Chemical Science

Cite this: *Chem. Sci.*, 2012, **3**, 2314

www.rsc.org/chemicalscience

EDGE ARTICLE

Redox divergent conversion of a [2]rotaxane into two distinct degenerate partners with different shuttling dynamics†

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Received 19th April 2012, Accepted 24th April 2012
DOI: 10.1039/c2sc20488f

The submolecular translational movement in novel hydrogen-bonded [2]rotaxanes containing benzylic amide macrocycles and two azo/hydrazodicarboxamide binding sites was analyzed by dynamic NMR spectroscopy. The results show that the activation free energies of the macrocycle shuttling in these systems depend on the oxidation level of both nitrogen-based binding sites embedded in the thread; the shuttling motion being more rapid in [2]rotaxanes at the lower oxidation level bis(hydrazo)-based rotaxanes. Moreover, by means of a fully controllable chemical switching, these two-station [2]rotaxanes are able to swap over three different dynamic states, which differ in macrocycle shuttling velocity: a) faster in a bis(hydrazo) [2]rotaxane, the lower oxidation state; b) moderate in a bis(azo) [2]rotaxane, the higher oxidation state; and c) practically stopped at the azodicarboxamide station of an azo/hydrazo [2]rotaxane, the intermediate oxidation state. Thus, from this latter resting state, two "fans" of different velocity can be turned on and off by simple chemical redox processes.

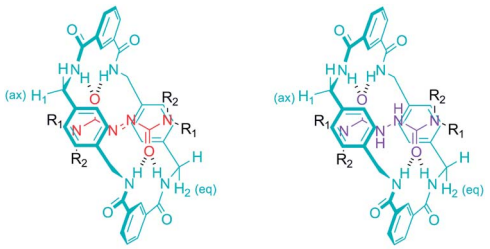
Introduction

The investigation on mechanically interlocked architectures has been a cutting-edge research topic for more than twenty years.[1,2] Progresses in the synthetic approaches toward these molecules along with a smart and consistently planned design of these entwined systems have enabled the development of a range of ways to control the submolecular motion by applying different external stimuli.[3,4] In that vein, the research aimed to mimic biological engines[5] or to develop increasingly more sophisticated electromechanical devices[4b,6] has produced a number of programmed systems for performing induced movements at will.

Among this group of molecules, bistable [2]rotaxanes,[2k,7] in which a threaded macrocycle is positionally distributed between the two different binding sites of a dumbbell-shaped molecule, engage a privileged place in this arena due to their potential use as molecular devices. One of the main interests in this field is primarily focused on getting a preferential and reversible placement of the ring in one of the two binding sites possessing well-differentiated affinities for the macrocycle. During the last decade, an intense research activity in this regard has allowed some of these systems, originally designed to operate in solution, to be studied even in surfaces and condensed phases,[8] thus proving that the mechanical motion is not a unique process of the liquid state and in turn further increasing the expectations that nanoscientists have deposited in this type of molecular architecture.[6b,9]

In this context, degenerate [2]rotaxanes,[7b,10] systems that have two identical binding sites, have been less frequently investigated. In these systems, the macrocycle shuttles back and forth between the two stations due to the collapse of the intercomponent interactions at one station before formation of new interactions at the second one.[4c] Traditionally, the researchers in this field have modified the macrocycle dislocation along the thread by means of the reversible incorporation of steric[7b,10b,e,k] or electrostatic[10g,n,o] "speed bumps" between the two isoenergetic stations.

Recently, we have demonstrated that azodicarboxamide groups can act as efficient templates for the assembly of hydrogen-bonded rotaxanes through a five-component clipping reaction.[7c] We also showed that these azo [2]rotaxanes (*e.g.*, **1**) can be quantitatively converted into their hydrazo partners (*e.g.*, [2H]-**1**) by reduction with hydrazine. This reversible transformation alters the nature and strength of the hydrogen bond network between macrocycle and thread and therefore also changes the internal dynamics governed by those interactions, such as the pirouetting of the ring around the thread.



1a $R_1 = Ph_2CHCH_2$; $R_2 = H$ [2H]-**1a**
1b $R_1 = R_2 = PhCH_2$ [2H]-**1b**

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† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. See DOI: 10.1039/c2sc20488f

By using this new class of binding site, we developed bistable and chemically stimuli-responsive molecular shuttles able to produce large amplitude positional changes with an efficient discrimination between two different stations of a benzylic amide macrocycle.[7c] In these interlocked systems, the switchability of the oxidation level of the only dinitrogenated station in the thread was the key for controlling the reversible exchange of the two accessible states of these shuttles.

