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Azodicarboxamides as Template Binding Motifs for the Building of Hydrogen-Bonded Molecular Shuttles

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Abstract: Azodicarboxamides ($R_2NCON{=}NCONR_2$) are shown to act as new templates for the assembly of unprecedented azo-functionalized hydrogen-bond-assembled [2]rotaxanes. Moreover, these binding sites can be reversibly and efficiently interconverted with their hydrazo forms through a hydrogenation−dehydrogenation strategy of the nitrogen−nitrogen bond. This novel chemically switchable control element has been implemented in stimuli-responsive molecular shuttles that work through a reversible azo/hydrazo interconversion, producing large amplitude net positional changes with a good discrimination between the binding sites of the macrocycle in both states of the shuttle. These molecular shuttles are able to operate by two different mechanisms: in a discrete mode through two reversible and independent chemical events and, importantly, in a continuous regime through a catalyzed ester bond formation reaction in which the shuttle acts as an organocatalyst. In this latter, the incorporation of both states of the shuttle into this simple chemical reaction network promotes a dynamic translocation of the macrocycle between two nitrogen and carbon-based stations of the thread allowing an energetically uphill esterification process to take place.

Introduction

The efficient use of nanomachinery capable of driving linear and rotary motion is essential to the suitable functioning of living cells.[1] The construction of molecular machines, ubiquitous in nature, remains, however, a major contemporary challenge.[2] The recent development of molecular-based systems including rotors,[3] muscles,[4] switches,[5] elevators,[6] motors,[7] and processive catalysts[8] has brought the prospect of synthetic molecular machines within sight.[9] Among these artificial molecular systems, stimuli-responsive molecular shuttles[2,10] are viewed as very promising elements for molecular machinery and the Brownian change in the position of their subunits has been used as a nanoscale mechanical switch to alter the properties of certain materials.[11] In principle, molecular shuttles can be considered as synthetic archetypes of biological machines, which utilize chemical reactions to control mechanical motion. However, despite the fact that several kinds of external triggers (light, electrons, temperature, solvent polarity) have been used to promote these positional changes,[12] chemically driven shuttles, excluding those controlled by acid−base proton transfer (pH controlled reactions),[13] remain scarce.[14] The switching elements in these shuttles have been used as components of more complex molecular machines that work by Brownian ratchet mechanisms in which directional transport of a particle is caused by a periodic or random switching between two or more potential energy surfaces.[15] In order to control this particular switching, biological machines[16] synergistically couple several chemical events for

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allowing a crucial but thermodynamically unfavorable process to work and, at same time, they get recycled back into a particular chemical reaction network.[16b] In this issue, catalytic reactions should be considered as prime candidates in the task for integrating this type of control into synthetic molecular machines working via an energy ratchet mechanism.

Here we describe our efforts in the search for new effective and useful chemical means to incite shuttling in interlocked hydrogen-bonded systems based on bistation hydrogen-bond-assembled [2]rotaxanes and how this switching process can be controlled as part of a simple molecular network represented by a chemically fueled catalytic cycle as a novel approach to give access to an enhanced and sophisticated generation of molecular shuttles.

In this regard, the choice of the hydrogen-bonding template is essential to the functioning of the system in the aforementioned way because they not only should be able to assist to the assembly of the interlocked structure but also should have encoded into their molecular structure a known reactivity pattern if one may desire a particular chemical behavior after the construction of the device. Despite growing interest in the development of molecular shuttles, the number of available templates for the formation of benzylic amide rotaxanes remains limited.[17] Bearing in mind the previous considerations, we reasoned that an azodicarboxamide motif could be an excellent candidate by playing an interesting dual role: (i) by templating the assembly of tetrabenzylic amide macrocycles around it to form [2]rotaxanes, because it is closely related to a fumaramide binding site, the best reported template for such processes, and (ii) by providing a macrocycle binding site with a known reactivity pattern, which could be modulated by the presence of the macrocycle or be used to alter the binding interaction between the interlocked components. As an initial approach, we were interested to investigate whether azodicarboxamides could act as templates and whether the hydrogenation of its azo bond could alter the near-ideal hydrogen-bonding structure between macrocycle and thread provoking a change in the internal dynamics governed by those interactions. It is remarkable that whereas azobenzenes are frequently used as threads of photoisomerizable [2]rotaxanes,[18] there are no reports on azodicarboxamides forming part of an interlocked molecule, and consequently their chemical azo/hydrazo interconversion constitutes an original approach for promoting positional changes in such systems.

