Co-conformational Exchange Triggered by Molecular Recognition in a Di(acylamino)pyridine-Based Molecular Shuttle Containing Two Pyridine Rings at the Macrocycle

Alberto Martinez-Cuezva,[a] Fernando Carro-Guillen,[a] Aurelia Pastor,[a] Marta Marin-Luna,[b] Raul-Angel Orenes,[c] Mateo Alajarin,[a] and Jose Berna*[a]

Abstract: We describe the incorporation of *endo*-pyridine units into the tetralactam ring of di(acylamino)pyridine-based rotaxanes. This macrocycle strongly associates with the linear interlocked component as confirmed by X-Ray diffraction studies of the rotaxane **2b**. Dynamic NMR studies of **2b** in solution afforded a rotational energy barrier higher than that of the related rotaxane **2a**, which lacks of pyridine rings in the macrocycle. The macrocycle distribution of the molecular shuttle **4b**, containing two *endo*-pyridine rings, shows that the major co-conformer is that with the cyclic component sitting over the di(acylamino)pyridine station. DFT calculations also support the marked preference of the ring for occupying the heterocyclic binding site. The association of *N*-hexylthymine with the di(acylamino)pyridine binding site of **4b** led to the formation of a rare S-shaped co-conformer in which the tetralactam ring interacts simultaneously with both stations of the thread.

Introduction

The control of molecular motion originated by the thermal energy is a key topic in the building of molecular machines.[1-8] Interlocked molecules are excellent prototypes of this compound class in virtue of their ability to undergo relative large amplitude motions under the action of an external signal.[9-12] Among these compounds, molecular shuttles having a rotaxane architecture play an essential role as switchable components inside the molecular machinery toolbox.[13-19] Thus, the relative movement of their threaded components can be controlled by the incorporation of binding sites with exchangeable affinities in strategic positions of axle and macrocycle.[8] The control of the submolecular motion in molecular shuttles can be triggered by a wide variety of stimuli such as redox, photochemical or acid-base processes.[8,10]

We recently reported the preparation of versatile chemical and electrochemical molecular shuttles controlled by an unprecedented methodology: the recognition of externally-added small molecules by one of the thread stations. Di(ac ylamino)pyridines (DAP) have been widely used as donor-acceptor-donor receptors of compounds possessing a complementary hydrogen-bonding (HB) array.[22-24] The inclusion of this strategic domain in the thread has been exploited as a novel template of tetrabenzylic amide macrocycles in the synthesis of hydrogen-bonded [2]rotaxanes.[20] Notably, the relative position of the macrocycle along the thread can be shifted in the presence of complementary HB acceptor-donor-acceptor systems, such *N*-hexylthymine or barbital.[20,21]

In order to expand the DAP-recognition concept to the synthesis of molecular shuttles, we designed a new type of [2]rotaxane containing a threaded dipyridine-based tetralactam ring. The justification for this modification lays in early studies on hydrogen-bonded interlocked compounds revealing the strong preference of pyridine-2,6-dicarbamido units to adopt a cisoid conformation, due to the presence of intracyclic hydrogen bonds.[25-30] Taking this preference into account we prepared a molecular shuttle built from a thread bearing one DAP moiety and one amide group as binding sites combined with a tetralactam ring bearing two *endo*-pyridine units. The aim of this study was the macrocycle shuttling triggered by the addition of *N*-hexylthymine.

Results and Discussion

Synthesis of a DAP [2]rotaxane with a dipyridine-based macrocycle

The successful synthesis of benzylic amide rotaxanes by the clipping methodology requires the stereoelectronic matching between the hydrogen-bond donor and acceptor atoms of the intermediate noncovalent complex formed between the thread (template) and the acyclic precursors of the macrocycle. [2]Rotaxanes with tetralactam macrocycles have been effectively synthesised by using different dicarboxamides[31-35] as templates.