We have now focused our attention on hydrogen-bonded [2]rotaxanes containing two binding sites of the azo and/or hydrazo type, both at same oxidation level at the first stage, for studying their translational dynamic behaviour. We reasoned that the modulation of the oxidation level of these particular systems could give rise to interlocked molecular architectures featuring novel dynamics of significance for the tuning of distance and/or time dependent properties of such molecular systems.

Taking into account that the interconversion between the lower bis(hydrazo) and higher bis(azo) oxidation levels of this particular system is projected to take place through an intermediate azo/hydrazo state, we first approached an estimation of how much different is the affinity of these stations for the benzylic amide macrocycle, in order to estimate its position in a putative azo/hydrazo [2]rotaxane, which is further prepared and analyzed.

Results and discussion

Affinity of azo/hydrazo single-binding sites for the benzylic amide macrocycle of [2]rotaxanes

An important factor for the successful design of bistable [2]rotaxane-based molecular shuttles is the adequate choice of the two binding sites for ensuring a good positional bias of the macrocycle in both translational isomers.[11] From a thermodynamic point of view, in order to obtain a preferential occupancy of 95% a minimum difference of 2 kcal mol^{-1} between the binding energies of the two stations is mandatory.[11b] Preliminary studies are usually done by determining the association constants between the macrocycle and two linear molecules each containing one of the two different binding sites, as a model of the two putative stations.[11a,12] This approximation is amenable only if both components are soluble in one of the habitual, deuterated NMR solvents and under experimental conditions in which the non-covalent interactions between macrocycle and station are established. Although the association constants between anilide,[13] thioamide[14] or anthracene[15]-based cyclic tetralactams and different threads have been thus determined, the low solubility of most of the described tetrabenzylic amide macrocycles[16] in non-disrupting hydrogen bond solvents prevents similar studies with these rings. Notwithstanding this, Leigh and co-workers described that the energy barrier of the *circumrotation* of one of these tetrabenzylic amides around a thread gives an explicit measure of the strength of the molecular interactions between the subcomponents of this kind of hydrogen-bonded [2]rotaxane.[17]

Thus, with the aim of estimating the relative strength of the intercomponent interactions between the macrocycle and the azo and hydrazo threads, we calculated the corresponding energy barriers for the macrocycle circumrotation of azo [2]rotaxane **1b** and hydrazo [2]rotaxane [2H]-**1b** by variable temperature ^{1}H NMR experiments in halogenated solvents using the coalescence method (Fig. 1). The insolubility of rotaxanes **1a** and [2H]-**1a** in non-disrupting hydrogen bond solvents avoids a similar study with these compounds. The kinetic and thermodynamic parameters extracted from these VT-NMR studies are compiled in Table 1.

Typically, these dynamic NMR studies have been used to analyze the *rotational* motion of the macrocyclic subcomponent in similar hydrogen bonded [2]rotaxanes. Indeed, it has been reported that the *half circumrotation* of the benzylic amide macrocycle present in [2]rotaxanes **1** can be understood as a 180° rotation of the ring plus a chair–chair flipping, which translates the equatorial methylenic protons (H_2) onto the axial positions (H_1).[17b] In the azo rotaxanes **1b**, the coalescence of the methylenic protons signals[18] of the macrocycle occurs at 333 K, corresponding to an energy barrier of 14.8 kcal mol^{-1}.[19] Remarkably, this value is the highest energy barrier found for the pirouetting of this benzylic amide macrocycle in all of the hydrogen-bonded [2]rotaxanes described so far (template, free energy of activation in kcal mol^{-1}/temperature in K/solvent):[20] fumaramide,[17d] 13.4/273/CD_2Cl_2; glycylglycine,[17a] 13.4/298/$C_2D_2Cl_4$; succinamide,[21] 12.9/298/$CDCl_3$; bis(nitrone),[22] 12.2/271/$C_2D_2Cl_4$; squaraine,[15] 10.6/213/$CDCl_3$; maleamide,[17d] 6.8/223/CD_2Cl_2. In stark contrast, the resonance of the analogous methylene protons in the hydrazo [2]rotaxanes [2H]-**1b** merges as only one signal at temperatures higher than 228 K, corresponding to an energy barrier of 10.4 kcal mol^{-1}, 4.4 units lower than the value calculated for the same ring pirouetting process in its azo partner **1b**. This difference shows that circumrotation in **1b** is clearly more dampened than in the corresponding hydrazo rotaxane [2H]-**1b**, as a proof of the higher affinity of the azo binding site when compared with the hydrazo one.