Results and Discussion

Synthesis and Interconversion of Azo/Hydrazo [2]Rotaxanes. Azodicarboxamide threads, **1** ($R_1 = CH_2CHPh_2$; $R_2 = H$) and **2** ($R_1 = R_2 = CH_2Ph$), were easily obtained by dehydrogenation of the hydrazo compounds [2H]-**1** and [2H]-**2**, in turn resulting from the reaction of diphenyl hydrazodicarboxylate[19] with 2,2-diphenylethylamine and dibenzylamine, respectively. Threads **1** and **2** were able to template the assembly of benzylic amide [2]rotaxanes **3** and **4** in acceptable yields (43% and 58%, respectively) (method A, Scheme 1).[20] Although such yields are lower than those obtained using comparable fumaramide threads[17d,21] under the same reaction conditions,[22] they are still

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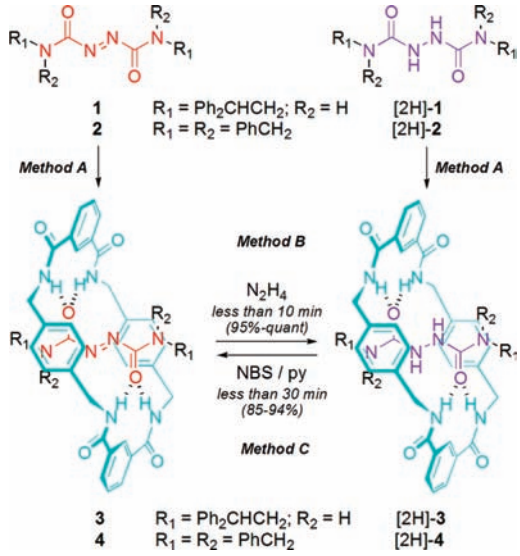
Scheme 1. Synthesis of Azodicarboxamide [2]Rotaxanes **3** and **4** and Their Corresponding Hydrazodicarboxamide [2]Rotaxanes [2H]-**3** and [2H]-**4**[a]



[a] Reagents and conditions: method A, isophthaloyl dichloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, **3**, 43%; [2H]-**3**, 6%; **4**, 58%, [2H]-**4**, 11%; method B, $N_2H_4 \cdot H_2O$, $CHCl_3$, [2H]-**3**, 95%; [2H]-**4**, quantitative; method C, NBS (*N*-bromosuccinimide), pyridine, CH_2Cl_2, **3**, 85%; **4**, 94%.

impressive for a five-component kinetically controlled interlocking reaction. Probably, the configurational lability of the azo bond[23] compared with the C=C of the fumaramide-based threads reduces its preorganization during the five-component "clipping" reaction. The azo rotaxanes **3** and **4** could be converted quantitatively into the corresponding hydrazo rotaxanes [2H]-**3** and [2H]-**4** by reduction (method B) with hydrazine.[24,25] In both cases, the hydrogenation was complete in a few minutes while a rapid loss of the initial orange color of the azo compounds was observed.

Alternatively, the hydrazodicarboxamide [2]rotaxanes [2H]-**3** and [2H]-**4** were obtained in low yields (6% and 11%, respectively) from the corresponding [2H]-**1** and [2H]-**2** threads by the established synthetic protocol[17b] for the preparation of the benzylic amide rotaxanes (method A). From these results, it is clear that hydrazodicarboxamides likely adopt a ground state conformation[26] in which the carbonyl hydrogen bond

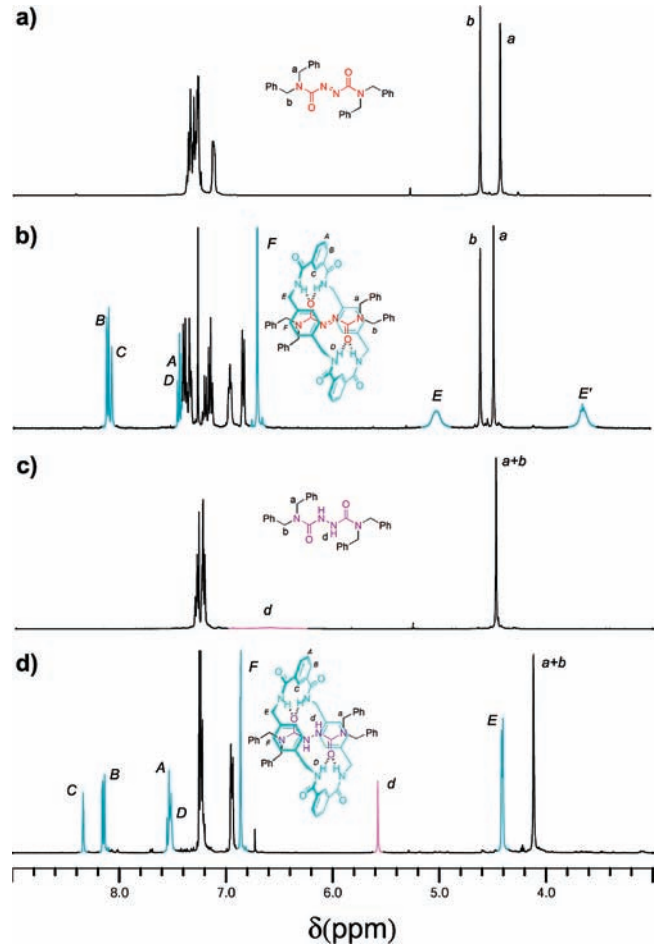


Figure 1. ^1H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) azodicarboxamide thread **2**, (b) azodicarboxamide rotaxane **4**, (c) hydrazodicarboxamide thread [2H]-**2**, and (d) hydrazodicarboxamide rotaxane [2H]-**4**.