We have previously reported the synthesis of the DAP-based thread **1** and the corresponding rotaxane **2a**, this latter one obtained in 33% yield through a five-component clipping reaction with *p*-xylylenediamine and isophthalic acid dichloride (Scheme 1).[20] Under the same reaction conditions, we have been now able to isolate the rotaxane **2b** in 7% yield by replacing 2,6-isophthaloyl dichloride by an analogous pyridine-

[a] Dr. A. Martinez-Cuezva, F. Carro-Guillen, Dr. A. Pastor, Prof. M. Alajarin and Dr. J. Berna
Departamento de Química Organica, Facultad de Quimica
Regional Campus of International Excellence *"Campus Mare Nostrum",* Universidad de Murcia, E-30100 Murcia (Spain)
E-mail: ppberna@um.es
[b] Dr. M. Marin-Luna
Instituto de Química Médica (CSIC)
Juan de la Cierva, 3, E-28006 Madrid (Spain)
[c] Dr. R.-A. Orenes
SAI, Universidad de Murcia, E-30100, Murcia (Spain)

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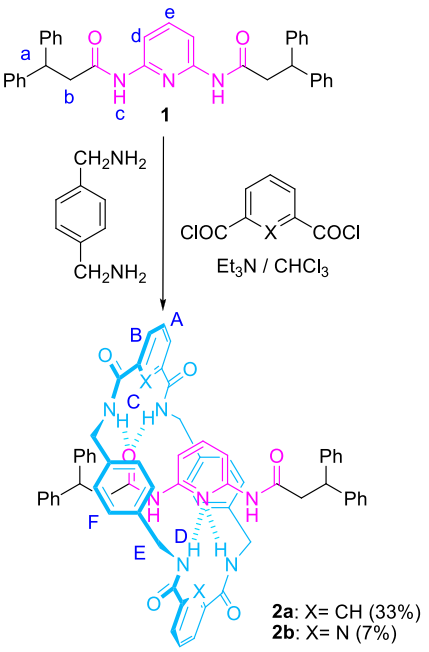
2,6-dicarbonyl reactant. The notable decrease of yield for the latter process clearly points out to a less favourable match between the open-chain precursor of the forming pyridine-based ring and the thread acting as template (see below). It should be noted that an identical structural variation caused a similar decrease of yield during the synthesis of glycylglycine [2]rotaxanes.[27]



Scheme 1. Synthesis of the single-binding site [2]rotaxanes **2a,b**.[36]

Molecular structure of the rotaxane 2b in the solid state.

In order to examine the molecular geometry of **2b**[37] at the solid state we obtained suitable monocrystals for X-ray diffraction analysis by slow cooling of a solution of the rotaxane in acetonitrile. As expected, both 2,6-pyridinedicarboxamide moieties of the macrocycle show the characteristic intracyclic HB array between every pyridinic nitrogen atom (N1 and N2) and their neighbouring NH groups (Figure 1). However only one of these two pyridinedicarboxamide subunits (N1) interacts with the DAP-domain of the thread by an intricate network of hydrogen bonds, which places their respective pyridine rings in an orthogonal disposition (92.7º). Thus, a bifurcated hydrogen bond is established between the pyridine nitrogen atom of the thread (N7) and the two NH groups of the 2,6-pyridinedicarboxamide fragment (N3H, 2.35 Å, 138º and N6H, 2.41 Å, 151º). The X-ray structure shows an additional hydrogen bond between the pyridine nitrogen atom of the ring (N1) and one of the NH groups of the thread (N9H, 2.18 Å, 177º).[38-42] The intertwined structure is additionally stabilized by π-π stacking interactions between the heterocyclic ring of the DAP moiety and both *p*-xylylene fragments (3.58 Å, 91º).

This entangled network precludes the simultaneous interaction of both pyridinedicarboxamide fragments with the thread, as it is commonly observed in structurally related rotaxanes such as **2a**.[20, 43] Indeed, two HB donors of the ring (N4H and N5H)[44] and two HB acceptors of the thread (O5 and O6) lack of intercomponent interactions. It seems reasonable to assume that this specific pattern similarly avoid the optimal double interaction between the open-chain precursors of the forming ring around the thread thus explaining the minor efficiency of the five-component assembly leading to **2b.**

