered as positive evidence that switchable catenanes and rotaxanes perform and can withstand simple device-processing steps.

In order to exercise some control over the fabrication of such devices, it is important that the kinetics of switching at the molecular level are understood in solution prior to introducing the bistable molecules into a solid-state device. Movement of the ring component along the dumbbell-shaped component in a [2]rotaxane is always associated with an energy barrier and so the rate of the process can be controlled sterically and electronically. A convenient way to investigate these energy barriers is to study the shuttling speeds in degenerate [2]rotaxanes, *i.e.*, molecular shuttles, by dynamic NMR spectroscopy.

The well-characterized molecular recognition[16] between bipyridinium dications, such as the herbicide paraquat[17] and the crown ether, bis-1,4-paraphenylene[34]crown-10 (BPP34C10) has been used extensively[1,18] in the template-directed synthesis[19] of catenanes and rotaxanes. The basis for the molecular recognition is found in [π–π] stacking, [C–H···O], and [C–H···π] interactions. These interactions have been employed in a thermodynamically controlled method of rotaxane synthesis we call slippage[20]. This method has been employed[21] to make degenerate two-station [2]rotaxanes, *i.e.*, molecular shuttles, comprised of two bipyridinium units and a BPP34C10 ring. Dynamic $^1$H NMR spectroscopy has revealed[22] that the shuttling process is fast (≈300 kHz) in these molecular shuttles at room temperature. Although there are numerous factors, such as the strength of the noncovalent bonding interactions between the components and the choice of solvents in addition to the temperature, that influence the rate of shuttling in degenerate two-station [2]rotaxanes, the constitution of the rod section in the dumbbell component between the two recognition sites is an important control element. We were interested in exploring how shuttling

speeds could be controlled (Fig. 1) in a homologous series of molecular shuttles with different sizes of "speed bumps". Here, we report the preparation of such a homologous series from a known degenerate, two-station [2]rotaxane and demonstrate how dynamic NMR spectroscopy can be employed to study the influence of "speed bumps" upon rates of shuttling.

## EXPERIMENTAL

### General

Solvents were purchased from Aldrich and E. M. Sciences and purified according to literature procedures[23]. Reagents were purchased from Aldrich. The hydroxymethyl-substituted [2]rotaxane **1**·4$PF_6$ was prepared according to a literature procedure[24]. Thin-layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel 60F (Merck 5554). The plates were inspected by using UV light prior to development with Draggendorff reagent[25]. Preparative TLC was carried out using glass plates precoated with 1000 or 250 μm of silica gel GF (Techware). Plates were inspected by UV light. Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. Positive-ion electrospray mass spectra (ESMS) were recorded on an API IIIR Applied Biosystems Ionspray™ Source. High resolution mass spectrometry was performed on an Ionspec Ultima 7T Fourier transform ion cyclotron resonance spectrometer. $^1$H NMR spectra were recorded on a Bruker Avance 500 spectrometer. All chemical shifts are quoted in ppm on the δ-scale, using residual solvent as the internal standard. Coupling constants (*J*) are given in Hz.

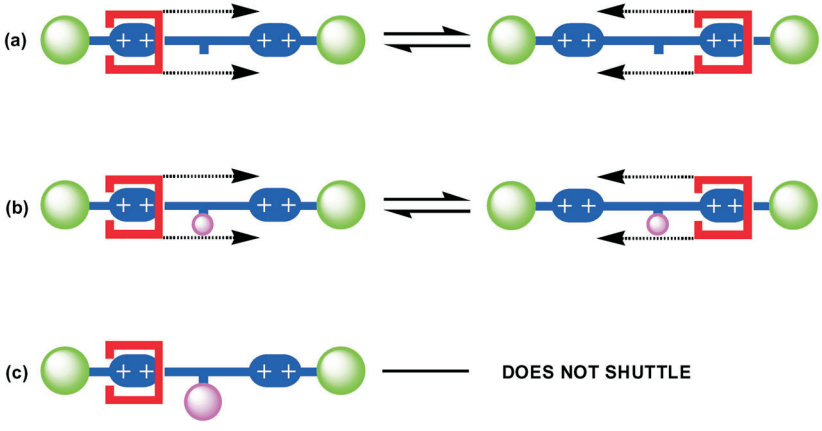



FIG. 1
Shuttling in degenerate, two-station [2]rotaxanes. In the absence of a steric barrier, fast shuttling is observed (a). When a small steric barrier is introduced between the two recognition sites, shuttling is slowed down (b). Finally, the steric barrier group can be of sufficient size to prevent shuttling altogether (c)