acceptors do not adopt the ideal orientation of an efficient template such as fumaramides.[17d] On other hand, the azo rotaxanes could be rapidly restored from their hydrazo partners by a conventional oxidation with NBS/pyridine in excellent yields (method C, 85−94%).

As one might expect, the azo/hydrazo reversible coupled transformation must necessarily alter the nature and strength of the hydrogen-bond network between macrocycle and thread and therefore also change the internal dynamics governed by those interactions such as pirouetting[27] of the ring around the thread. In fact, the components of the more soluble azo/hydrazo pair, rotaxanes **4** and [2H]-**4**, display noticeable differences in their ^1H NMR spectra in $CDCl_3$ at room temperature. The most substantial ones are due to the macrocyclic methylene protons. Whereas in **4** these protons appear as two very broad signals at 5.02 and 3.64 ppm, the same protons in [2H]-**4** emerge as a sharp and well-resolved signal (δ = 4.42 ppm) at room temperature (Figure 1). A comparable NMR change was observed for the macrocyclic methylene protons during the isomerization of fumaramide rotaxanes[28] into their maleamide

(20) Whereas *N*,*N*′-disubstituted hydrazo rotaxane **3** proved to be very insoluble in common non-hydrogen-bond-disrupting deuterated solvents, rotaxane **4** was readily soluble probably because it cannot form intermolecular hydrogen bonds with other rotaxane molecules, see: Altieri, A.; Gatti, F. G.; Kay, E. R.; Leigh, D. A.; Martel, D.; Paolucci, F.; Slawin, A. M. Z.; Wong, J. K. Y. *J. Am. Chem. Soc.* **2003**, *125*, 8644–8654.
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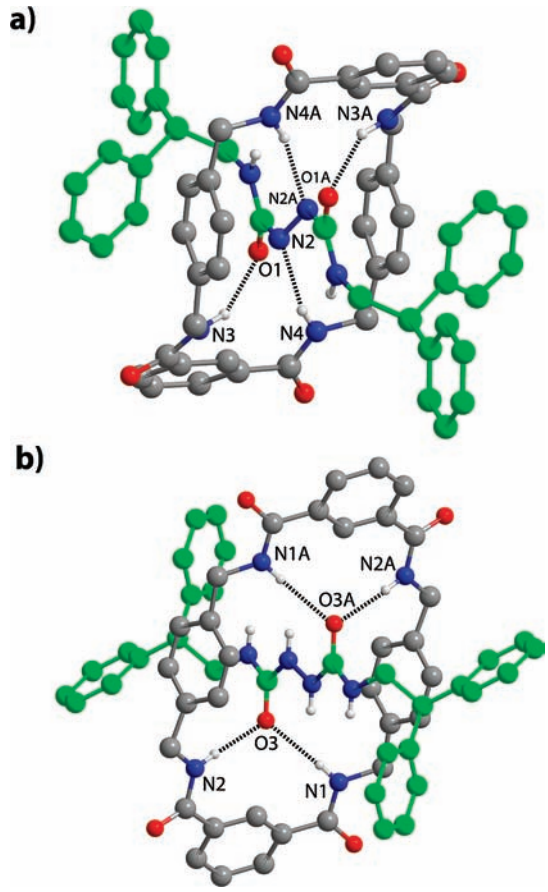


Figure 2. X-ray structures of (a) azodicarboxamide [2]rotaxane **3** and (b) hydrazodicarboxamide [2]rotaxane [2H]-**3** crystallized from DMF/H_2O. For clarity, carbon atoms of the macrocycles are shown in gray and the carbon atoms of the threads in green; oxygen atoms are depicted in red, nitrogen atoms are depicted in blue, and selected hydrogen atoms are white. Also for clarity, solvent molecules have been omitted. Intramolecular hydrogen-bond lengths [Å] (and angles [deg]): (a) O1HN3/O1AHN3A 2.09 (158.5); N2HN4/N2AHN4A 2.55 (149.4); (b) O3HN1/O3AHN1A 2.27 (174.8); O3HN2/O3AHN2A 2.16 (176.7).

