Optically sensed, molecular shuttles driven by acid–base chemistry†

Sarah J. Vella, Jorge Tiburcio and Stephen J. Loeb*

Received (in Austin, TX, USA) 12th July 2007, Accepted 28th August 2007
First published as an Advance Article on the web 10th September 2007
DOI: 10.1039/b710708k

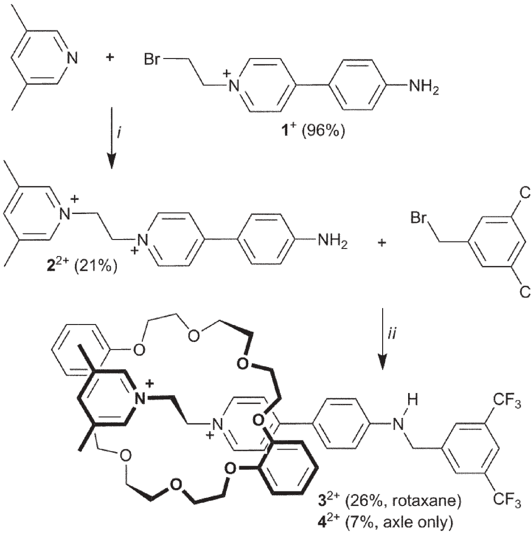
A pair of bistable [2]rotaxane, molecular shuttles were prepared that combine 1,2-bis(pyridinium)ethane and benzylanilinium recognition sites; acid–base controlled shuttling of DB24C8 was accompanied by a change in colour and/or fluorescence intensity.

A number of molecular switches based on the concept of a molecular shuttle have been reported.[1] The design of such a bistable rotaxane requires two different recognition sites on the axle and a method for controlling the positioning of the wheel component. Ideally, this equilibrium situation can be tuned such that each of the two possible positions of the wheel can be stabilised almost exclusively resulting in the apparent observation of two distinct states; ON and OFF. Conversion between the two states can then be induced by altering the position of the equilibrium *via* some type of external perturbation.[2] In addition, a desirable feature would be the ability to observe this ON/OFF molecular switching by some easily detectable optical signal such as a change in colour or fluorescence intensity.[3]

We recently reported the formation of [2]pseudorotaxanes utilising benzylanilinium axles and dibenzo-24-crown-8 ether (**DB24C8**) wheels.[4] This motif combines the strong N–H···O hydrogen bonding and acid/base control of the dialkylammonium template with the enhanced π-stacking properties found for the recognition of 1,2-bis(pyridinium)ethane dications.[5] We have also reported control over [2]pseudorotaxane formation for a specific type of 1,2-bis(pyridinium)ethane axle and **DB24C8** due to the switching ON/OFF of an intramolecular charge transfer (ICT).[6] We report herein, the synthesis of two acid–base driven [2]rotaxane molecular shuttles that incorporate both the benzylanilinium and 1,2-bis(pyridinium)ethane recognition sites.

The [2]rotaxane molecular shuttles were synthesized as shown in Scheme 1. A Suzuki coupling reaction was used to synthesize 4-pyridylaniline[7] which was subsequently reacted in neat 1,2-dibromoethane to form the bromoethylpyridinium species $\mathbf{1}^+$. Further reaction with 3,5-lutidine, which also conveniently acts as a stopper,[8] gave $\mathbf{2}^{2+}$ which was combined in a two-phase solvent system with five equivalents of **DB24C8** and half an equivalent of 3,5-bis(trifluoromethyl)benzyl bromide to give the [2]rotaxane molecular shuttle $\mathbf{3}^{2+}$.

