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Homo and heteroassembly of amide-based [2]rotaxanes using α,α'-dimethyl-*p*-xylylenediamines

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The formation of [2]rotaxanes via a fumaramide-templated clipping reaction using α,α'-dimethyl-*p*-xylylenediamines is described. This process selectively affords two out of seven possible interlocked isomers due to a noticeable effect of the methyl groups on the in/out disposition of the amide CO groups.

There are a number of processes, in Nature, in which the reaction of polyvalent substrates leads to the selective formation of a discrete compound instead of a complex mixture of scrambled products resulting from the random connection of the involved building blocks.[1] Aimed to export the benefits of these transformations to the building of discrete compounds from polyfunctional starting materials, several sorting processes and discrimination events have been reported.[2] Understanding the origin of the selectivity of such approaches in which reversible connecting events are generally involved has been crucial for the preparation of a large variety of compounds including macrocycles,[3] cages,[4] capsules,[5,6] and mechanically interlocked compounds.[7-9] In this arena, it is worth noting the formation of [n]rotaxanes (n>2) in which different rings selectively binds to another component with multiple binding sites.[7,10]

Since more than a couple of decades, the synthesis of rotaxanes[11] is a topic of growing interest due to their use in the building of artificial molecular machines.[12] Among these, the amide-based hydrogen bonded rotaxanes have been employed for the development of a broad range of functional systems[11-13] including, among others, catalysts,[14] sensors,[15] prodrugs,[16] and stimuli-responsive materials.[17] An important subset of these rotaxanes was developed by Leigh through a robust synthetic methodology based on a five-component clipping reaction involving two units of *p*-xylylenediamine, two units of isophthaloyl dichloride and a dicarboxamide-type template.[18] During this process, a reversible preorganization of a linear ring precursor around the template is involved before the last amide bond kinetically traps the interlocked structure.[19] To the best of our knowledge, in spite of the widespread use of this rotaxane formation protocol, no sorting effects have been reported until now. In this context, we were interested in knowing if the incorporation of stereogenic centers on the benzylic positions of the diamine building block promotes some kind of selection in the distribution of the stereoisomers resulting of this driven-template protocol[20] as a consequence of a marked preference of the substituents for adopting a particular arrangement. Herein we report the assembly of hydrogen bonded [2]rotaxanes from α,α'-dimethyl-*p*-xylylenediamine **1** as a mixture of its racemic and chiral forms and isophthaloyl chloride **2** in the presence of a tetrasubstituted fumaramide **3** as a template (Fig. 1A).

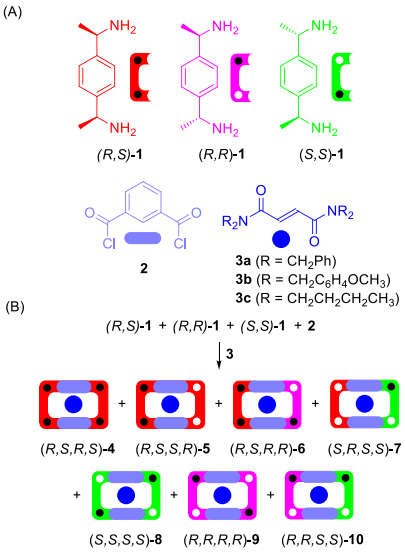

Figure 1 (A) Schematic definition of the building blocks: α,α'-dimethyl)-*p*-xylylenediamines (**1**), isophthaloyl dichloride (**2**) and the fumaramides **3**. (B) Five-component assembly of rotaxanes **4-10** from *(R,S)*-**1**, *(R,R/S,S)*-**1**, **2** and **3**. The seven possible stereoisomers resulting of the coupling (2+2+1) are shown (achiral rotaxanes **4**, **5** and **10** and the chiral rotaxanes **6**-**9**). Methyl groups on the top face of the average plane of the macrocycle are represented by black dots (●) and those under the bottom face are represented by white dots (○). See ESI, for a full interpretation of the cartoons.