isomers, which was ascribed to an acceleration in the rotational motion of the ring. Consequently these NMR data seem to point out that pirouetting of the ring is slower in the azo rotaxane **4** than in the hydrazo partner [2H]-**4**. Furthermore, this fact also indicates that a hydrazodicarboxamide moiety is a weaker binding site than its azo partner confirming our explanation on why the yields obtained in the assembly of both rotaxanes are so different. Therefore the postassembly chemical reduction of the azo rotaxanes promotes a structural mismatch between the recognition binding sites of the interlocked subcomponents, reducing the intercomponent interaction and thus decreasing the energy barrier for the macrocycle pirouetting of the rotaxane. Such unprecedented chemical control can be added to those previously reported involving the use of external oscillating electrical fields[27] or photochemical stimuli.[28]

Interlocked Structures in the Solid State. X-ray crystal structures of rotaxanes **3** and [2H]-**3** (Figure 2) crystallized from DMF/H_2O demonstrate a good fit between thread and macrocycle. However, the nature of the established noncovalent interactions between thread and macrocycle were found to be different in both interlocked structures. Whereas the NH groups of the macrocycle form two bifurcated hydrogen bonds (2.158, 2.268 Å) with the CO groups of the hydrazo[29,30] thread in [2H]-**3**, two NH groups of the macrocycle of **3** establish strong hydrogen bonds (2.091 Å) with the carbonyl groups of the thread and the other two NH groups of the same ring interact with the nitrogen atoms of the azo function through weak NH···N_{sp^2} hydrogen bonds (2.547 Å).[31,32] It should be realized that all the electronegative atoms in the structure[33] are involved in the formation of at least one hydrogen bond, which in turn modifies the acceptor/donor capability of their nearby heteroatoms through electronic (inductive/mesomeric) effects to form other hydrogen bonds.[34] This fact could have a significant influence in the establishment of other nonbonding interactions during the crystal lattice formation, and it must be considered as a plausible cause of the formation, in **3**, of a hydrogen-bond network different from the preferred double set of bifurcated hydrogen bonds that predominates in solution of nonpolar solvents for this [2]rotaxane class.[35]

It is also worth noting that the observed conformation for the hydrazocarboxamide moiety notably differs from the structure of the related biurea $(H_2NCONH)_2$ in the solid state in which the strong repulsion of the lone pairs on the adjacent N atoms is the origin of the observed rotation about the N−N bond. In fact, biurea shows a folded conformation with an angle of 84.02° between the planes defined by the two NCN connectivities.[36] In stark contrast, the same value for [2H]-**3** is negligible. We reasoned that this unfavorable planar arrangement of the CO−N−N−CO framework is only possible thanks to the stability gained as a result of the hydrogen bond saturation of the system.[26]

Synthesis and Chemical Switching of Azo/Hydrazo Molecular Shuttles. It is conceivable that tuning the binding affinity of a nitrogenated station for a benzylic amide macrocycle in a molecular shuttle, mediated by a chemical transformation as the one described above, can be exploited for the building of synthetic molecular machines. To test this idea, we have investigated the ring-shuttling processes in a two-station [2]rotaxane in chloroform solution. The rotaxane is composed of a dumbbell component, containing an azodicarboxamide and a succinic amide ester binding site, threaded through a tetrabenzylic amide macrocycle.

(29) The hydrazodicarboxamide group can be considered as two adjacent urea functions. For some examples of urea-template synthesis of [2]rotaxanes see: (a) Biscarini, F.; Cavallini, M.; Leigh, D. A.; León, S.; Teat, S. J.; Wong, J. K. Y.; Zerbetto, F. *J. Am. Chem. Soc.* **2002**, *124*, 225–233. (b) Huang, Y.-L.; Hung, W.-C.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6629–6633.

(30) For an example of a hydrazopyridinium-containing [2]catenane see: Ashton, P. R.; Brown, C. L.; Cao, J.; Lee, J.-Y.; Newton, S. P.; Raymo, F. M.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Eur. J. Org. Chem.* **2001**, 957–965.

(31) For a representative study of the N−H···N_{sp^2} hydrogen interaction see: Llamas-Saiz, A. L.; Foces-Foces, C. *J. Mol. Chem.* **1990**, *238*, 367–382.

(32) For some examples of intermolecular CONH···N═N hydrogen bonds see: (a) Cromer, D. T.; Larson, A. C. *J. Chem. Phys.* **1974**, *60*, 176–184. (b) Blaton, N. M.; Peeters, O. M.; De Ranter, C. J.; Willems, G. J. *Acta Crystallogr.* **1979**, *B35*, 2629–2634. (c) Okabe, N.; Kisaichi, H. *Acta Crystallogr.* **1992**, *C48*, 2047–2049. (d) Klapötke, T. M.; Miró Sabaté, C. *New J. Chem.* **2009**, *33*, 1605–1617.