Comparing the ^{1}H NMR spectrum, in MeCN-d_3, of [2]rotaxane $\mathbf{3}^{2+}$ with that for the stoppered axle $\mathbf{4}^{2+}$ indicates that the ethylene protons *d* and *e*, as well as the *ortho* pyridinium protons *c* and *f* shift downfield since they are involved in hydrogen-bonding with the crown ether, and the proton resonances *b*, *g* and *h* shift upfield due to π-stacking interactions. In contrast, protons belonging to the benzylaniline portion of the axle, *i*, *k*, *l* and *m*, do not shift indicating **DB24C8** only interacts with the 1,2-bis(pyridinium)-ethane recognition site. This is to be expected since unprotonated benzylaniline is incapable of complexing with **DB24C8**.[4]



Scheme 1 Preparation of [2]rotaxane molecular shuttle $\mathbf{3}^{2+}$. *Reagents and conditions*: (*i*) MeCN, reflux, 48 h; (*ii*) 5 equiv. **DB24C8** in a two-layer MeNO$_2$/NaOTf (aq) mixture at room temperature for 7 days; in the absence of crown this produces the axle $\mathbf{4}^{2+}$. All cations are isolated as the CF$_3$SO$_3^-$ (OTf$^-$) salts.

Single crystals of [**3**][OTf]$_2$ were grown by slow evaporation of an MeCN solution. Fig. 1 shows the structure of $\mathbf{3}^{2+}$ and verifies that **DB24C8** resides at the 1,2-bis(pyridinium)ethane binding site.‡ The crown ether adopts a less common C-shaped conformation[9] instead of the typical S-shaped one seen for most

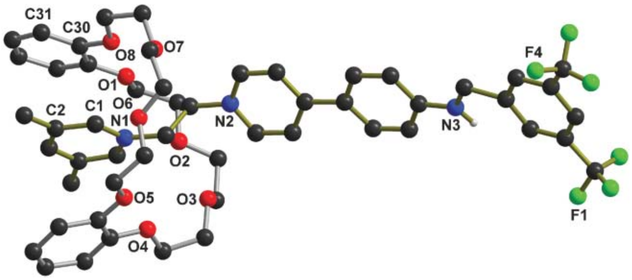


Fig. 1 A ball-and-stick representation of the X-ray crystal structure of molecular shuttle $\mathbf{3}^{2+}$ showing the numbering scheme. Blue = nitrogen, red = oxygen, green = fluorine, black = carbon. Carbon atoms are numbered continuously along the pyridinium axle and around the macrocycle wheel.

Department of Chemistry and Biochemistry, University of Windsor, Windsor, Ontario, Canada. E-mail: loeb@uwindsor.ca; Fax: 1 519 973 7098; Tel: 1 519 253 3000

† Electronic supplementary information (ESI) available: Detailed synthesis of compounds **1**–**5**. See DOI: 10.1039/b710708k

other crystal structures with this binding motif.[10] This is attributed to the presence of a significant intramolecular charge transfer from the aniline nitrogen to the pyridinium nitrogen which reduces the positive charge at the pyridinium nitrogen and increases the electron density of the pyridinium ring thus disfavouring π-stacking. Consequently, **DB24C8** interacts in a double π-stacking manner with the lutidinium ring; centroid to centroid distances are 3.82 and 3.75 Å. Both the N–*CH₂CH₂*–N and C–*NH*–*CH₂*–C chains adopt the stepped *anti* conformation favourable for interaction with **DB24C8**.

Since we have previously shown that a benzylanilinium group (*i.e.* a protonated aniline) will bind **DB24C8** quite effectively,[4] it was of interest to add H^+ to $\mathbf{3}^{2+}$ to create H-$\mathbf{3}^{3+}$ and set up a competition for **DB24C8** between the two types of recognition sites. Fig. 2 shows the ^{1}H NMR spectra, in CD_2Cl_2, of the molecular shuttle states $\mathbf{3}^{2+}$ and H-$\mathbf{3}^{3+}$. For both $\mathbf{3}^{2+}$ and H-$\mathbf{3}^{3+}$, only one set of peaks is observed. For $\mathbf{3}^{2+}$, the spectrum is very similar to that observed in MeCN-d_3 and indicates that **DB24C8** resides at the 1,2-bis(pyridinium)ethane site. While for H-$\mathbf{3}^{3+}$, it appears that upon protonation **DB24C8** prefers to reside at the benzylanilinium recognition site. A comparison of the ^{1}H NMR spectra of rotaxane H-$\mathbf{3}^{3+}$ and axle H-$\mathbf{4}^{3+}$ shows that protons *a*–*f*, those located at the 1,2-bis(pyridinium)ethane site, do not shift indicating this site does not interact with **DB24C8**. In contrast, protons associated with the benzylanilinium site, *i*, *j*, *k* and *l* shift downfield as a result of hydrogen-bonding and *h* and *m* shift upfield due to π-stacking.

