Bistable Molecular Shuttles

Remarkable Positional Discrimination in Bistable Light- and Heat-Switchable Hydrogen-Bonded Molecular Shuttles**

Andrea Altieri, Giovanni Bottari, Francois Dehez, David A. Leigh, Jenny K. Y. Wong, and Francesco Zerbetto**

Stimuli-responsive molecular "shuttles"[1–11] (that is, mechanically interlocked molecules in which a macrocycle can be translocated between different sites in response to an external signal) all operate through the same basic principle. The external stimulus does not intrinsically induce directional motion of the macrocycle. Rather, it alters the equilibrium between different translational co-conformers by increasing the binding strength of the less populated station and/or destabilizing the initially preferred binding site. The motion of the components arises from the background thermal energy, the net result being a change in the position of the macrocycle through biased Brownian motion (Figure 1).

Given this mode of action, a major problem in designing photoactive shuttles that can function as practical components for molecular machinery is finding ways of generating sufficiently large, long lived, binding-energy differences between pairs of positional isomers.[2–10] A Boltzmann distribution at 298 K requires a value of $\Delta\Delta G$ between translational co-conformers of approximately 2 kcal mol^{-1} for 95% occupancy of one station. Achieving such discrimination in two states to form a positionally bistable shuttle (that is, both $\Delta\Delta G_{\text{orange-blue}}$ and $\Delta\Delta G_{\text{orange-green}} \geq 2$ kcal mol^{-1}) by modifying only intrinsically weak, noncovalent binding modes, without adding external reagents, presents a significant challenge. The problem has previously been overcome, in part, by using photochemistry to block the position of the macrocycle in single-binding-site rotaxanes.[5,10] In these systems the macrocycle is only able to sit on an azobenzene[5] or stilbene unit[10] in the *E* diastereomer of the rotaxane and must reside elsewhere in the *Z* form. Unfortunately, the integrity of macrocycle positioning in such systems is likely to be limited

[*] Prof. D. A. Leigh, A. Altieri, Dr. G. Bottari, Dr. J. K. Y. Wong
School of Chemistry, University of Edinburgh
The King's Buildings, West Mains Road, Edinburgh EH9 3JJ (UK)
Fax: (+44) 131-667-9085
E-mail: David.Leigh@ed.ac.uk

Prof. F. Zerbetto, Dr. F. Dehez
Dipartimento di Chimica "G. Ciamician"
Università degli Studi di Bologna
via F. Selmi 2, 40126 Bologna (Italy)
Fax: (+39) 051-2099456
E-mail: gatto@ciam.unibo.it

[**] This work was supported by the European Union Future and Emerging Technology Programme *MechMol*, the EPSRC and the MURST project "Dispositivi Supramolecolari". D.A.L. is an EPSRC Advanced Research Fellow (AF/982324)

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/anie.200250745

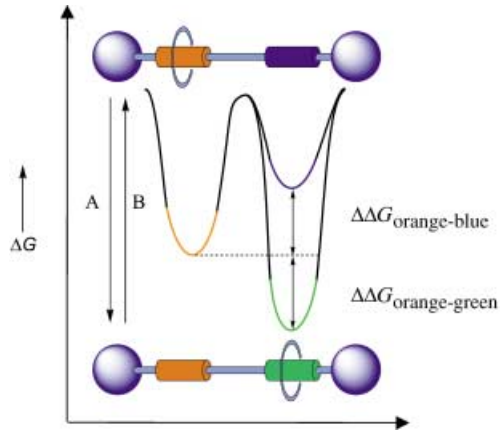


Figure 1. Macrocycle translation in a stimuli-responsive molecular shuttle. Stimulus A induces a blue-to-green transformation, and stimulus B induces a green-to-blue transformation. The equilibrium distribution of the macrocycle between two stations is determined by the difference in their binding energies ($\Delta\Delta G_{\text{orange-blue}}$, $\Delta\Delta G_{\text{orange-green}}$) and the temperature.

unless the thread is very short. Here we describe photo- and thermally responsive shuttles (**1**–**3**) in which the macrocycle moves over a relatively large distance (approximately 1.5 nm) between two discrete stations with remarkable positional integrity (even at room temperature), despite the fact that the discrimination between the binding sites is caused only by "matched" and "mismatched" hydrogen-bonding motifs. Each translational form is stable until a new stimulus is applied.