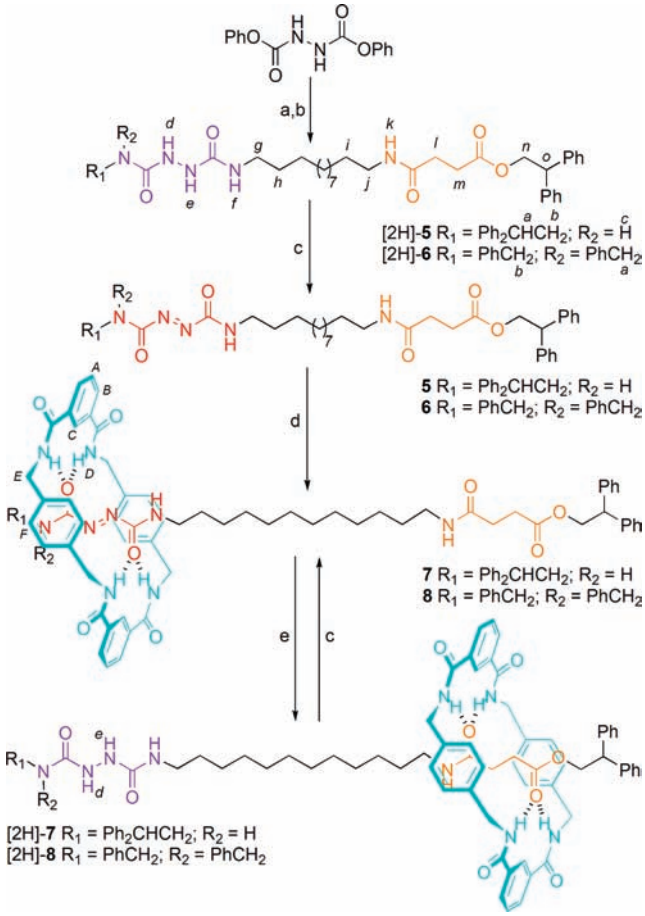
(33) Multiple hydrogen bonds are established between the solvating water molecules and the rotaxanes. Detailed information on these interactions is given in the Supporting Information.

(34) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48–76.

(35) For other examples of [2]rotaxanes with the same binding site but showing a different hydrogen bonding pattern in solution and in the solid state, see refs 17d, e, 20, and 29a.

(36) Brown, D. S.; Russell, P. R. *Acta Crystallogr.* **1976**, *B32*, 1056–1058.

Scheme 2. Synthesis of Bistable Molecular Shuttles Based on Azodicarboxamide Binding Sites **7** and **8** and Their Corresponding 1,2-Hydrazodicarboxamides [2H]-**7** and [2H]-**8**[a]



[a] Reagents and conditions: (a) $Ph_2CHCH_2NH_2$ or $(PhCH_2)_2NH$, Et_3N, $CHCl_3$; (b) $Ph_2CHCH_2O_2C(CH_2)_2CONH(CH_2)_{12}NH_2$ (2,2-diphenylethyl 3-(12-aminododecylcarbamoyl)propanoate), Et_3N, $CHCl_3$, [2H]-**5**, 35%; [2H]-**6**, 54%; (c) NBS, pyridine, CH_2Cl_2, **5**, 91%; **6**, 95%; **7**, 86%; **8**, 93%; (d) isophthaloyl dichloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, **7**, 34%; **8**, 45%; (e) $N_2H_4 \cdot H_2O$, $CHCl_3$, [2H]-**7**, 88%; [2H]-**8**, 92%. Full experimental procedures can be found in the Supporting Information.

Molecular shuttles **7** and **8** were prepared as outlined in Scheme 2. Threads **5** and **6** were prepared by standard procedures starting from diphenyl hydrazodicarboxylate,[19] which was sequentially aminated, first with the commercially available 2,2-diphenylethylamine or dibenzylamine and then with 2,2-diphenylethyl 3-(12-aminododecylcarbamoyl)propanoate,[22] which already contains the succinic amide ester station. The obtained hydrazo compounds [2H]-**5** and [2H]-**6** were dehydrogenated with NBS/pyridine leading finally to the azo threads **5** and **6** in 32% and 51% overall yield, respectively. Compounds **5** and **6** were subjected to rotaxane-forming conditions (*p*-xylylenediamine, isophthaloyl dichloride, triethylamine, chloroform, 4 h, high dilution) furnishing the molecular shuttles **7** and **8** in 34% and 45% yield, respectively.