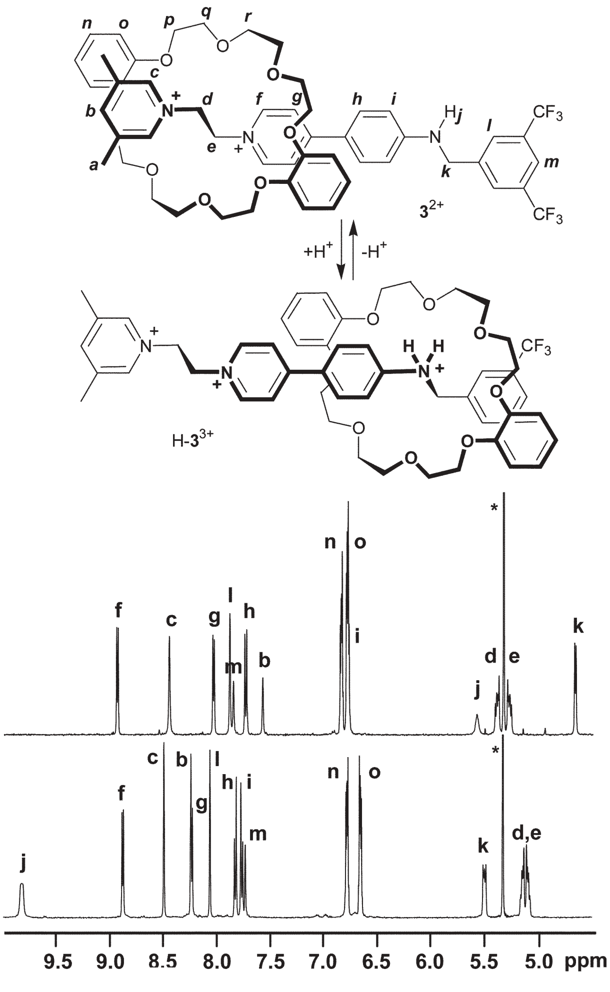


Fig. 2 A comparison of the ^{1}H NMR spectra of $\mathbf{3}^{2+}$ (top) and H-$\mathbf{3}^{3+}$ (bottom) in CD_2Cl_2 at 298 K.

Thus, the ^{1}H NMR spectra in CD_2Cl_2 of unprotonated and protonated molecular shuttles $\mathbf{3}^{2+}$ and H-$\mathbf{3}^{3+}$ provide direct evidence that when the axle is unprotonated **DB24C8** prefers the 1,2-bis(pyridinium)ethane site and when the axle is protonated the crown prefers the benzylanilinium site. This implies that in CD_2Cl_2, this new molecular shuttle behaves very much like a bistable ON/OFF switch. Addition of base (NEt_3) returns the shuttle to its original state and the shuttling process can be cycled by repeated addition of acid (CF_3SO_3H) and base without significant degradation of the compound as observed by ^{1}H NMR spectroscopy.

As designed, this new molecular shuttle contains a 4-pyridinium aniline ICT chromophore.[6] Thus, the switching between $\mathbf{3}^{2+}$ and H-$\mathbf{3}^{3+}$ is accompanied by a vivid colour change from bright orange to colourless. Fig. 3 shows the absorption spectra for the two states of the shuttle. The ICT between the aniline nitrogen and the pyridinium nitrogen in $\mathbf{3}^{2+}$ produces an absorption peak at 410 nm (CH_2Cl_2), but upon protonation of the aniline nitrogen, which triggers the crown to move to the benzylanilinium site, the ICT is eliminated and the intense colour disappears. Therefore, the shuttling of **DB24C8** can be verified by ^{1}H NMR spectroscopy and indirectly signalled by a visible colour change detected with the naked eye.