Interestingly, in the experiments carried out at low temperature with the hydrazo [2]rotaxane [2H]-**1b** it was also possible to monitor the coalescence of the signals corresponding to the *s-cis* and *s-trans* methylene groups of the terminal *N*,*N*-dibenzyl urea moieties of the thread. As result, we calculated an energy value of 12.4 kcal mol^{-1} (at $T_c = 260$ K) for the Bn_2N–CO bond rotation

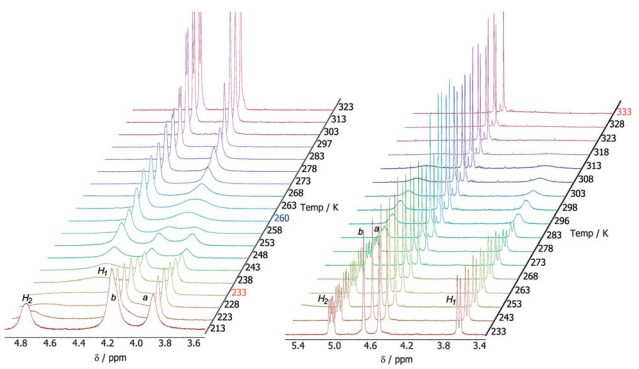


Fig. 1 Variable temperature ^{1}H NMR spectra (stacked expansions of the aliphatic region, 400 MHz) of [2H]-**1b** (left) and **1b** (right) in CD_2Cl_2 at 223–300 K and $C_2D_2Cl_4$ at 300–380 K. H_1 and H_2 are the benzylic protons of the macrocycle and H_a and H_b are the benzylic protons of the thread.

Table 1 Kinetic and thermodynamic parameters for macrocycle pirouetting and amide bond rotation obtained from temperature-dependent ^{1}H NMR spectra of the [2]rotaxanes **1b** and [2H]-**1b** in deuterated solvents. Where $\Delta\nu$ is the separation, in Hz, between the resonance peaks of H_1 and H_2 (or H_a and H_b) at slow exchange regime, k_c is the rate exchange in s^{-1} and T_c is the coalescence temperature in K. $\Delta G^{\neq}$ is the energy barrier in kcal mol^{-1}

	Macrocycle pirouetting				Amide bond rotation CO–NBn_2			
Comp.	$\Delta\nu$	k_c	T_c[a]	$\Delta G^{\neq}$[b]	$\Delta\nu$	k_c	T_c[a]	$\Delta G^{\neq}$[b]
[2H]-**1b**	237	527	228	10.4	102	227	260	12.4
1b	560	1245	333	14.8	69	153	>393	>19.3

[a] NMR temperature calibration was performed using pure methanol (low temperature) or ethylene glycol (high temperature) samples. [b] Calculated value ± 0.2.

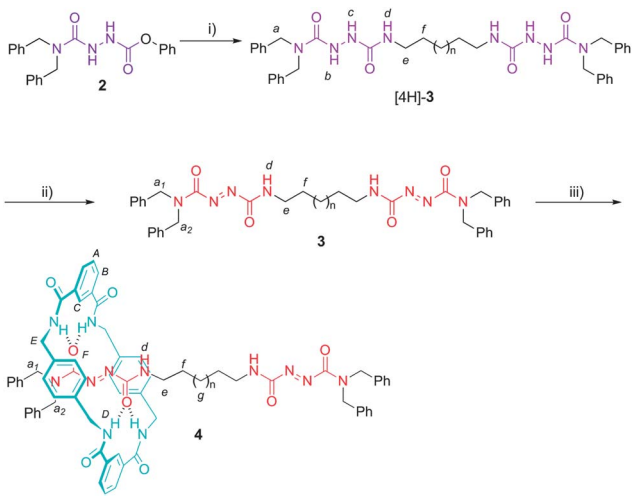
in the encapsulated thread, which is notably lower than the barriers calculated for R_2N–CO rotations of related tertiary amide fragments in threaded fumaramides (*ca* 20 kcal mol^{-1}).[17c] A more habitual value, 19.3 kcal mol^{-1}, was estimated for the rotation of the same bond in the azo rotaxane **1b**, assuming that the coalescence of the signals of their benzylic protons would occur at temperatures higher than 393 K (Table 1).[23]