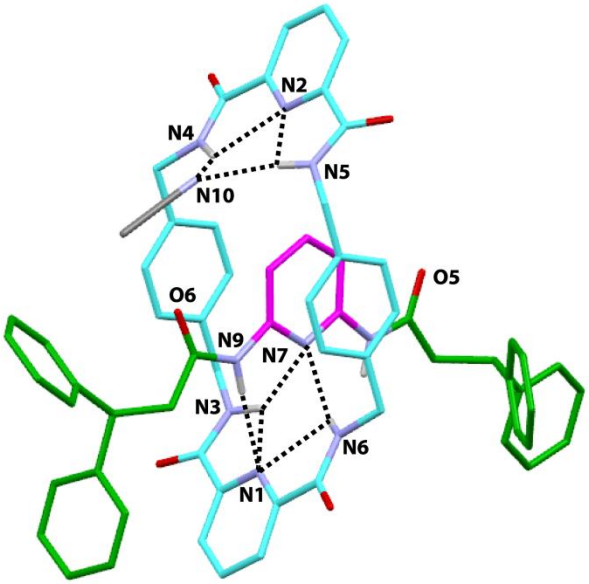


Figure 1. X-ray crystal structure of the [2]rotaxane **2b** (with an acetonitrile molecule as a cosolvate). For clarity, carbon atoms of the thread are shown in green, except those of the pyridine ring which are shown in pink; carbon atoms of the macrocycle are shown in blue, oxygen atoms are depicted in red, nitrogen atoms are depicted in light blue, and selected hydrogen atoms are in white. Intramolecular hydrogen-bond lengths [Å] (and angles [°]): N3–H03–N7 2.35 (138.0); N6–H06–N7 2.41 (150.6); N3–H03–N1 2.32 (106.1); N6–H06–N1 2.37 (107.1); N9–H09–N1 2.18 (176.7).

Dynamic behaviour of rotaxane 2b in solution

The differences in the intercomponent HB patterns found in the X-ray structures of rotaxanes **2a** and **2b** led us to compare their dynamic behaviour in solution. Thus, we next determined the energy barrier of rotation of the macrocycle around the thread in **2b**, which provides an explicit measure of the strength of the molecular interactions between both subcomponents. At a given temperature, if the intercomponent interactions are weak enough, the two methylenic protons of the macrocycle should be equivalent due to the fast averaging of their environments on the NMR time scale. The lowering of the temperature would decrease the rate of this exchange process, resulting in the splitting of the broad singlet corresponding to the resonance of these protons.

(Variable-temperature) VT ^{1}H NMR experiments (400 MHz, CD_2Cl_2) carried out with the rotaxane **2b** showed the splitting of the signals of the methylene protons of the ring, H_E, at 188 K (Figure 2). Consequently, we determined an energy barrier of 9.5 kcal mol^{-1} (T_c = 218 K) for the pirouetting of the macrocycle around the thread.[45-48] This value is higher than the analogous barrier previously estimated for the rotaxane **2a**.[21] In Figure 2, the splitting of the resonances for the H_A, H_B and H_D protons of the macrocycle, merging as broad signals at 283 K, is also observed.