The basis for the new shuttles lies in the photochemical and thermal interconversion of fumaramide and maleamide groups.[12] The *trans*-olefin bisamide acts as an excellent template for the formation of benzylic amide macrocycle-based rotaxanes (for example, *E*-**4**; Figure 2) because the amide carbonyl groups of the thread are rigidly held in positions that fit the hydrogen-bond-donating sites of the forming macrocycle (an arrangement maintained even in crystals of *E*-**4** obtained from DMSO; Figure 2a).[13] Irradiation of fumaramide rotaxanes at 254 nm[14] produces the corresponding *cis*-maleamide rotaxane, in which the maximum number of intercomponent hydrogen bonds changes from four to two (Figure 2b), considerably reducing the binding strength[15] between the macrocycle and the thread. By incorporating a second binding site into the thread, we reasoned it might be possible to generate photoinduced, thermally reversible translation of the rotaxane components.

We prepared three different molecular shuttles (**1**–**3**; Scheme 1), each containing a fumaramide/maleamide site plus a non-photoactive second station with a predicted intermediate macrocycle-binding affinity. Since the transition state of the rotaxane-forming reaction is similar in structure to the final rotaxane,[16] it seemed likely that the macrocycle-binding affinity of a given station should be related to its ability to template the formation of the rotaxane. Several factors are known to affect both template efficacy and the nature of the intercomponent hydrogen-bonding interactions (NH···O=C bond lengths, angles etc.; Figure 2) including: the hydrogen-bond basicity of the functional groups (amides are superior to esters[13]), preorganization (fumaramide is superior to succinamide[17]), and distance between the binding sites (succinamide is superior to adipamide[18]).

Some features of the synthetic routes to **1**–**3** are noteworthy. Although *E*-**1** was prepared from the corresponding *trans*-olefin-containing *E*-**5** (an "*E* thread") in good yield, the other *E* threads could not be utilized owing to their insufficient solubility in solvents that do not disrupt hydrogen bonding. Rotaxanes *Z*-**2** and *Z*-**3** were therefore prepared from the corresponding *Z*-threads and converted to the *E* rotaxanes thermally (120 °C, 1–7 days, $C_2H_2Cl_4$, 80–95 %). In fact, the *E* isomers of each molecular shuttle could be converted to the *Z* forms with light (*E*→*Z*, direct irradiation at 254 nm, CH_2Cl_2, 30 min, 39–54 %; or with a catalytic benzophenone sensitizer at 350 nm, CH_2Cl_2, 5 min, 60–65 %) and back again through heating or reversible Michael addition (catalytic ethylenediamine, 60 °C, 4 h, 75–85 %).

Since the xylylene rings of the macrocycle shield encapsulated regions of the thread, the position of the macrocycle in