General Method for the Synthesis of the [2]Rotaxane Esters **2a**–**2e**·$PF_6$

The requisite acyl chloride (0.5 mmol) was added to a solution of the hydroxymethyl-substituted [2]rotaxane[21,24] **1**·4$PF_6$ (28 mg, 10 μmol) in THF (0.6 ml) and pyridine (0.1 ml) and the reaction mixture was stirred for 3 h. An aqueous solution of $NH_4PF_6$ (10%, 10 ml) was then added and the orange-red solid which precipitated was filtered off and subjected to preparative TLC ($SiO_2$: 5 mM $NH_4PF_6$ in $Me_2CO$). The resulting acyl derivatives **2a**–**2e**·4$PF_6$ were washed with $H_2O$ and dried.

*Shuttle **2a**·4$PF_6$ with an acetyl "speed bump"*. Orange-red powder. Yield 22 mg (77%), m.p. >250 °C. High resolution ESMS, *m/z*: 1283.0769 (calculated for $C_{147}H_{166}F_{24}N_4O_{18}P_4$: 1283.0752, $[M - 2PF_6]^{2+}$). $^1$H NMR ($CD_3CN$): 8.83–8.89 (m, 8 H); 7.95 (br d, 8 H); 7.71 (br s, 3 H); 7.50 (d, *J* = 9, 4 H); 6.99–7.29 (m, 34 H); 6.76 (d, *J* = 9, 4 H); 5.92 (s, 8 H); 5.88 (s, 4 H); 5.70 (s, 4 H); 5.15 (s, 2 H); 4.01–4.12 (m, 8 H); 3.75–3.81 (m, 8 H); 3.42–3.70 (m, 32 H); 1.97 (s, 3 H); 1.25 (s, 36 H).

*Shuttle **2b**·4$PF_6$ with a propionyl "speed bump"*. Orange-red powder. Yield 20 mg (70%), m.p. >250 °C. High resolution ESMS, *m/z*: 1290.0851 (calculated for $C_{148}H_{168}F_{24}N_4O_{18}P_4$: 1290.0830, $[M - 2PF_6]^{2+}$). $^1$H NMR ($CD_3CN$): 8.83–8.88 (m, 8 H); 7.99 (br d, 8 H); 7.70 (br s, 3 H); 7.49 (br d, *J* = 9, 4 H); 6.98–7.30 (m, 34 H); 6.77 (d, *J* = 9, 4 H); 5.90 (s, 8 H); 5.88 (s, 4 H); 5.71 (s, 4 H); 5.18 (s, 2 H); 4.00–4.14 (m, 8 H); 3.75–3.82 (m, 8 H); 3.42–3.68 (m, 32 H); 2.33 (q, 2 H); 1.25 (s, 36 H); 1.05 (t, 3 H).

*Shuttle **2c**·4$PF_6$ with a benzoyl "speed bump"*. Orange-red powder. Yield 24 mg (82%), m.p. >250 °C. High resolution ESMS, *m/z*: 1314.0783 (calculated for $C_{152}H_{168}F_{24}N_4O_{18}P_4$: 1314.0830, $[M - 2PF_6]^{2+}$). $^1$H NMR ($CD_3CN$): 8.79–8.98 (m, 8 H); 8.23 (br d, 4 H); 7.98 (d, 4 H); 7.36–7.90 (m, 12 H); 6.95–7.30 (m, 34 H); 6.75 (br d, 4 H); 5.93 (br s, 8 H); 5.91 (br d, 4 H); 5.70 (br d, 4 H); 5.43 (s, 2 H); 4.01–4.13 (m, 8 H); 3.75–3.81 (m, 8 H); 3.39–3.70 (m, 32 H); 1.26 (s, 36 H).

*Shuttle **2d**·4$PF_6$ with an isobutyryl "speed bump"*. Orange-red powder. Yield 21 mg (73%), m.p. >250 °C. High resolution ESMS, *m/z*: 1297.0925 (calculated for $C_{149}H_{170}F_{24}N_4O_{18}P_4$: 1297.0908, $[M - 2PF_6]^{2+}$). $^1$H NMR ($CD_3CN$): 8.75–8.89 (m, 8 H); 8.19 (d, 4 H); 7.35–7.78 (m, 11 H); 6.95–7.28 (m, 34 H); 6.75 (br d, 4 H); 5.90 (br s, 10 H); 5.82 (br s, 2 H); 5.73 (s, 2 H); 5.15 (br s, 2 H); 5.12 (s, 2 H); 3.98–4.14 (m, 8 H); 3.70–3.81 (m, 8 H); 3.40–3.68 (m, 32 H); 2.48 (m, 1 H); 1.21 (s, 36 H); 1.06 (d, 6 H).