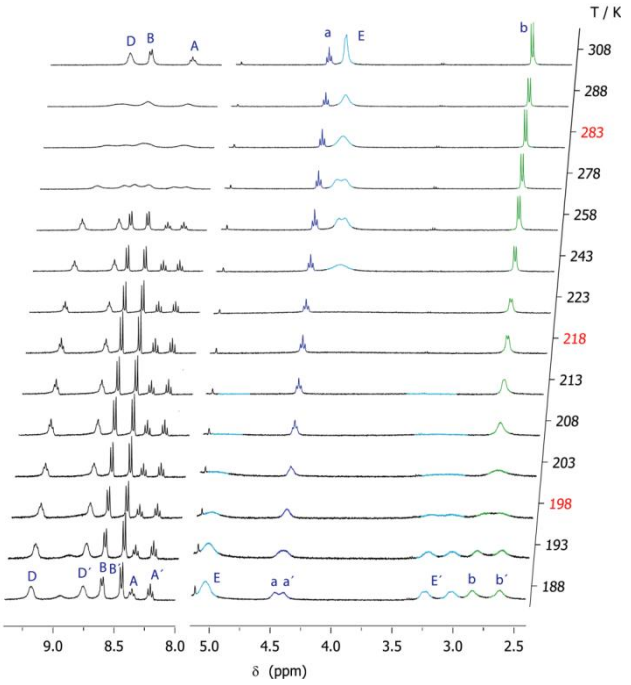


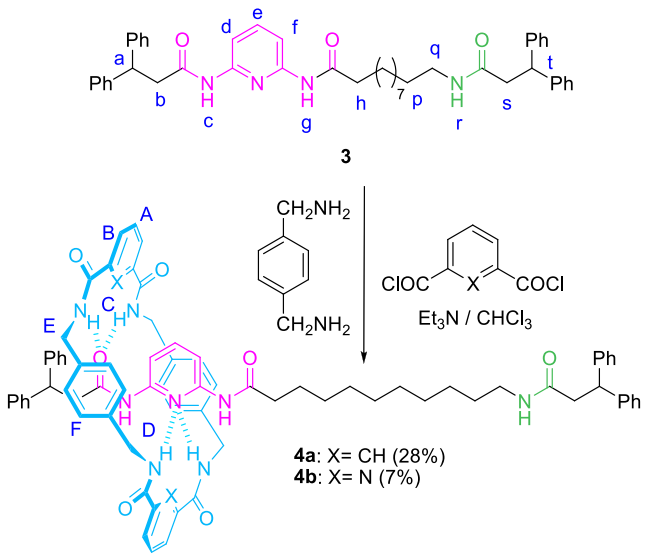
Figure 2. Partial VT-^{1}H NMR spectra (400 MHz, CD_2Cl_2) of **2b**. The lettering assignments correspond to the labelling in Scheme 1.

As with rotaxane **2a**,[21] the VT ^{1}H NMR experiments of **2b** also disclosed the coalescence of the aliphatic signals of the dessymmetrized thread (H_a and H_b) at 198 K. This observation supports the loss of symmetry of the molecule due to the inclination of the average plane of the macrocycle from the symmetry plane of the thread at low temperatures.

These results confirm that the incorporation of two pyridine rings into the macrocyclic component of **2b** causes a noticeable reduction of the spinning rate of the ring when compared with **2a**, most probably due to the presence of stronger intercomponent HB interactions in the former rotaxane. Although this reason seems to be in opposition to the arguments given above for explaining the low yield of the template synthesis of **2b**, both results are in line with those obtained with peptido[2]rotaxanes by Leigh and co-workers.[27] The authors of this research pointed out that this effect is a consequence of the stronger preference of the pyridine-2,6-dicarboxamide units to adopt a cisoid conformation when compared to the isophthalamide unit.

Di(acylamino)pyridine-based molecular shuttles

Taking into account the differences found between the HB patterns of rotaxanes **2a** and **2b**, both in the solid state and in solution, we decided to explore the effect of the incorporation of two *endo*-pyridine motifs on the ring distribution of a related di(acylamino)pyridine-based molecular shuttle. With this idea in mind we synthesised rotaxane **4b** (Scheme 2), an analogue of the previously reported **4a**.[21] In line with the outcome of the clipping step in the preparation of both rotaxanes **2**, whereas **4a** was obtained in 28% yield, the new rotaxane **4b** only could be obtained in 7% yield by using an analogous five-component reaction.



Scheme 2. Synthesis of the DAP-based molecular shuttles **4a,b**.[36]

We next established the level of occupancy of the DAP binding site by the two different macrocycles in rotaxanes **4a** and **4b** following a well-known protocol.[49] The percentage of occupancy was estimated by comparing the upfield shift experienced by the proton at 4-position of the pyridine ring (H_e in compounds **4a,b**, Scheme 2) following rotaxane formation, with the same shift occurring in the synthesis of rotaxanes **2a,b**, associated with a 100% occupation of the DAP station (Table S1). This analysis showed that the occupation of the DAP site in **4b** (80%) was clearly higher than in **4a** (68%).[21]

These results may be rationalized by considering again the stronger HB interactions between the interlocked components of the rotaxane **4b**. The intricate hydrogen bond network established in **4b** increases the population of the co-conformer in which the dipyridine-based macrocycle is over the DAP station. With the aim of confirming this assumption we carried out a computational study (M062x-6-311+g(d)//B3LYP/6-31g) on the two main co-conformations[50,51] of rotaxane **4b**, those with the macrocycle binding to either the DAP unit or the distal amide group. For computational efficiency, we selected as simplified

models the co-conformers DAP-**4c** and A-**4c**, in which isobutyl groups act as stoppers instead of the diphenylmethyl ones of **4a,b** (Figure 3).

The analysis of the relative energies of both co-conformers shows that DAP-**4c** is more stable than A-**4c** by 4.0 kcal·mol^{-1} in agreement with the experimental results.