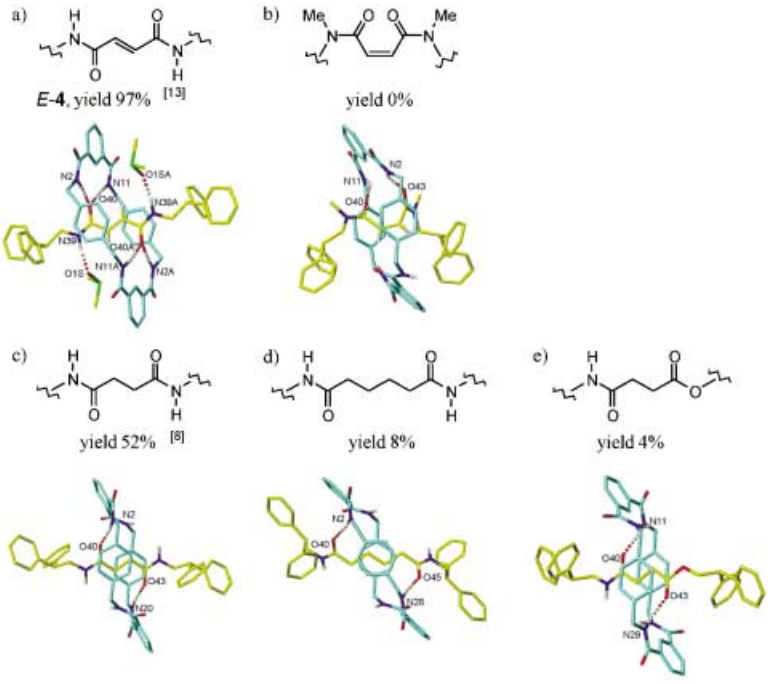
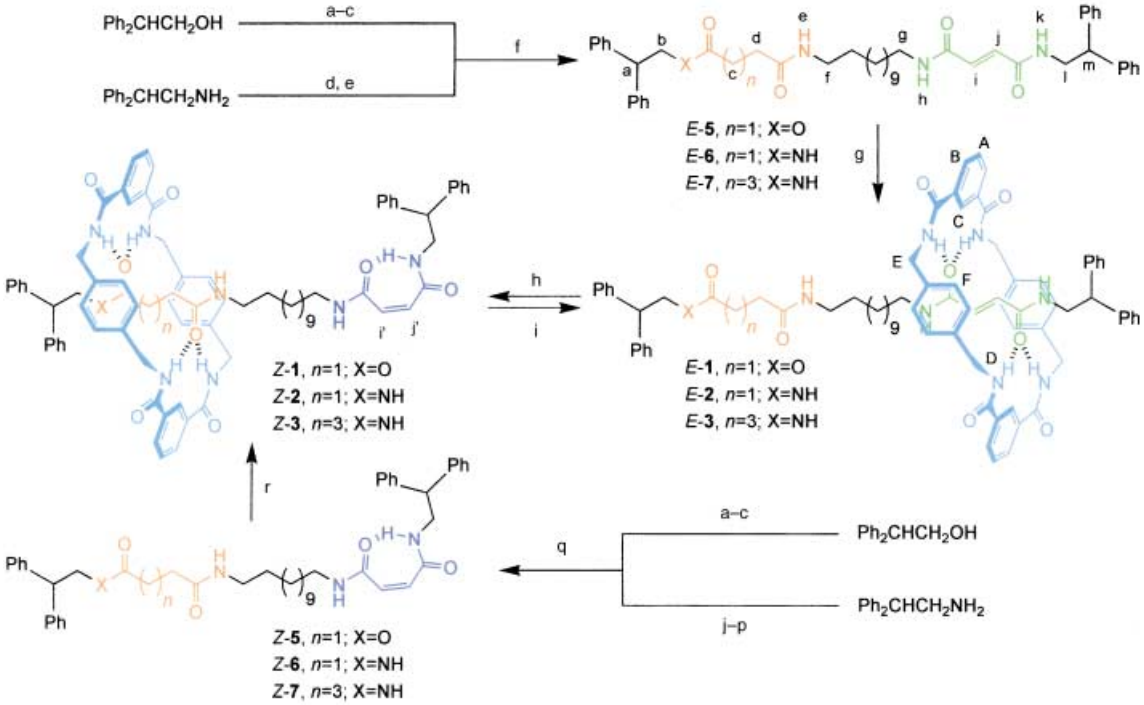


Figure 2. X-ray structures of model single-binding-site [2]rotaxanes showing hydrogen-bonding characteristics of predicted "strong" (a), "weak" (b), and "intermediate strength" (c–e) hydrogen-bonding stations; a) fumaramide rotaxane *E*-**4** crystallized from DMSO; b) *N*,*N*′-dimethyl derivative of the corresponding maleamide (*Z*) rotaxane; c) succinamide analogue of *E*-**4**; d) adipamide analogue of *E*-**4**; e) succinic amide ester analogue of *E*-**4**. Intramolecular hydrogen-bond lengths [Å] (and angles [°]): a) O40-HN2/O40A-HN2A 2.13 (173.7); O40-HN11/O40A-HN11A 1.89 (169.3); b) O40-HN11 2.08 (139.3); O43-HN2 2.00 (142.1); c) O40-HN2/O43-HN20 1.88 (165.3); d) O40-HN2/O45-HN28 2.00 (168.8); e) O40-HN11/O43-HN29 1.89 (156.1). Atoms: carbon (macrocycle), blue; carbon (thread), yellow; oxygen, red; nitrogen, dark blue; amide hydrogen, white. In all cases, the rotaxane "stoppers" are -CH_2CHPh_2 groups.