Back to the rotational motion of the macrocycle, the estimated energy difference of 4.4 kcal mol^{-1} between both pirouetting energy barriers informs us about the notably different affinity for the macrocycle of the azo and hydrazo binding sites. With these results in our hands, we were confident of succeeding in the elaboration of a molecular shuttle with azo and hydrazodicarboxamide binding sites showing a reasonable good positional discrimination (*vide infra*).

Macrocycle shuttling in double-binding site azo/hydrazo [2] rotaxanes

Typically, investigations on ring shuttling dynamics have been carried out in degenerate [2]rotaxanes bearing two identical binding sites. The more common interlocking interactions were π–π charge transfers,[7b,10a,c,d,f,i,j,l,n,o] whereas only a few contributions have been disclosed studying hydrogen-bonded interlocked systems.[10b,g,m] With the aim of analyzing the effect of the oxidation level of the binding site, we first synthesized the hydrogen-bonded [2]rotaxane **4** (Scheme 1). The two-station thread **3** was easily obtained by a high-yielding two-step protocol that involves the phenoxy displacement of phenyl *N*,*N*-dibenzylaminocarbonylhydrazinecarboxylate[7c] (**2**) with 1,12-dodecanediamine, followed by oxidation with NBS/pyridine.

The movement of the macrocyclic tetralactam along the bis(azodicarboxamide) thread of rotaxane **4** was analyzed by studying the temperature-dependent behaviour of their ^{1}H NMR spectra. At a temperature higher than or equal to room temperature the ring is continuously moving between both stations and an averaged co-conformation is observed by ^{1}H NMR (see Fig. 2, top). When the thermal energy of the system is gradually reduced, the ring motion is progressively attenuated until the splitting of the NMR signals occurs as a result of a co-conformational freezing (see Fig. 2, bottom). In such



Scheme 1 The synthesis of the degenerate [2]rotaxane **4** bearing two azodicarboxamide binding sites. Reagents and conditions: i) $H_2N(CH_2)_{12}NH_2$, $CHCl_3$, reflux, 71%; ii) NBS (*N*-bromosuccinimide), pyridine, CH_2Cl_2, r.t., 85%; iii) isophthaloyl dichloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, r.t., 28%.

conditions, two different magnetic environments arise, for instance, for the CONH*C*$\mathbf{H}_2$ protons (H_e in Scheme 1) of the thread (3.37 ppm at 298 K; 3.50 and 3.21 ppm at 223 K), one is next to an empty station whereas the other is contiguous to an occupied one. From the separation of these signals at the slow dynamic regime (120 Hz) and the coalescence temperature (253 K) an energy barrier of 12.0 kcal mol^{-1} for the macrocycle shuttling is calculated. A similar VT-NMR study with the easily available hydrazo partner [4H]-**4** (Scheme 2) yielded, as expected, a lower energy barrier of 10.5 kcal mol^{-1} at 228 K, corresponding to an easier shuttling motion. Table 2 summarizes the dynamic ^{1}H NMR data for the macrocycle shuttling of the degenerate [2]rotaxanes **4** and [4H]-**4**.

These results thus show how the rate of the ring translocation may be modulated in these degenerate [2]rotaxanes just by modifying the oxidation level of the binding sites. In consequence, this factor should be taken into account for the design of similar interlocked systems oriented to control distance- and/or time-dependent properties.