Another attractive feature of this molecular shuttle design is the ability to make modular structural changes. To demonstrate the versatility of this system, we conceptually exchanged the 3,5-bis(trifluoromethyl)benzyl group for an anthracenyl group to give $\mathbf{5}^{2+}$. The synthesis of $\mathbf{5}^{2+}$ was the same as outlined for $\mathbf{3}^{2+}$ except 9-bromomethylanthracene was used in place of 3,5-bis(trifluoromethyl)benzyl bromide (see ESI†). The inclusion of an anthracene group introduces the ability to monitor the molecular shuttling behaviour by fluorescence spectroscopy.[11]

As with $\mathbf{3}^{2+}$ and H-$\mathbf{3}^{3+}$, the ^{1}H NMR spectra for $\mathbf{5}^{2+}$ and H-$\mathbf{5}^{3+}$ demonstrate that, in CD_2Cl_2, this molecular shuttle act as a bistable switch showing only one set of resonances for each spectrum. The UV-visible spectra of $\mathbf{5}^{2+}$ and H-$\mathbf{5}^{3+}$ are also very similar to $\mathbf{3}^{2+}$ and H-$\mathbf{3}^{3+}$; the unprotonated species having a large absorption band at 420 nm which disappears upon protonation.

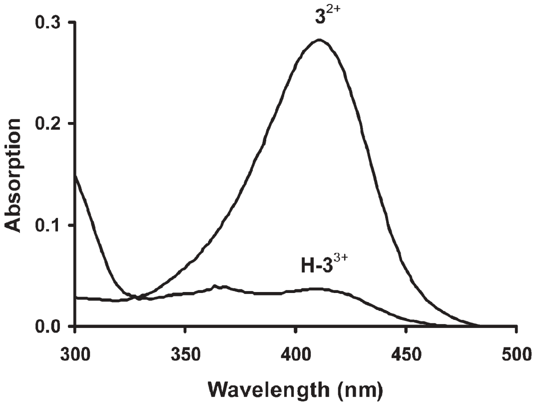


Fig. 3 UV-vis absorption spectra for $\mathbf{3}^{2+}$ and H-$\mathbf{3}^{3+}$ in CH_2Cl_2 solution at a concentration of 2.0×10^{-3} M.

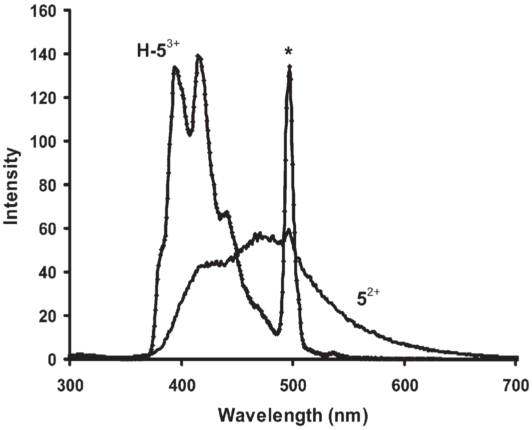


Fig. 4 Fluorescence emission spectra for $\mathbf{5}^{2+}$ and H-$\mathbf{5}^{3+}$ in CH_2Cl_2 solution at a concentration of 2.0×10^{-3} M. Excitation wavelength = 250 nm, * denotes an artefact of the instrumentation which occurs at double the excitation wavelength; 500 nm.

With the elimination of the ICT absorption band, three absorption maxima of the anthracene fragment become apparent at 389, 368 and 348 nm. Fig. 4 shows the emission spectra of $\mathbf{5}^{2+}$ and H-$\mathbf{5}^{3+}$ in CH_2Cl_2. The spectrum of $\mathbf{5}^{2+}$ is complicated but definitely shows stunted emission, probably due primarily to quenching of fluorescence by the lone pair of electrons on the aniline nitrogen.[11] Protonation partially restores normal anthracene fluorescence as seen in the spectrum of H-$\mathbf{5}^{3+}$.

Molecular shuttles combining 1,2-bis(pyridinium)ethane and benzylanilinium recognition sites and utilising **DB24C8** as the mobile fragment have been described. The system incorporates a 4-pyridinium aniline chromophore unit, and is modular enough to allow easy incorporation of bulky stoppers that may also possess useful spectroscopic handles. While ^{1}H NMR spectroscopy was ultimately used to elucidate the position of the crown ether on the axle, the protonation/deprotonation steps used to drive switching could be sensed optically by a measurable change in colour or fluorescence intensity and thus provide indirect evidence of molecular shuttling.