*Shuttle **2e**·4$PF_6$ with a pivaloyl "speed bump"*. Orange-red powder. Yield 19 mg (66%), m.p. >250 °C. High resolution ESMS, *m/z*: 1304.988 (calculated for $C_{150}H_{172}F_{24}N_4O_{18}P_4$: 1304.0986, $[M - 2PF_6]^{2+}$). $^1$H NMR ($CD_3CN$): 8.82–8.92 (m, 8 H); 8.29 (d, 2 H); 8.16 (d, 2 H); 7.89 (d, 2 H); 7.81 (s, 1 H); 7.82 (d, 2 H); 7.79 (s, 0.5 H); 7.55 (s, 0.5 H); 7.52 (s, 1 H); 7.45 (d, 2 H); 6.95–7.30 (m, 36 H); 6.88 (d, 2 H); 6.84 (d, 2 H); 5.94 (s, 8 H); 5.91 (s, 2 H); 5.87 (s, 2 H); 5.77 (s, 2 H); 5.70 (s, 2 H); 5.17 (s, 2 H); 4.01–4.12 (m, 8 H); 3.72–3.81 (m, 8 H); 3.40–3.70 (m, 32 H); 2.48 (m, 1 H); 1.26 (s, 36 H); 1.23 (s, 9 H).

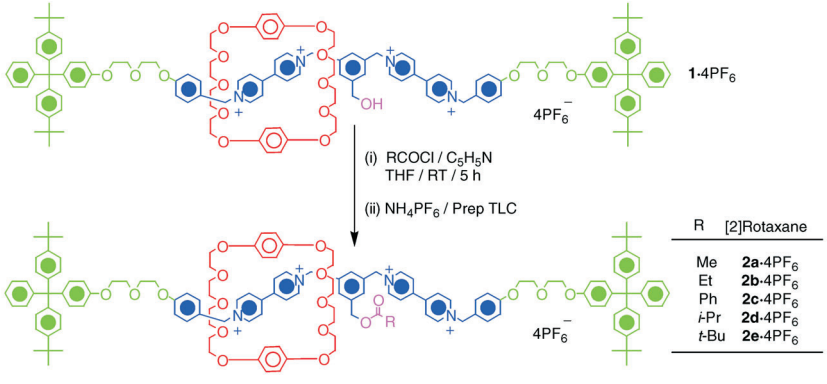
Dynamic $^1$H NMR Spectroscopy

Molecular shuttles **2a**–**2e**·4$PF_6$ were investigated by $^1$H NMR (500 MHz) spectroscopy at various temperatures in the range between the melting (228 K) and boiling (353 K) points of MeCN at 10-degree intervals. Various probe protons were identified on the dumbbell and ring components of the molecules and from their resonant line shape behaviors the coalescence temperatures were determined. The lowest temperature at which the coalescence of signals was observed for a particular probe proton before the signals started to split into two

was noted. Around these temperatures, the spectra were recorded at one-degree intervals and the final coalescence temperature, $T_c$, was obtained using MeOH (for temperatures below 298 K) and ethylene glycol (for temperatures above 298 K) as standards. Also the chemical shift difference $\Delta\nu$ (in Hz) between the coalescing signals in the absence of exchange at low temperatures was measured. The kinetic data were obtained[26] from (i) the approximate expression $k_c = \pi(\Delta\nu)/(2)^{1/2}$ at $T_c$ for the site exchange of equal intensity signals and from (ii) the approximate expression $k_c = \pi[\Delta\nu_{AB}^2 + 6J_{AB}^2]^{1/2}/(2)^{1/2}$ at $T_c$ for the site exchange between the A and B protons of an AB system where $\Delta\nu_{AB}$ is the separation (in Hz) at low temperature between the A and B signals in the absence of exchange and $J_{AB}$ is the coupling constant (in Hz). The use of both of these expressions was associated with further approximations. In the case of the first expression, the signals were not always singlets, *i.e.*, the exchanging protons were coupled to other protons, and in the case of the second expression, the signals were not always "pure" AB systems, *i.e.*, the A and B protons were also coupled to other protons as well as to each other. In both cases, these additional couplings were ignored and in the case of the AB systems a value for $J_{AB}$ of 10 Hz was used for the geminal ($OCH_2$) probe protons. The Eyring equation was used to calculate Gibbs energies of activation, $\Delta G_c^{\ddagger}$, at the coalescence temperatures, $T_c$.