The ^{1}H NMR spectra ($CDCl_3$, 400 MHz, 298 K) of thread **5** and rotaxane **7** are shown in Figure 3. The position of the macrocycle could be determined by comparing these two spectra. The succinic amide ester signals (H_m, H_l, and H_k, orange) appear at nearly identical chemical shifts in both thread and rotaxane, thus proving that this station remains unoccupied in **7**, whereas the NH azodicarboxamide protons (H_c and H_f, red) are deshielded by 0.7 ppm in the azo rotaxane with respect

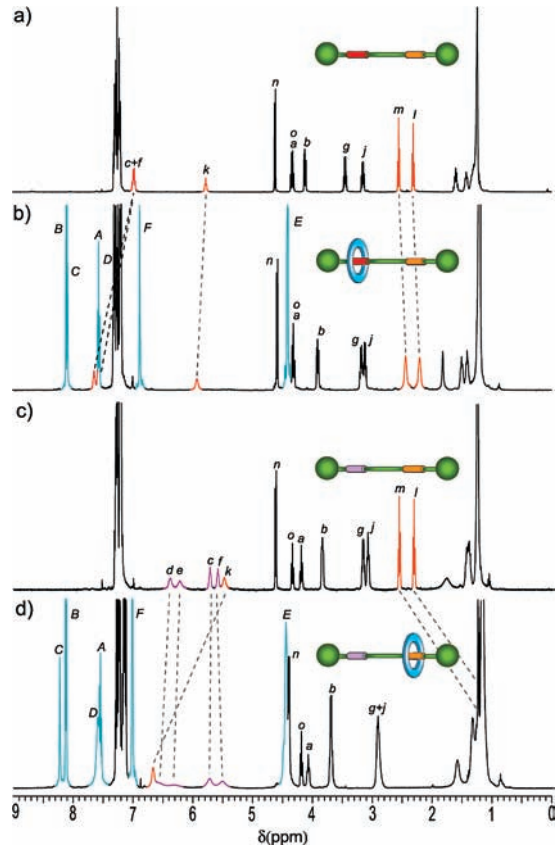


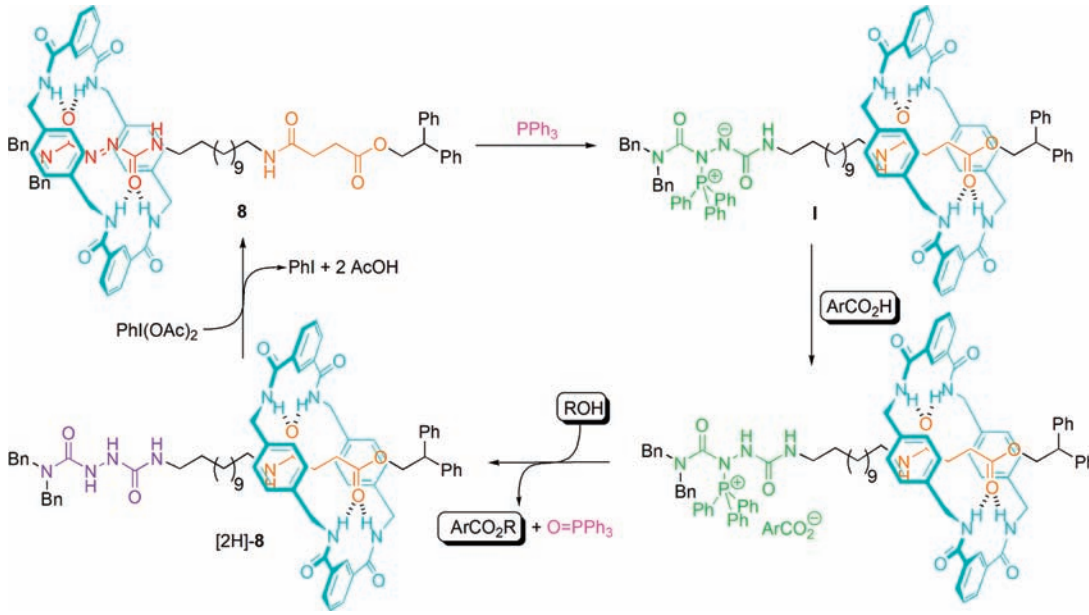
Figure 3. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) azodicarboxamide thread **5**, (b) azodicarboxamide rotaxane **7**, (c) hydrazodicarboxamide thread [2H]-**5**, and (d) hydrazodicarboxamide rotaxane [2H]-**7**. The assignments correspond to the lettering shown in Scheme 2.

to its isolated thread **5** due to the polarization caused by hydrogen bonding of the azodicarboxamide carbonyl groups with the macrocycle. Accordingly, we conclude that the macrocycle in **7** is located mainly over the azodicarboxamide unit (>94% of the time in $CDCl_3$, 298 K).[37]