Scheme 1. Synthesis of bistable molecular shuttles **1**–**3**. a) Succinic anhydride, Et_3N, CH_2Cl_2, 90%; b) $H_2N(CH_2)_{12}NHBoc$, 4-dimethylaminopyridine (DMAP), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI·HCl), CH_2Cl_2, 68%; c) trifluoroacetic acid, $CHCl_3$, quantitative; d) fumaric acid monoethylester, DMAP, EDCI·HCl, CH_2Cl_2, 85%; e) NaOH in H_2O, EtOH, 91%; f) DMAP, EDCI·HCl, DMF, *E*-**5**, 76%; g) isophthaloyl dichloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, *E*-**1**, 57%; h) *hν* at 254 nm for 30 min, CH_2Cl_2, *Z*-**1**, 54%; *Z*-**2**, 48%; *Z*-**3**, 39%, or *hν* at 350 nm for 5 min, benzophenone, CH_2Cl_2, *Z*-**1**, 65%; *Z*-**2**, 65%; *Z*-**3**, 60%; i) $C_2H_2Cl_4$ at 120°C for 7 days, *E*-**1**, 80%; *E*-**2**, 80%; or 1 day, *E*-**3**, 95%; j) maleic anhydride, anhydrous THF, 75%; k) succinic anhydride, anhydrous THF, 95%; l) $SOCl_2$, 1,12-diaminododecane, CH_2Cl_2, 35%; m) adipic acid monoethylester, DMAP, EDCI·HCl, CH_2Cl_2, 86%; n) KOH in H_2O, EtOH, 95%; o) $H_2N(CH_2)_{12}NHBoc$, DMAP, EDCI·HCl, $CHCl_3$, 92%; p) trifluoroacetic acid, $CHCl_3$, quantitative; q) DMAP, EDCI.HCl, $CHCl_3$, *Z*-**5**, 70%; *Z*-**6**, 70%; *Z*-**7**, 70%; r) isophthaloyl dichloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, *Z*-**1**, 2%; *Z*-**2**, 40%; *Z*-**3**, 20%. Boc = *tert*-butoxycarbonyl. Full experimental procedures can be found in the Supporting Information.[25]

$CDCl_3$ could be determined for each pair of rotaxane diastereomers by comparing the chemical shift of the protons in the rotaxane with those of the corresponding thread (or suitable model compounds in the case of *E*-**2** and *E*-**3**).[19] The spectra of *E*/*Z*-**1** and *E*/*Z*-**5** in $CDCl_3$ (400 MHz, 298 K) are shown in Figures 3 and 4. The H_i and H_j protons of the fumaramide group are shielded in the rotaxane *E*-**1**, compared to the thread *E*-**5**, by $\delta = 1.09$ and 1.02 ppm, whereas the chemical shifts of the H_c and H_d protons of the succinic amide ester group are similar in both compounds (Figure 3). In the maleamide isomer, the situation is completely reversed (Figure 4). The *Z* olefin protons ($H_{i'}$ and $H_{j'}$) resonate at almost identical chemical shifts in the rotaxane and thread, whereas the succinic amide ester methylene groups (H_c and H_d) are each shielded by > 1.3 ppm in the rotaxane. A similar series of shifts occurs in the ^{1}H NMR spectra of the other molecular shuttle pairs. Thus, even at 298 K, the occupancy of the fumaramide station in *E*-**1**, *E*-**2**, and *E*-**3** is greater than 95% (the limit we can determine with reasonable confidence using this method). The occupancy of the alternative, nonphotoactive station in the corresponding maleamide rotaxanes is similarly high for *Z*-**1** and *Z*-**2**. In *Z*-**3** the maleamide:adipamide occupancy ratio is reduced to approximately 15:85 (see Supporting Information), which corresponds to a $\Delta\Delta G$ of approximately 1.1 kcal mol^{-1}.