## RESULTS AND DISCUSSION

The post-assembly covalent modifications of the [2]rotaxane[21,24] **1**·4$PF_6$ are summarized in Scheme 1. Five esters, **2a**–**2e**·4$PF_6$, incorporating methyl, ethyl, phenyl, isopropyl, and *tert*-butyl R-groups were prepared. In all these degenerate, two station [2]rotaxanes, except for the *tert*-butyl derivative **2e**·4$PF_6$, the molecular shuttling process could be studied by variable temperature $^1$H NMR spectroscopy in $CD_3CN$ solution. Table I lists limiting chemical shift differences ($\Delta\nu$) for selected probe protons in compounds




SCHEME 1
Post assembly covalent modification of the degenerate molecular shuttle **1**·4$PF_6$ to give the [2]rotaxanes **2a**–**2e**·4$PF_6$

**2a**–**2d**·4$PF_6$, the appropriate rate constants ($k_c$) at the coalescence temperatures ($T_c$), and the derived free energies of activation ($\Delta G_c^{\ddagger}$) at the relevant coalescence temperatures for the shuttling processes. In the case of the pivaloyl ester **2e**·4$PF_6$, de-slippage started to compete with shuttling at the relatively high temperatures (*ca* 80 °C) required to carry out the dynamic $^1$H NMR experiment. Consequently, only a limiting $\Delta G_c^{\ddagger}$ value could be obtained for this compound. The other four esters, namely **2a**–**2d**·4$PF_6$, were amenable to investigation by dynamic $^1$H NMR spectroscopy. Figure 2 records a typical set of variable temperature $^1$H NMR spectra for the acetyl ester **2a**·4$PF_6$. It reveals temperature-dependent behavior for (i) a proton

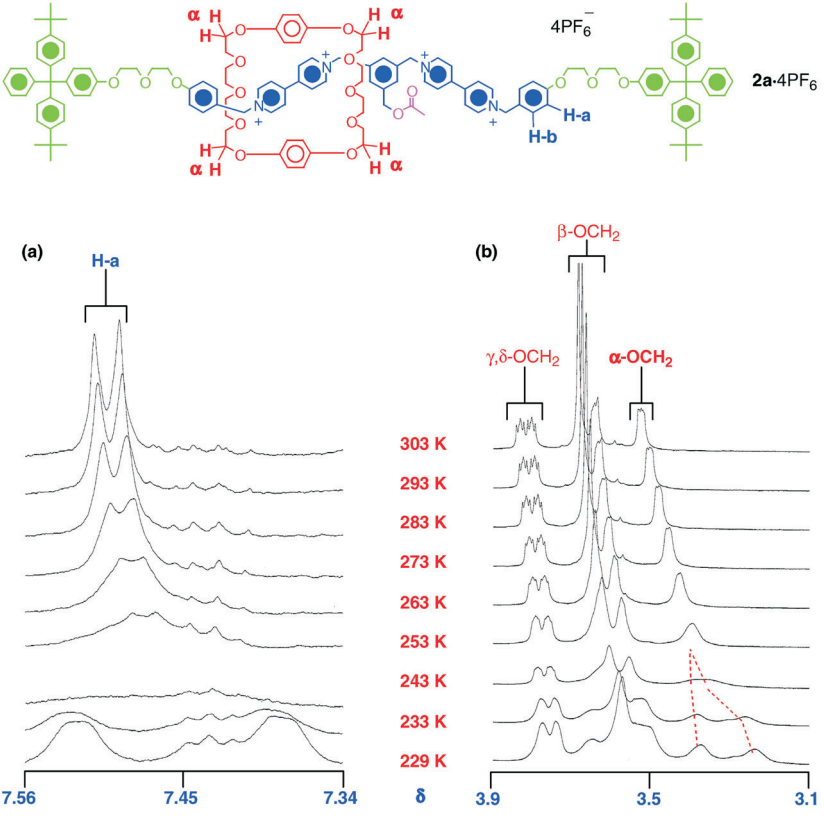



FIG. 2

Partial $^1$H NMR spectra (500 MHz, $CD_3CN$) recorded at different temperatures displaying the coalescence of the signals for two sets of probe protons in **2a**·4$PF_6$. Signals arising from dumbbell probe protons H-a (a). Signals arising from α-$OCH_2$ ring protons (b)