Notes and references

‡ X-Ray crystal data were collected on a Brüker APEX CCD diffractometer following standard procedures.[12,13] The crystals were of poor quality which is reflected in the quality of the data as represented by R_{int}. However, the solution was straightforward and the metric parameters chemically reasonable. One of the triflate anions was poorly defined and restrained to have the same geometry as the well defined one. *Summary of crystal data* for [**3**][OTf]$_2$·2H$_2$O: $C_{55}H_{65}F_{12}N_3O_{16}S_2$, M = 1316.22, T = 173(2) K, monoclinic, space group $P2_1/c$, a = 23.985(10), b = 15.436(6), c = 17.782(7) Å, β = 102.815(8)°, V = 6420(4) Å^3, D_c = 1.362 g cm^{-3}, μ = 0.183 mm^{-1}, Z = 4, reflections collected = 33416 (R_{int} = 0.1162), final R indices [$I > 2\sigma(I)$]: $R1$ = 0.1189, $wR2$ = 0.3152, R indices (all data): $R1$ = 0.2993. $wR2$ = 0.4122, GoF = 0.976 with data/variables/restraints = 11273/784/31. CCDC 656476. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b710708k

1 For a general review, see: (*a*) V. Balzani, A. Credi and M. Venturi, *Molecular Devices and Machines*, Wiley-VCH, Weinheim, 2003; (*b*) A. Mateo-Alonso, G. Fioravanti, M. Marcaccio, F. Paolucci, G. M. A. Rahman, C. Ehli, D. M. Guldi and M. Prato, *Chem. Commun.*, 2007, 1945; (*c*) D. S. Marlin, D. G. Cabrera, D. A. Leigh and A. M. Z. Slawin, *Angew. Chem., Int. Ed.*, 2006, **45**, 1385; (*d*) H. Murakami, A. Kawabuchi, R. Matsumoto, T. Ido and N. Nakashima, *J. Am. Chem. Soc.*, 2005, **127**, 15891; (*e*) G. Bottari, F. Dehez, D. A. Leigh, P. J. Nash, E. M. Perez, J. K. Y. Wong and F. Zerbetto, *Angew. Chem., Int. Ed.*, 2004, **42**, 5886; (*f*) G. Bottari, D. A. Leigh and E. M. Perez, *J. Am. Chem. Soc.*, 2003, **125**, 13360; (*g*) for the original report of a molecular shuttle, see: P. L. Anelli, N. Spencer and J. F. Stoddart, *J. Am. Chem. Soc.*, 1991, **113**, 5131.

2 (*a*) A. Mateo-Alonso, C. Ehli, G. M. A. Rahman, D. M. Guldi, G. Fioravanti, M. Marcaccio, F. Paolucci and M. Prato, *Angew. Chem., Int. Ed.*, 2007, **46**, 3521; (*b*) A. B. Braunschweig, W. R. Dichtel, O. S. Miljanic, M. A. Olson, J. M. Spruell, S. I. Khan, J. R. Heath and J. F. Stoddart, *Chem.–Asian J.*, 2007, **2**, 634; (*c*) V. Balzani, M. Clemente-Leon, A. Credi, M. Semeraro, M. Venturi, H.-R. Tseng, S. Wenger, S. Saha and J. F. Stoddart, *Aust. J. Chem.*, 2006, **59**, 193; (*d*) K. Noergaard, B. W. Laursen, S. Nygaard, K. Kjaer, H.-R. Tseng, A. H. Flood, J. F. Stoddart and T. Bjoernholm, *Angew. Chem., Int. Ed.*, 2005, **44**, 7035; (*e*) A. Altieri, G. Bottari, F. Dehez, D. A. Leigh, J. K. Y. Wong and F. Zerbetto, *Angew. Chem., Int. Ed.*, 2003, **42**, 2296; (*f*) for an example containing a 1,2-bis(pyridinium) recognition site, see: A. M. Elizarov, S. H. Chiu and J. F. Stoddart, *J. Org. Chem.*, 2002, **67**, 9175.