Using identical reaction conditions as for the hydrogenation of **3** and **4** (Scheme 1), molecular shuttle **7** was quickly (less than 5 min), cleanly, and quantitatively converted into its hydrazo derivative [2H]-**7**, this reduction concomitantly activates the translocation of the macrocycle to the succinic amide ester station. The hydrazodicarboxamide protons (H_c, H_f, H_d, and H_e, purple) resonate at nearly identical chemical shifts in rotaxane and thread (compare Figure 3c,d), whereas the succinic amide ester methylene groups (H_m and H_l, orange) are each shielded by >1.5 ppm in the rotaxane. In the latter, the succinic amide ester NH (H_k, orange) appears shifted 1.3 ppm downfield compared with its thread. These spectroscopic data confirm that rotaxane [2H]-**7** adopts the coconformation where the ring sits around the succinic amide ester binding site.[37] A comparable series of shifts occur in the ^{1}H NMR spectra of the molecular shuttle **8**/[2H]-**8** (for stacked ^{1}H NMR spectra, see Supporting Information). The translocation of the macrocycle is fully reversed upon oxidation with the chemical pair NBS/pyridine, which regenerates the azodicarboxamide site and triggers the ring motion to this station by biased Brownian motion.

(37) (a) The occupancy level of the preferred station in both molecular shuttle states was estimated using the method described in ref 22. (b) For an alternative method see: Günbaş, D. D.; Zalewski, L.; Brouwer, A. M. *Chem. Commun.* **2010**, *46*, 2061–2063.

Scheme 3. Proposed Cyclic Chemical Functioning of the Shuttle **8** by Means of an Ester Bond Formation Reaction between an Acid, $ArCO_2H$ (Where Ar is 4-$O_2NC_6H_4$), and an Alcohol, ROH (Where R is $C_6H_5CH_2$) Mediated by a Classical Mitsunobu Protocol with Triphenylphosphane Followed by an *in Situ* Oxidation of the Hydrazo Generated Shuttle [2H]-**8**



Pleasantly, hydrogenation and dehydrogenation of both shuttles are fast, high yielding, and preparatively simple and generate large amplitude net positional changes, with excellent discrimination between the binding sites exhibited by the macrocycle in both chemical states of the shuttles. Remarkably, this chemically induced shuttling processes in these bistable [2]rotaxanes should add to the scarce number of examples of molecular shuttles using a chemical stimulus under mild reaction conditions.[14]

Organocatalytic Function of the Molecular Shuttle 8. In recent years, the realization of energy ratchet mechanisms in molecular-level structures has become essential to the development of functional molecular machines more complex than simple switches.[2,5] We turned our attention toward the design of a chemically driven molecular shuttle able to work in cyclic manner for generating synthetically useful covalent bonds as a novel strategy to incorporate a new type of control over the switching periodicity of the potential energy surface of a bistable [2]rotaxane. In particular, we reasoned that having an azodicarboxamide function integrated in the thread, a feasible transformation could involve the catalytic formation of ester bonds by a Mitsunobu protocol,[38,39] focusing on shuttles **8**/[2H]-**8**.[19a,40] During this process, the macrocycle will be continuously translocated between the nitrogen and carbon-based stations assisted by triphenylphosphane, which acts a chemical activator of the azo group, and iodosobenzene diacetate[41] as stoichiometric oxidant of the resulting hydrazo unit (Scheme 3).

Initially we ran a stoichiometric ester bond formation reaction to ascertain the ability of the monostation thread **2** to carry out this transformation, obtaining benzyl 4-nitrobenzoate in a good yield (Table 1, entry 1). Using reaction conditions similar to those described by Toy,[41] we next performed the organocatalytic Mitsunobu reaction with **2** to obtain the ester in 53% yield (Table 1, entry 2), which was increased to 71% by changing the solvent to acetonitrile and raising the temperature to 50 °C (Table 1, entries 3−5). The two-station thread **6** also behaved similarly in these substoichiometric conditions (Table 1, entry 7). Having achieved an efficient substoichiometric version of the Mitsunobu reaction with the thread **6**, we next tested [2]rotaxane **4** and proved that the reactivity of its azo function is nearly extinguished by the steric shielding caused by the surrounding macrocycle, which apparently precludes the initial triphenylphosphane attack (Table 1, entry 6). Delightfully, the molecular shuttle **8** served as a successful organocatalyst of the ester bond formation giving the product in 65% yield (Table 1, entry 8) thus proving that if a second station is available for hosting the macrocycle, initially over the azo function, the ring movement then allows the catalytic esterification to take place.

Although the hydrogen bonds between the azodicarboxamide station and the macrocycle can survive even in relatively polar

Table 1. Stoichiometric and Substoichiometric Mitsunobu Esterification of 4-Nitrobenzoic Acid with Benzylic Alcohol by Azodicarboxamide Rotaxanes and Threads[a]

entry	azo (equiv)	PPh_3[b] (equiv)	$PhI(OAc)_2$ (equiv)	solvent	temp (°C)	yield (%)
1	**2** (1)	1		THF	25	61
2	**2** (0.1)	2	2	THF	25	53
3	**2** (0.3)	2	2	THF	25	42
4	**2** (0.1)	2	2	THF	50	67
5[c]	**2** (0.1)	2	2	CH_3CN	50	71
6	**4** (0.1)	2	2	CH_3CN	50	16
7	**6** (0.1)	2	2	CH_3CN	50	69
8	**8** (0.1)	2	2	CH_3CN	50	65

[a] Reactions were carried out at 0.1 M concentrations of the azo compound using 1 equiv of carboxylic acid and 2 equiv of alcohol, in anhydrous degassed solvents and protected from moisture (see Supporting Information). [b] Except entry 1, triphenylphosphane was slowly added via syringe pump. [c] An additional experiment carried out in the absence of PPh_3 yielded the ester but in only 9% yield.