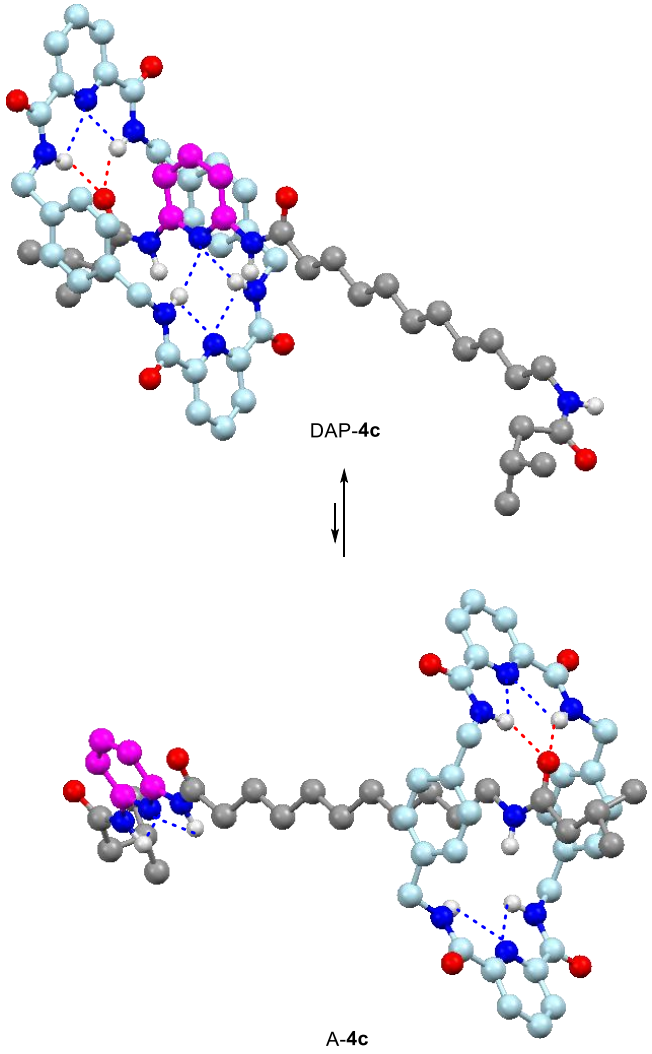


Figure 3. Co-conformational equilibrium of DAP-**4c** and A-**4c** as result of DFT calculations.

Molecular recognition for triggering the ring motion of hydrogen-bonded shuttle 4b

In our previous studies we proved that the ring motion in two-station [2]rotaxanes containing benzylic amide macrocycles can be tuned by molecular recognition of complementary external binders to the DAP-domain placed at the thread.[20] We next assayed the effect of the association of two HB acceptor-donor-acceptor systems, barbital and *N*-hexylthymine, in the ring motion of rotaxane **4b**. Preliminary NMR studies (see Figure S2) confirmed that the complexation of barbital to **4b** is notably weaker than that of the thymine derivative, thus we decided to focus on the study with this latter binder.

We run titration experiments with rotaxane **4b** by using *N*-hexylthymine (**T**) as guest. The corresponding association constant K_{assoc} was determined by monitoring the changes in the ^{1}H NMR spectra of rotaxane **4b** with the progressive addition of the guest. We found the formation of a 1:1 complex **4b**·**T** (Fig. S3a-c) with a K_{assoc} of 339 M^{-1}, which is of the same order than that for the complex **4a**·**T** (K_{assoc} = 286 M^{-1}), although both are notably lower than the one obtained for the complex **3**·**T** (K_{assoc} = 615 M^{-1}). The decrease of the affinity of rotaxanes **4a** and **4b** for **T**, in comparison with that of the thread **3**, is obviously due to the dynamic competition between the macrocycle and the guest for the occupation of the DAP binding site.

The addition of an excess of thymine **T** to the rotaxane **4b** shows the downfield shifting of the NH_c and NH_g protons of the DAP unit ($\Delta\delta$ = 3.02 and 1.95 ppm, Figure 4) and that of the H_e proton ($\Delta\delta$ = 0.53 ppm, Figure 4). These observations support the association by triple hydrogen bonding between thymine **T** and the DAP domain of the thread with the concomitant displacement of the ring.