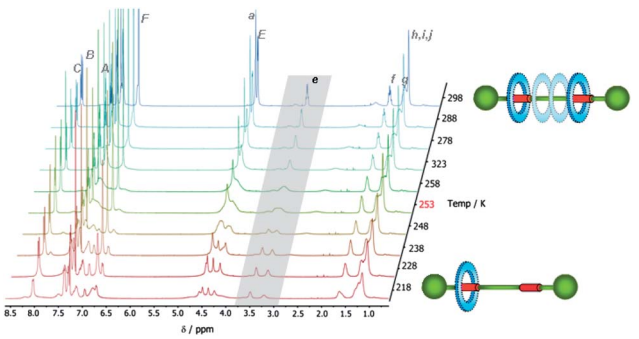
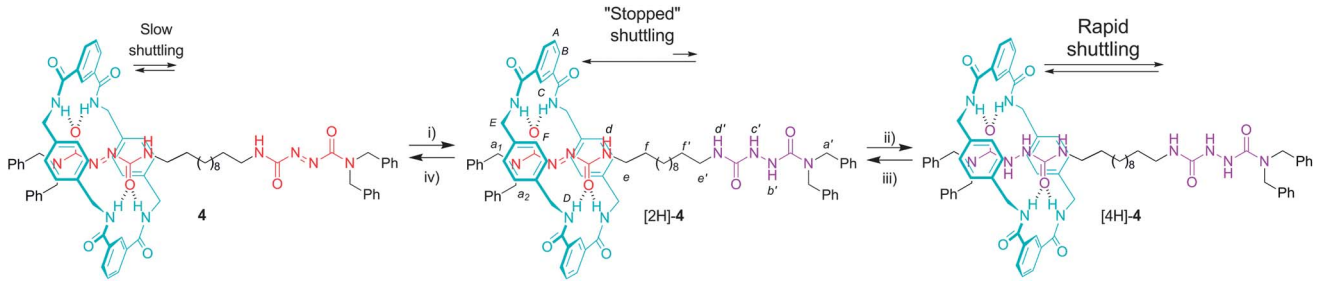


Fig. 2 Variable temperature ^{1}H NMR spectra (400 MHz) of **4** in CD_2Cl_2 at 218–298 K. The assignments correspond to the lettering shown in Scheme 1.



Scheme 2 Interconversion between the three oxidation levels of double nitrogen-based binding-site [2]rotaxanes. Reagents and conditions: i) $N_2H_4 \cdot H_2O$, $CHCl_3$, −10 °C, 39%; ii) $N_2H_4 \cdot H_2O$, $CHCl_3$, r.t., 98%; iii) NBS, pyridine, CH_2Cl_2, −20 °C, 52%; iv) NBS, pyridine, CH_2Cl_2, r.t., 95%.

Table 2 Kinetic and thermodynamic parameters for macrocycle shuttling obtained from VT-^{1}H NMR spectra of the degenerate [2]rotaxanes **4** and [4H]-**4** in deuterated solvents

	Macrocycle shuttling			
Comp.	$\Delta\nu$ (Hz)	k_c (s^{-1})	T_c (K)[a]	$\Delta G^{\ddagger}$ (kcal mol^{-1})[b]
4	120	249	253	12.0
[4H]-**4**	160	355	228	10.5

[a] NMR temperature calibration was performed using a pure methanol sample. [b] Calculated value ± 0.2.

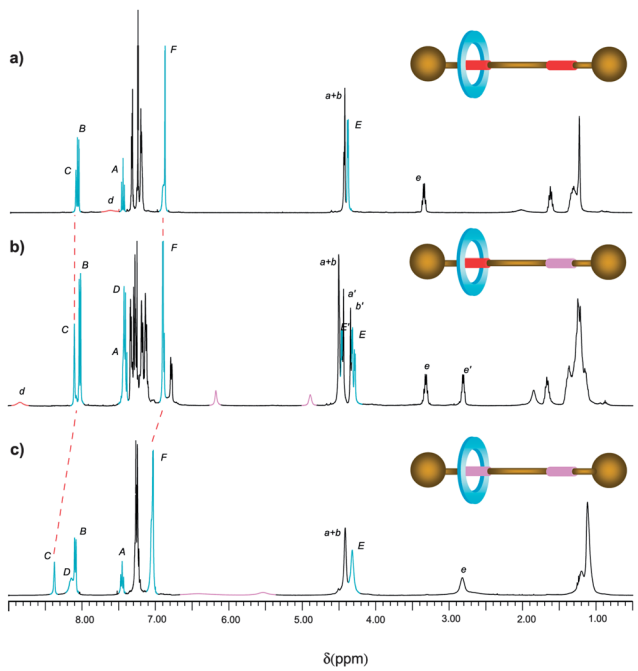


Fig. 3 ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of degenerate [2]rotaxanes **4** (a) and [4H]-**4** (c) and the non-degenerate rotaxane [2H]-**4** (b). The assignments correspond to the lettering shown in Scheme 2.