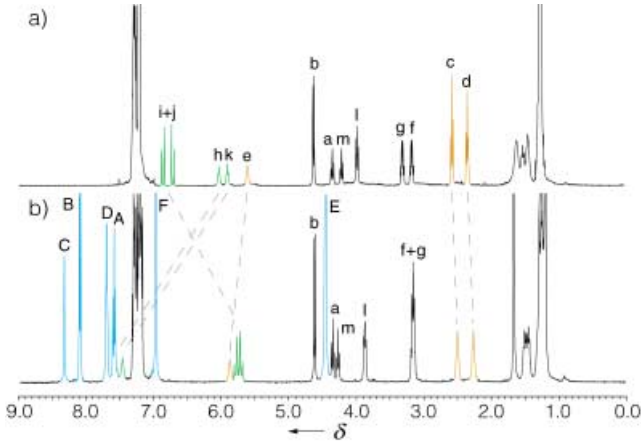


Figure 3. ^{1}H NMR spectra (400 MHz) of: a) Thread *E*-**5** and b) rotaxane *E*-**1** in $CDCl_3$ at 298 K. The assignments correspond to the lettering shown in Scheme 1.

It is interesting to note that our predictions of the relative station-binding affinities from rotaxane yield and hydrogen-bond lengths and angles are not completely accurate. Although the maleamide station is significantly populated in *Z*-**3**, the same station does not compete at all with the succinic amide ester site in *Z*-**1** (Figure 4), even though the yields[20]

and X-ray structure suggest that the adipamide group should be a better binding site than the succinic amide ester.

Overall, the discrimination of the macrocycle for the different stations is excellent and, at temperatures which require substantial energy differences to significantly bias the population distribution, somewhat remarkable (most notably between the fumaramide and succinamide stations in *E*-**2**, which offer virtually identical hydrogen-bonding surfaces to the macrocycle). To probe this further, molecular modeling[16,17,21–24] was carried out by simulated annealing followed by geometrical optimization using the TINKER program with the MM3 force field. The difference in co-conformer stability for each pair of rotaxane diastereomers was calculated by comparing the energies (including zero point energies) of the occupied and unoccupied stations in each co-conformer to give the following $\Delta\Delta G$ values: a) 3.6 kcal mol^{-1} for *E*-**1** (fumaramide versus succinic amide ester occupancy), b) 2.9 kcal mol^{-1} for *Z*-**1** (succinic amide ester versus maleamide); c) 3.6 kcal mol^{-1} for *E*-**2** (fumaramide versus succinamide); d) 3.0 kcal mol^{-1} for *Z*-**2** (succinamide versus maleamide); e) 3.9 kcal mol^{-1} for *E*-**3** (fumaramide versus adipamide); f) 3.1 kcal mol^{-1} for *Z*-**3** (adipamide versus maleamide).

Whilst in each case there is probably overbinding as a result of solvation and folding not being included in the model, the calculations are broadly in agreement with the experimental results (that is, $\Delta\Delta G$ values are greater than 2 kcal mol^{-1}), although at this level they do not reproduce the anomalously poor binding of the adipamide station in *Z*-**3**.[20] However, the calculations do offer a simple explanation for why the positional discrimination is so good in these rotaxane systems: When they are not occupied, each station (except fumaramide) can intramolecularly hydrogen bond to itself, and so the positional isomer that has that station occupied must have at least one hydrogen bond less than the positional isomer with the fumaramide station occupied (Figure 5). The use of "self-binding" to compensate for the lack of station occupancy could prove a useful concept for driving submolecular motion in molecular machines that rely only on weak, noncovalent interactions.

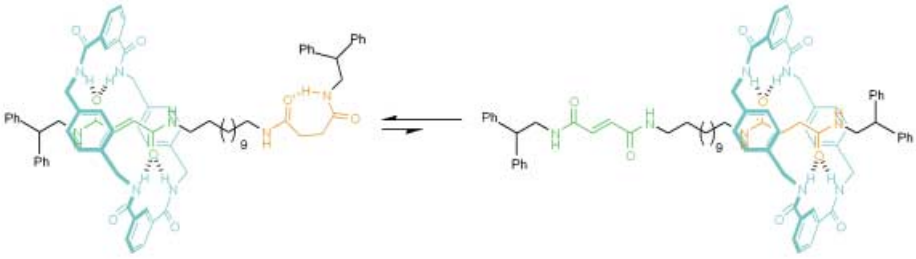


Figure 5. Translational isomerism in fumaramide-succinamide shuttle *E*-**2**.[25] Positional discrimination is excellent (greater than 95:5 at 298 K in $CDCl_3$) even though the fumaramide and succinamide stations present nearly identical surfaces to the macrocycle. The reason for this behavior is the self-binding of the succinamide station when it is unoccupied