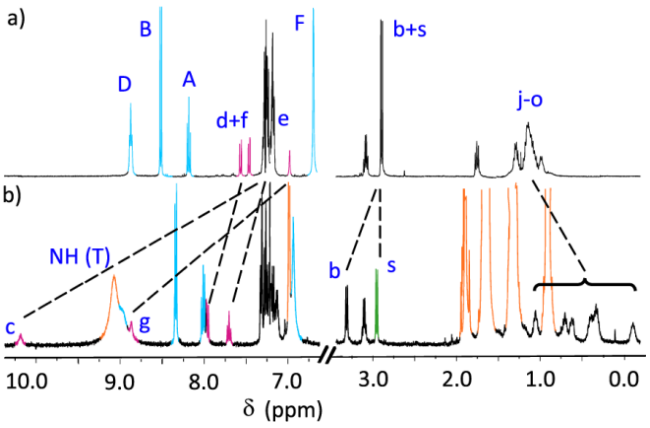


Figure 4. Selected regions of the ^{1}H NMR spectra (400 MHz, CD_2Cl_2, 298 K) of a) shuttle **4b**; and b) shuttle **4b** in the presence of an excess (20 equiv.) of *N*-hexylthymine (**T**, orange signals) (see Scheme 2 for signal assignments).

Remarkably, significant splitting of the signals corresponding to the protons of the alkyl chain ($H_{j\text{-}o}$), resonating between 1.10 ppm and -0.11 ppm, was also observed. This unexpected observation may be rationalized in terms of a major co-conformation in which the *endo*-pyridine rings of the macrocycle simultaneously interacts with the two stations of the shuttle: the carbonyl group of the amide station and the nearest carbonyl group of the DAP binding site (Figure 5). This co-conformation induces the folding of the alkyl chain for adopting an "S" shaped conformation at room temperature.[52] In stark contrast, the association of the shuttle **4a,** including isophthalamide motifs, and *N*-hexylthymine leads to the formation of a completely different co-conformer in which the ring mainly interacts with the amide domain.[21] The "S" shaped co-conformer of the rotaxane

in the complex **4b·T** was found to be unstable at temperatures higher than 312 K, due to the decomplexation of the thymine derivative (see Fig. S6).

The ring dynamics of the "S" shaped co-conformer was completely truncated by decreasing the temperature to 233 K (see Fig. S7). At this stage the splitting of the resonances of the aromatic *p*-xylylene protons (H_F) of the macrocycle indicates the slowdown of the rotational motion around the S-shaped thread. Figure 5 shows the molecular structure of the complex **4c·T** optimized by DFT calculations. It reveals that the pyridine-2,6-dicarbamido groups of the macrocycle have lost their typical intracyclic hydrogen bonds in favour of setting up two new NH···O interactions with the thread, placing the phenyl rings of the macrocycle "sandwiching" part of the alkyl chain between them.

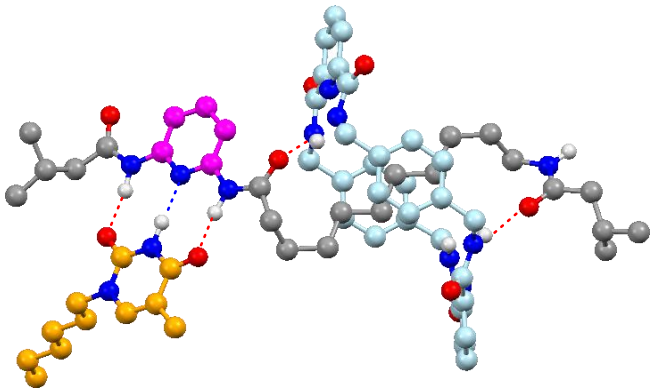


Figure 5. Molecular structure of the complex **4c·T** computed at DFT level, showing the "S"-shaped conformation of the thread.

Thus, both experimental and computational results show that the complexation of a thymine derivative to the DAP binding site of **4b** favours the formation of a stable "S"-shaped co-conformer, in which the macrocycle interacts simultaneously with both stations of the thread. Probably, one of the causes of this phenomenon is the enthalpic gain of forming intercomponent hydrogen bonds with both isophthalamide units which compensate the entropically unfavourable linear conformation that must be adopted by the thread.

In our previous work, we described the recovery of the original state of a DAP-based shuttle complexed with barbital by the addition of a competitive binder.[20] A similar strategy could be also used with the complex **4b·T** by using a suitable receptor[53] able to associate with the thymine derivative more efficiently than the DAP binding site. However, in this case, the initial co-conformer of rotaxane **4b** was easily restored by means of a simple chromatography.