3 (*a*) E. M. Perez, D. T. F. Dryden, D. A. Leigh, G. Teobaldi and F. Zerbetto, *J. Am. Chem. Soc.*, 2004, **126**, 12210; (*b*) D. H. Qu, G. C. Wang, J. Ren and H. Tian, *Org. Lett.*, 2004, **6**, 2085; (*c*) Q. C. Wang, D. H. Qu, J. Ren, K. C. Chen and H. Tian, *Angew. Chem., Int. Ed.*, 2004, **43**, 2661; (*d*) D. A. Leigh, M. Á. F. Morales, E. M. Pérez, J. K. Y. Wong, C. G. Saiz, A. M. Z. Slawin, A. J. Carmichael, D. M. Haddleton, A. M. Brouwer, W. J. Burma, G. W. H. Wurpel, S. León and F. Zerbetto, *Angew. Chem., Int. Ed.*, 2005, **44**, 3062.

4 S. J. Loeb, J. Tiburcio and S. J. Vella, *Org. Lett.*, 2005, **7**, 4923.

5 (*a*) S. J. Loeb and J. A. Wisner, *Angew. Chem., Int. Ed.*, 1998, **37**, 2838; (*b*) S. J. Loeb and J. A. Wisner, *Chem. Commun.*, 1998, 2757; (*c*) S. J. Loeb and J. A. Wisner, *Chem. Commun.*, 2000, 845; (*d*) A. L. Hubbard, G. J. E. Davidson, R. H. Patel, J. A. Wisner and S. J. Loeb, *Chem. Commun.*, 2004, 138; (*e*) S. J. Loeb and J. A. Wisner, *Chem. Commun.*, 2000, 1939; (*f*) S. J. Loeb and D. A. Tramontozzi, *Org. Biomol. Chem.*, 2005, **3**, 1393.

6 S. J. Vella, J. Tiburcio and S. J. Loeb, *Org. Lett.*, 2006, **8**, 3421.

7 This is a known compound which is also commercially available.

8 (*a*) G. J. E. Davidson, S. J. Loeb, N. A. Parekh and J. A. Wisner, *J. Chem. Soc., Dalton Trans.*, 2001, 3135; (*b*) S. J. Loeb, J. Tiburcio and S. J. Vella, *Chem. Commun.*, 2006, 1598.

9 For examples of the C-conformation for **DB24C8** with this recognition motif see ref. 4, and D. J. Hoffart and S. J. Loeb, *Angew. Chem., Int. Ed.*, 2005, **44**, 901.

10 S. J. Loeb, J. Tiburcio, S. J. Vella and J. A. Wisner, *Org. Biomol. Chem.*, 2006, **4**, 667.

11 (*a*) A. P. de Silva, *Chem. Rev.*, 1997, **97**, 1515, and references therein; (*b*) P. R. Ashton, R. Ballardini, V. Balzani, I. Baxter, A. Credi, M. C. T. Fyfe, M. T. Gandolfi, M. Gomez-Lopez, M.-V. Martinez-Diaz, A. Piersanti, N. Spencer, J. F. Stoddart, M. Venturi, A. J. P. White and D. J. Williams, *J. Am. Chem. Soc.*, 1998, **120**, 11932; (*c*) F. Han, Y. Bao, Z. Yang, T. M. Fyles, J. Zhao, X. Peng, J. Fan, Y. Wu and S. Sun, *Chem.–Eur. J.*, 2007, **13**, 2880; (*d*) Y. Shiraishi, Y. Tokitoh, G. Nishimura and T. Hirai, *Org. Lett.*, 2005, **7**, 2611; (*e*) V. Amendola, L. Fabbrizzi, C. Mangano, P. Pallavicini, A. Perotti and A. Taglietti, *J. Chem. Soc., Dalton Trans.*, 2000, 185; (*f*) K. Ghosh and G. Masanta, *Chem. Lett.*, 2006, **35**, 414.

12 G. M. Sheldrick, SHELXTL 5.03 Program Library, Brüker Analytical Instrument Division, Madison, WI, USA.

13 DIAMOND 3.1 - Visual Crystal Structure Information System CRYSTAL IMPACT, Postfach 1251, D-53002 Bonn, 2006.