(38) (a) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935–939. (b) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382.
(39) For selected recent general reviews dealing with Mitsunobu reactions, see: (a) Dandapani, S.; Curran, D. P. *Chem.—Eur. J.* **2004**, *10*, 3130–3138. (b) But, T. Y. S.; Toy, P. H. *Chem.—Asian J.* **2007**, *2*, 1340–1355. (c) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551–2651.
(40) Ito, S.; Tsunoda, T. *Pure Appl. Chem.* **1999**, *71*, 1053–1057.
(41) But, T. Y. S.; Toy, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 9636–9637.

solvents such as THF or acetonitrile,[22] these solvents may compete with the hydrogen bond donors of the thread. In such case, Brownian macrocycle escape from the azo station allows, in some extension, the phosphane attack to form the corresponding Morrison−Brunn−Huisgen[42] betaine, like **I** (Scheme 3).[43] This betaine was detected by high-resolution mass spectrometry. Thus, in its mass spectrum, peaks at m/z = 1554.7446, and 777.8780, corresponding to $[M + H]^+$ and $[M + 2H]^{2+}$, respectively, were observed, and their isotopic resolutions are in excellent agreement with the theoretical distributions (see Supporting Information). Triphenylphosphane addition to the azodicarboxamide station alters its affinity for the macrocycle and notably increases the steric bulk between the amide groups. In fact, Corey−Pauling−Koltun space-filling models show that a tetrabenzylic amide macrocycle would be unlikely to wrap the azophosphonium moiety of the betaine and therefore the succinic amide ester becomes the positional minimum energy. This intermediate then follows the well-known mechanistic pathway[44] of the Mitsunobu reaction to give the ester and the hydrazo [2]rotaxane [2H]-**8**, which, after *in situ* reoxidation, recycles the coconformer **8** by an excess of bis(acetoxy)iodobenzene, and it is ready to start again the catalytic wheel of the ester bond formation. This particular functioning provides an original method to trigger a continuous ring translocation ruled by the esterification and oxidation reactions, which could be employed in the tuning of distance- or time-dependent properties of other interlocked systems designed to this purpose. From a thermodynamic point of view, it should be noted that although the esterification reaction is an endergonic process, the oxidation of phosphane promoted by the reduction of the azodicarboxamide binding site makes the overall process exergonic. In these reaction conditions, this molecular shuttle operates in a cyclic manner as long as the fueling chemicals are accessible into this dynamic system, which is able to move a threaded macrocycle between two nitrogen- and carbon-based stations of a programmed track to make an esterification process going downhill.

(42) (a) Morrison, D. C. *J. Org. Chem.* **1958**, *23*, 1072–1074. (b) Brunn, E.; Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 513–515.

(43) It should be noted that the phosphane attack could occur at the nitrogen in α or *β* position to the $Bn_2NC(O)$- group of **8**. For simplicity, we have depicted the betaine derived from the attack to the α nitrogen.

(44) For a DFT computational study of the Mitsunobu reaction, see: Schenk, S.; Weston, J.; Anders, E. *J. Am. Chem. Soc.* **2005**, *127*, 12566–12576.

Conclusions

In summary, we have described the ability of different azodicarboxamides to act as new templates for the assembly of unprecedented azo-functionalized [2]rotaxanes. Moreover, they can be reversibly and efficiently interconverted with their hydrazo forms by very well-known chemical methods in fast and clean manners. This novel, chemically switchable binding site class has been used for the building of bistable, stimuli-responsive molecular shuttles that work through reversible hydrogenation−dehydrogenation of the nitrogen−nitrogen bond, producing large amplitude net positional changes with a good discrimination between the binding sites of the macrocycle in both states of the shuttle. These molecular shuttles are able to operate by two different mechanisms: in a discrete mode through two reversible and independent chemical events triggering reduction and oxidation reactions and in a continuous mode through a catalyzed ester bond formation reaction in which the shuttle acts as an organocatalyst. We believe such features open a new expectation for the elaboration of more complex molecular machines by enabling them to participate inside of a chemical reaction network and so giving rise to controllable dynamic systems closer to those operating in nature.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds and full crystallographic details of rotaxanes **3** and [2H]-**3** including cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

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