Chemical interconversion between different dynamic states of a double binding-site [2]rotaxane.

By changing the oxidation level of the dinitrogenated stations we have been able to build two types of [2]rotaxanes showing very different dynamic states, as summarized in the previous paragraphs. We now describe how by a fine tuning of the reaction conditions we have achieved an efficient chemical interconversion between all three available oxidation levels of the two-station [2]rotaxanes corresponding to three different dynamic states (Scheme 2). A partial reduction of the bis(azo) rotaxane **4** with hydrazine at −10 °C provides the non-degenerate [2]rotaxane [2H]-**4** in 39% yield, which is further reduced to [4H]-**4** when subjected to the action of a second equivalent of hydrazine, now at room temperature. In the reverse sense, [2H]-**4** is obtained in 52% yield by means of a partial oxidation of [4H]-**4** with one equivalent of *N*-bromosuccinimide in the presence of pyridine at low temperature (−20 °C). A subsequent oxidation step at room temperature recovers the original bis(azo) rotaxane **4**, thus completing a redox cycle that is fully controllable. Obviously, by running the same reactions at room temperature and using an excess of the corresponding reagent we could quickly and cleanly interconvert **4** and [4H]-**4** (see ESI†) without stopping at the intermediate oxidation stage, azo/hydrazo rotaxane.

The position of the macrocycle in [2H]-**4** was established by analyzing the shifting of the ^{1}H NMR signals of the H_C and H_F protons after the modification of its oxidation level. For this analysis, we first studied these chemical shifts variations in [2]rotaxanes with a dinitrogenated single-binding site. The hydrogenation of the azo rotaxane **1b** promotes the downfield shift ($\Delta\delta = 0.15$ ppm) of the signal ascribed to the F protons of the macrocycle (1,4-disubstituted benzene) with respect to the resonance of the same protons in the corresponding parent hydrazo rotaxane [2H]-**1b**. Another signal that also changes by reduction of the thread of **1b** is that of the C protons of the macrocycle (isophthalic moiety), which is shifted downfield by 0.26 ppm.[7c] As we expected, a partial reduction of **4** keeps unaltered the chemical shifts of the responsive macrocycle protons (H_C and H_F) as the macrocycle in [2H]-**4** is also located at the azo station. However, a further reduction of [2H]-**4** forces the ring to be located in one of the hydrazo stations of [4H]-**4** which, in turn, promotes the expected signals shifting (see Fig. 3).

The comparison of the ^{1}H NMR spectra of [2H]-**4** with that shown by its corresponding azo-hydrazo thread [2H]-**3** (for the synthesis of this compound, see ESI†) confirms the preferred azo binding of the ring (Fig. 4). Thus, whereas the signals corresponding to the NH protons of the trisubstituted hydrazodicarboxamide station ($H_{b'}$, $H_{c'}$, $H_{d'}$) appear at similar

chemical shifts in both species, thus proving that this station remains depopulated in [2H]-**4**, the NH proton of the trisubstituted azodicarboxamide station (H_d) in the same rotaxane is shifted downfield by 2.3 ppm with respect to the same signal in the thread due to the polarization caused by the hydrogen bonding of the azodicarboxamide carbonyl groups with the amide protons of the macrocycle (Fig. 4).

From a statistical point of view (Fig. 5), these transformations allow the chemical exchange of two rotaxanes with two equally populated stations through a third one with a net positional integrity of macrocycle of more than 90% (see ESI†). From a dynamic point of view, these transformations enable swapping over three different dynamic levels that differ in macrocycle shuttling behaviour: a) faster in the two-station [2]rotaxane with lower oxidation state; b) slower in the two-station [2]rotaxane with higher oxidation state; and c) in the two-station [2]rotaxane, with an intermediate oxidation state, the ring spent most of its time at the azodicarboxamide station. The partial reduction and oxidation reactions for accessing [2H]-**4**, with an intermediate oxidation level, is in fact an original manner for discontinuing the ring motion in these systems. Previously reported methods for achieving this task usually include a steric[7b,10b,e,k] or electrostatic[10g,n,o] barrier in the middle of the linker of the two isoenergetic stations of degenerate [2]rotaxanes, this barrier acting as a brake of the macrocycle movement.