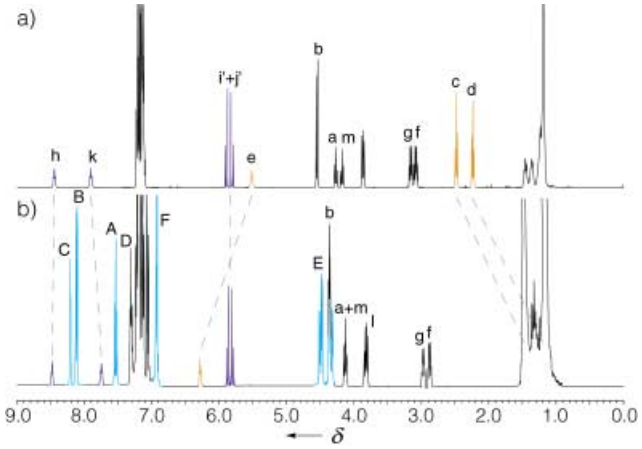


Figure 4. ^{1}H NMR spectra (400 MHz) of: a) Thread *Z*-**5** and b) rotaxane *Z*-**1** in $CDCl_3$ at 298 K.

Received: December 11, 2002 [Z50745]

Keywords: hydrogen bonds · macrocycles · molecular devices · photochemistry · rotaxanes

[1] For recent reviews see a) V. Balzani, A. Credi, F. M. Raymo, J. F. Stoddart, *Angew. Chem.* **2000**, *112*, 3484–3530; *Angew. Chem. Int. Ed.* **2000**, *39*, 3349–3391; b) Special issue on *Molecular Machines*: *Acc. Chem. Res.* **2001**, *34*, 409–522; c) Special issue on *Molecular Machines and Motors*: *Struct. Bonding (Berlin)* **2001**, *99*.

[2] A. C. Benniston, A. Harriman, *Angew. Chem.* **1993**, *105*, 1553–1555; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1459–1461.

[3] A. C. Benniston, A. Harriman, V. M. Lynch, *J. Am. Chem. Soc.* **1995**, *117*, 5275–5291.

[4] A. C. Benniston, *Chem. Soc. Rev.* **1996**, *25*, 427–436.

[5] H. Murakami, A. Kawabuchi, K. Kotoo, M. Kunitake, N. Nakashima, *J. Am. Chem. Soc.* **1997**, *119*, 7605–7606.

[6] P. R. Ashton, R. Ballardini, V. Balzani, A. Credi, K. R. Dress, E. Ishow, C. J. Kleverlaan, O. Kocian, J. A. Preece, N. Spencer, J. F. Stoddart, M. Venturi, S. Wenger, *Chem. Eur. J.* **2000**, *6*, 3558–3574.

[7] N. Armaroli, V. Balzani, J. P. Collin, P. Gaviña, J. P. Sauvage, B. Ventura, *J. Am. Chem. Soc.* **1999**, *121*, 4397–4408.

[8] A. M. Brouwer, C. Frochot, F. G. Gatti, D. A. Leigh, L. Mottier, F. Paolucci, S. Roffia, G. W. H. Wurpel, *Science* **2001**, *291*, 2124–2128.

[9] G. W. H. Wurpel, A. M. Brouwer, I. H. M. van Stokkum, A. Farran, D. A. Leigh, *J. Am. Chem. Soc.* **2001**, *123*, 11327–11328.

[10] C. A. Stanier, S. J. Alderman, T. D. W. Claridge, H. L. Anderson, *Angew. Chem.* **2002**, *114*, 1847–1850; *Angew. Chem. Int. Ed.* **2002**, *41*, 1769–1772.

[11] For examples featuring the use of stimuli other than light to induce shuttling in rotaxanes see a) R. A. Bissell, E. Córdova, A. E. Kaifer, J. F. Stoddart, *Nature* **1994**, *369*, 133–137; b) J. P. Collin, P. Gaviña, J. P. Sauvage, *New J. Chem.* **1997**, *21*, 525–528; c) C. Gong, H. W. Gibson, *Angew. Chem.* **1997**, *109*, 2426–2428; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2331–2333; d) A. S. Lane, D. A. Leigh, A. Murphy, *J. Am. Chem. Soc.* **1997**, *119*, 11092–11093; e) C. P. Collier, E. W. Wong, M. Belohradsky, F. M. Raymo, J. F. Stoddart, P. J. Kuekes, R. S. Williams, J. R. Heath, *Science* **1999**, *285*, 391–394; f) H. Shigekawa, K. Miyake, J.