Conclusions

Herein, we report the synthesis and dynamic behaviour of two new di(acylamino)pyridine-based [2]rotaxanes, a single binding site [2]rotaxane and a molecular shuttle with an additional amide group as second station. Both are decorated with two endo pyridine rings in the tetralactam macrocycle. The results have been compared with those obtained with the rotaxanes of analogous structure but containing two isophthaloyl moieties in the macrocycle.

The synthesis of the two new [2]rotaxanes was conducted by a five-component clipping reaction however, this procedure led to the final products with a notable decrease of yield respect to the reported examples. The reduction of the synthetic efficiency of the clipping step was rationalized taking into account the intricate network of hydrogen bonds found in the X-ray structure of the DAP [2]rotaxane with the dipyridine-based macrocycle. The formation of a strong hydrogen-bonded linkage between the DAP station and one of the 2,6-pyridinedicarboxamide moieties of the ring prevents the simultaneous interaction of both pyridinedicarboxamide fragments with the thread, which additionally would hamper the optimal association between the open-chain precursor of the pyridine-based macrocycle around the DAP-thread.

The analysis of the dynamic behaviour of the [2]rotaxane with one DAP station concludes that the presence of the two *endo* pyridine rings in the tetralactam macrocycle causes a reduction of its spinning rate around the thread, which has been also explained in terms of stronger intercomponent HB interactions.

Expectedly, the major co-conformer of the molecular shuttle containing an additional amide group is that with the cyclic component sitting over the DAP station. DFT molecular calculations supports the marked preference of the ring for inhabiting the di(acylamino)pyridine binding site.

Finally, we have demonstrated that the co-conformational exchange can be triggered by molecular recognition by using N-hexylthymine. Nevertheless, the complexation of the thymine derivative to the DAP binding site favours the formation of an unexpected "S"-shaped conformer, in which the macrocycle simultaneously interacts with both stations: the DAP-domain and the amide station.

Experimental Section

Unless stated otherwise, all reagents were purchased from Aldrich Chemicals and used without further purification. HPLC grade solvents (Scharlab) were nitrogen saturated and were dried and deoxygenated using an Innovative Technology Inc. Pure-Solv 400 Solvent Purification System. ^{1}H- and ^{13}C-NMR spectra were recorded at 298 K on a Bruker Avance 300 and 400 MHz instruments. Mass spectra were recorded with Agilent 5973 (EI), Agilent VL (ESI) and HPLC/MS TOF 6220 mass spectrometers.

General procedure for the synthesis of the DAP-based [2]rotaxanes 2 and 4

The corresponding thread (1 equiv) and Et_3N (24 equiv) in anhydrous $CHCl_3$ (200 mL) were stirred vigorously whilst solutions of *p*-xylylenediamine (8 equiv) in anhydrous $CHCl_3$ (20 mL) and the corresponding acid dichloride (8 equiv) in anhydrous $CHCl_3$ (20 mL) were simultaneously added over a period of 4 h using motor-driven syringe pumps. After a further 4 h the resulting suspension was filtered through a Celite pad, washed with water (2 x 50 mL), a saturated solution of $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL). The organic phase is then

dried over $MgSO_4$ and the solvent removed under reduced pressure. The resulting solid was subjected to column chromatography (silica gel) to yield unconsumed thread, [2]rotaxane and [2]catenane.

Synthesis of 2b

Rotaxane **2b** was synthesised following the general procedure employing thread **1**[20] and 2,6-pyridinedicarbonyl dichloride as starting materials. The solid crude was subjected to column chromatography on silica gel using $CHCl_3$/MeOH (97/3) mixture as eluent to give the title product as a white solid (23 mg, 7%); m. p. > 300 ºC; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.76 (bs, 4H, NH_D), 8.55 (bs, 4H, H_B), 8.22 (bs, 2H, H_A), 7.41 (d, *J* = 8.0 Hz, 2H, H_d), 7.25-7.09 (m, 22H, Ph + NH_c), 7.05 (t, *J* = 8.0 Hz, 1H, H_e), 6.50 (s, 8H, H_F), 4.37 (t, *J* = 8.0 Hz, 2H, H_a), 4.22 (bs, 8H, H_E), 2.70 (d, *J* = 8.0 Hz, 4H, H_b); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.9 (CO), 163.6 (CO), 150.1 (C), 148.6 (C), 143.8 (C), 141.5 (CH), 139.8 (CH), 137.2 (CH), 129.2 (CH), 128.6 (CH), 127.7 (CH), 127.2 (CH), 126.1 (CH), 110.4 (CH), 46.9 (CH), 43.5 (CH_2), 43.5 (CH_2); HRMS (ESI) calcd for $C_{65}H_{58}N_9O_6$ $[M + H]^+$ 1060.4505, found 1060.4547.