More interestingly, this chemical redox cycle allows to use the intermediate oxidation state [2H]-**4** as a chemically commutable rotaxane from which two macrocycle translocations of different velocity can be triggered. We envisioned that by introducing such an operational pattern into the architecture of other molecular devices would give access to new classes of switches different than those enabled with an on/off response. To the best of our knowledge, this is the first time that such a chemically-responsive molecular shuttle has been built and characterised, at least based on amide-based rotaxane chemistry.[1,2]

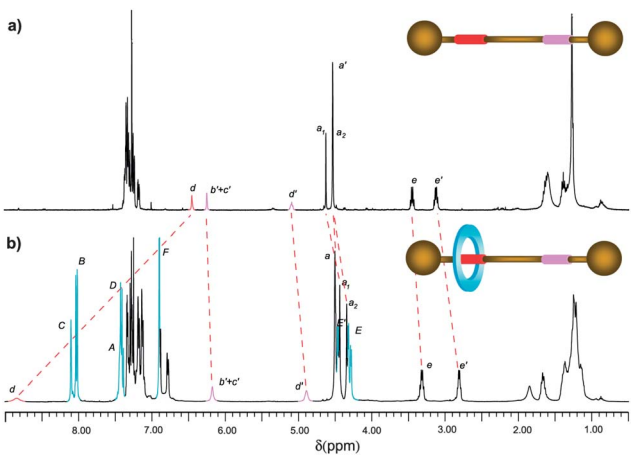


Fig. 4 Stacked ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) thread [2H]-**3** and (b) [2]rotaxane [2H]-**4** (b). The assignments correspond to the lettering shown in Scheme 2.

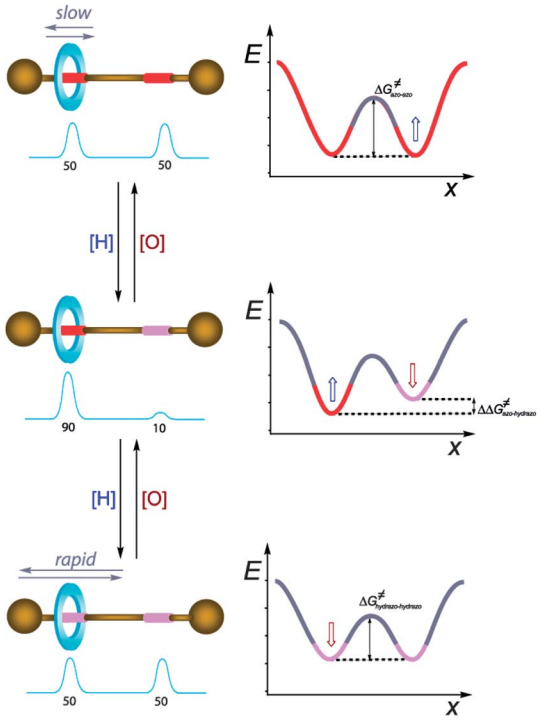


Fig. 5 The population distribution (%) of the macrocycle (in blue) and the idealized free-energy profile for its movement between the two stations of a double binding-site [2]rotaxane in their three available oxidation levels. Red and blue arrows point out the effect of the oxidation and reduction reactions, respectively, on the energy well corresponding to the interaction between macrocycle and thread.

Conclusions

Submolecular translational motions in degenerate azodicarboxamide [2]rotaxanes have been studied by means of dynamic ^{1}H NMR spectroscopy. The calculated activation barriers for the macrocycle shuttling were found to be dependent on the oxidation level of the binding sites of the thread. These results were consistent with the relative affinities of the azo and hydrazo binding sites toward the macrocycle. Fine tuning of the reaction conditions for the interconversion of the three available oxidation states of a double-binding sited [2]rotaxane allowed access to three different dynamic levels that differ in their macrocycle shuttling behaviour. From the intermediate oxidation state, an azo/hydrazo [2]rotaxane, two states with translational motions of different velocity can be easily accessed at will, which are enabled to be switched on and off by easily amenable and high yielding redox processes.

Acknowledgements

This work was supported by the MICINN (Projects CTQ2008-05827/BQU and CTQ2009-12216/BQU) and Fundación Séneca-CARM (Project 08661/PI/08). J. B. thanks the MICINN for a Ramón y Cajal contract.

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