H-a in the dumbbell portion of the rotaxane and (ii) one of the *O*-methylene groups (α-$OCH_2$) in the ring component. Separate analyses of the spectra using the approximate coalescence method[26] give very similar $\Delta G_c^{\ddagger}$ values of 11.4 and 11.5 kcal $mol^{-1}$ at $T_c$ values of 238 and 240 K, respectively. An appraisal of the $\Delta G_c^{\ddagger}$ values listed in Table I indicates that they increase gradually across the series on going from R = Me (**2a**·$4PF_6$) to R = Et (**2b**·$4PF_6$) but then they are very similar for R = i-Pr (**2c**·$4PF_6$) and R = Ph (**2d**·$4PF_6$), before increasing dramatically for R = *t*-Bu (**2e**·$4PF_6$). The only surprise across the series was the lower than expected $\Delta G_c^{\ddagger}$ value of 14.6–14.9 kcal $mol^{-1}$ for the benzoyl ester **2c**·$4PF_6$. It is not inconceivable that π–π stacking interactions, involving its benzene ring and other aromatic rings in the [2]rotaxane may assist in making the passage of the BPP34C10 ring between the two bipyridinium units easier than might have been anticipated.

TABLE I
Kinetic and thermodynamic parameters[a] obtained from the temperature-dependent $^1H$ NMR spectra recorded on the [2]rotaxanes **2a**–**2e**·$4PF_6$

| Compound | Probe protons | $\Delta\nu^b$, Hz | $k_c^c$, $s^{-1}$ | $T_c^d$, K | $\Delta G_c^{\ddagger e}$ kcal $mol^{-1}$ | R-Group |
|---|---|---|---|---|---|---|
| **1**·$4PF_6$ | α-$CH_2O$ | – | – | <225 | – | H |
| **2a**·$4PF_6$ | α-$CH_2O$ | 68.4 | 161 | 238 | 11.4 | Me |
| | H-a | 70.5 | 157 | 240 | 11.5 | |
| **2b**·$4PF_6$ | α-$CH_2O$ | 70.0 | 165 | 243 | 11.7 | Et |
| | H-a | 17.0 | 38 | 238 | 12.1 | |
| | H-b | 73.0 | 162 | 255 | 12.3 | |
| **2c**·$4PF_6$ | α-$CH_2O$ | 60.1 | 144 | 300 | 14.6 | Ph |
| | H-a | 9.0 | 20 | 283 | 14.9 | |
| **2d**·$4PF_6$ | α-$CH_2O$ | 62.3 | 149 | 308 | 15.0 | i-Pr |
| | H-a | 17.0 | 38 | 283 | 14.5 | |
| | *t*-Bu | 2.5 | 6 | 255 | 14.0 | |
| **2e**·$4PF_6$ | α-$CH_2O$ | 16.0 | <65 | >353 | >17.2 | *t*-Bu |

[a] Determined by variable-temperature $^1H$ NMR spectroscopy (500 MHz) in $CD_3CN$. [b] Limiting frequency separation. [c] Rate constant at the coalescence temperature. [d] Coalescence temperature. [e] Free energy barrier at the coalescence temperature calculated from the Eyring equation.

## CONCLUSIONS

On the basis of only five examples, it is clear that shuttling in donor–acceptor rotaxanes can be tuned over a wide range (at least 6 kcal $mol^{-1}$ in energy barrier differences) of frequencies. It might be possible to exploit such controllable "speed bumps" in amphiphilic, bistable [2]rotaxane switches that would employ the donor–acceptor recognition motif[18] in a manner opposite from that[15] which has been employed so far in solid-state electronic devices.

## SYMBOLS

| | |
|---|---|
| $\Delta\nu$ | limiting frequency separation, Hz |
| $k_c$ | rate constant at the coalescence temperature, $s^{-1}$ |
| $T_c$ | coalescence temperature, K |
| $\Delta G_c^{\ddagger}$ | Gibbs energy barrier at the coalescence temperature calculated from the Eyring equation, kcal $mol^{-1}$ |

*This work was supported by the Defense Advanced Research Projects Agency (DARPA). The variable temperature NMR investigations were supported by the National Science Foundation under equipment grant number CHE-9974928.*

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