Synthesis of 4b

Shuttle **4b** was synthesised following the general procedure employing thread **3**[21] and 2,6-pyridinedicarbonyl dichloride as starting materials. The solid crude was subjected to column chromatography on silica gel using AcOEt/hexane (80/20) mixture as eluent to give the title product as a white solid (66 mg, 7%); m.p.= 127-129 ºC; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.92 (t, *J* = 5.9 Hz, 4H, NH_D), 8.48 (d, *J* = 7.8 Hz, 4H, H_B), 7.15 (t, *J* = 7.8 Hz, 2H, H_A), 7.53 (d, *J* = 8.1 Hz, 1H, H_d), 7.49 (s, 1H, NH_c), 7.43 (d, *J* = 7.9 Hz, 1H, H_f), 7.30-7.10 (m, 21H, Ph + H_e), 7.02 (s, 1H, NH_g), 6.67 (s, 8H, H_F), 5.80-5.70 (m, 1H, NH_r), 4.65-4.43 (m, 6H, H_{E+t+a}), 4.25-4.05 (bs, 4H, H_E), 3.06 (dd, *J* = 12.7, 6.8 Hz, 2H, H_q), 2.89 (d, *J* = 7.5 Hz, 2H, H_b), 2.88 (d, *J* = 7.9 Hz, 2H, H_s), 1.71 (t, *J* = 7.4 Hz, 2H, H_h), 1.30-0.80 (m, 16H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 172.2 (CO), 171.1 (CO), 170.1 (CO), 163.9 (CO), 150.1 (C), 149.4 (C), 149.1 (C), 144.7 (C), 144.0 (C), 141.6 (CH), 139.9 (CH), 137.7 (C), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.2 (CH), 128.0 (CH), 127.3 (CH), 126.9 (CH), 126.1 (CH), 111.0 (CH), 110.2 (CH), 47.9 (CH), 47.4 (CH), 44.0 (CH_2), 43.4 (CH_2), 39.8 (CH_2), 37.8 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.63 (CH_2), 29.59 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 27.2 (CH_2), 24.9 (CH_2); HRMS (ESI) calcd for $C_{76}H_{79}N_{10}O_7$ $[M + H]^+$ 1243.6128, found 1243.6135.

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Keywords: template synthesis • rotaxane • hydrogen bond • molecular recognition • molecular shuttles

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[45] The free energy of activation, $\Delta G_c^{\neq}$ was calculated by the Eyring equation, $\Delta G_c^{\neq} = -RT_c \cdot ln(k_c h/k_b T_c)$, where $k_c = (\pi\Delta\upsilon)/\sqrt{2}$ or $k_c = \pi\sqrt{(\Delta\upsilon^2 + 6J^2)}/\sqrt{2}$ and R, h and k_b are the gas, Planck and Boltzmann constants, respectively.
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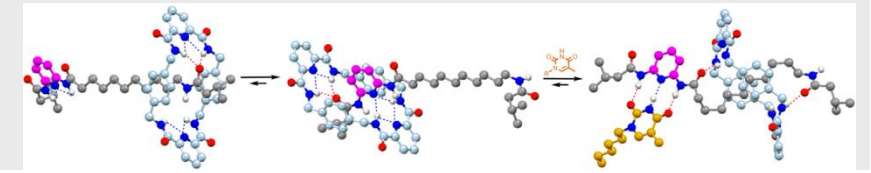

Sticky rings! Rotational and translational internal motions of di(acylamino)pyridine rotaxanes containing dipyridine-based rings are examined. The association of one of this interlocked compounds and a derivate of thymine leads to the formation of a stable S-shaped co-conformer.

*A. Martinez-Cuezva, F. Carro-Guillen, A Pastor, M. Marin-Luna, R.-A. Orenes, M. Alajarin, and J. Berna**

Co-conformational Exchange Triggered by Molecular Recognition in a Di(acylamino)pyridine-Based Molecular Shuttle Containing Two Pyridine Rings at the Macrocycle