Sumaoka, A. Harada, M. Komiyama, *J. Am. Chem. Soc.* **2000**, *122*, 5411 – 5412; g) M. C. Jimenez-Molero, C. Dietrich-Buchecker, J. P. Sauvage, *Chem. Eur. J.* **2002**, *8*, 1456 – 1466; h) Y. Luo, C. P. Collier, J. O. Jeppesen, K. A. Nielsen, E. Delonno, G. Ho, J. Perkins, H. R. Tseng, T. Yamamoto, J. F. Stoddart, J. R. Heath, *ChemPhysChem* **2002**, *3*, 519 – 525.

[12] G. Campari, M. Fagnoni, M. Mella, A. Albini, *Tetrahedron: Asymmetry* **2000**, *11*, 1891 – 1906.

[13] F. G. Gatti, D. A. Leigh, S. A. Nepogodiev, A. M. Z. Slawin, S. J. Teat, J. K. Y. Wong, *J. Am. Chem. Soc.* **2001**, *123*, 5983 – 5989.

[14] The wavelength for the reaction has not yet been optimized (F. G. Gatti, S. León, J. K. Y. Wong, G. Bottari, A. Altieri, A. M. Farran Morales, S. J. Teat, C. Frochot, D. A. Leigh, A. M. Brouwer, F. Zerbetto, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 10 – 15).

[15] ^{1}H NMR experiments show that the macrocycle spins more than 10^6 times faster in the *Z* form of the rotaxane than the *E* form in CD_2Cl_2 at 233 K.

[16] G. Brancato, F. Coutrot, D. A. Leigh, A. Murphy, J. K. Y. Wong, F. Zerbetto, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4967 – 4971.

[17] V. Bermudez, N. Capron, T. Gase, F. G. Gatti, F. Kajzar, D. A. Leigh, F. Zerbetto, S. W. Zhang, *Nature* **2000**, *406*, 608 – 611.

[18] D. A. Leigh and J. K. Y. Wong, unpublished results.

[19] Unlike rotaxanes with dipeptide stations separated by alkyl chains,[11d] *E*-**1**–**3** do not behave as solvent-switchable shuttles; even in [D_6]DMSO the fumaramide station is still occupied by the macrocycle for at least 85% of the time.

[20] The yield of the adipamide-maleamide rotaxane *Z*-**3** (20%) is reproducibly higher than that of the model single-site adipamide rotaxane shown in Figure 2 (8%). The significant differences in yield (and the anomalously poor binding of the adipamide unit to the macrocycle in *Z*-**3**) may indicate that the intramolecularly hydrogen-bonded nine-membered ring (S. H. Gellman, G. P. Dado, G.-B. Liang, B. R. Adams, *J. Am. Chem. Soc.* **1991**, *113*, 1164 – 1173) has differing stabilities in the one- and two-station adipamide threads and rotaxane *Z*-**3**.

[21] N. L. Allinger, Y. H. Yuh, J. H. Lii, *J. Am. Chem. Soc.* **1989**, *111*, 8551 – 8582.

[22] J. W. Ponder, F. Richards, *J. Comput. Chem.* **1987**, *8*, 1016 – 1024.

[23] F. Biscarini, M. Cavallini, D. A. Leigh, S. León, S. J. Teat, J. K. Y. Wong, F. Zerbetto, *J. Am. Chem. Soc.* **2002**, *124*, 225 – 233.

[24] In analogy to the MM3 H-bonding of (C)H atoms connected to sp^2 carbon atoms, we introduced a term to reproduce weak H-bonding of the acidic succinic methylene groups (well depth: 0.22 kcal mol^{-1}; equilibrium H-bonding separation: 2.78 Å).

[25] The rotaxane structures shown illustrate the position of the macrocycle on the thread and particularly favored intercomponent hydrogen-bonding motifs. Most of the low-energy co-conformations of the rotaxanes are probably folded with the unoccupied station folding back to hydrogen bond to the macrocycle.