Attending to the different ways for approaching two diamine units to the isophthaloyl chloride, the rotaxane assembly in the presence of a fumaramide thread could render up to seven

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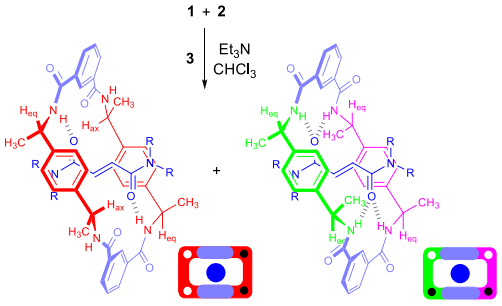
interlocked species (Figure 1B), three achiral and four chiral rotaxanes (two enantiomeric pairs). The assembly of these rotaxanes results from the combination of two meso diamine units (in a parallel or antiparallel orientation) and the two enatiomeric forms of the chiral diamine. For instance, the incorporation of two units of *meso*-**1** in a parallel fashion affords the rotaxane **4** locating all the methyl groups in the same face of the average plane of the ring whereas the antiparallel association of two units of *meso*-**1** leads to the interlocked **5** in which two methyl groups are in the same face of the ring and the other two in the opposite face.

A 2:3 mixture of *(R,S)*-**1** and *(R,R/S,S)*-**1** diamines was prepared from 1,4-diacetylbenzene through a one-pot Leuckart-Wallach synthesis.[21,22] With this mixture of diamines **1** in hand, the rotaxane assembly was carried out in the presence of a tetrasubstituted fumaramide, such as **3a**, following the stablished protocol.[18,19] This assay provided a mixture of only two stereoisomeric rotaxanes, **5a** and **10a** in a 3:2 ratio, in moderate yield (46% conversion, 17% combined yield based on the recovered starting material) (Scheme 1). This yield is lower than that obtained for the five–component coupling employing the same fumaramide-based thread and the unsubstituted *p*-xylylenediamine.[23] In order to improve this yield we incorporated a methoxy group at the benzylic stoppers for enhancing the hydrogen bonding (HB) acceptor ability of the amide CO groups of the thread.[23] The result of this reaction using **3b** was similar, leading to a 3:2 mixture of **5b** and **10b** but, pleasantly, the rotaxane production increased up to 31% (32% conversion).

Aimed to separate these mixtures of rotaxanes several chromatographic resolutions were unsuccessfully attempted, although a fractional crystallization enabled the complete purification of **5a,b** leaving a binary mixture enriched in the minor component **10a,b**. The crystal growing of each component of the tetrabenzyl derivatives **5a** and **10a** allowed their unambiguous characterization at the solid state revealing: a) the major rotaxane, **5**, results from the assembly of the diamine *(R,S)*-**1**, minor component in the starting material, through a parallel approaching to the isophthaloyl dichloride and b) the minor rotaxane, **10**, results from the assembly of both chiral diamines, (*R,R*)-**1** and (*S,S*)-**1** to the isophthaloyl dichloride. These results show that a sorting process occurs during this five-component clipping in which only two out of seven possible rotaxanes are formed.[24] Aimed to advance in the understanding of the selectivity of these processes we directed our attention to the conformations of rotaxanes **5a** and **10a** in the solid and solution states.



5a (R = CH_2Ph)
5b (R = $CH_2C_6H_4OCH_3$)
5c (R = $CH_2CH_2CH_2CH_3$)

10a (R = CH_2Ph)
10b (R = $CH_2C_6H_4OCH_3$)
10c (R = $CH_2CH_2CH_2CH_3$)

Scheme 1 Selective assembly of rotaxanes **5** and **10** using *α,α'*-dimethyl-*p*-xylylenediamine. See ESI for further experimental details.

Figure 2 displays the molecular structure of **5a** and **10a** at the solid state. The macrocycle of both rotaxanes adopt the habitual chair-like conformation. However, the disposition of the amide CO and methyl groups is markedly different in both structures. Rotaxane **5a** (Fig. 2A) arranges two methyl groups in alternating *pseudoaxial* positions of the macrocycle and the other two in alternating *pseudoequatorial* positions. Interestingly, the amide CO groups close to the $CH(CH_3)_{eq}$ moieties show an *in* disposition probably in order to avoid repulsive interactions with the equatorial methyl groups. To our knowledge, this C_2 symmetric conformation of the threaded ring has only been described before for a non-interlocked macrocycle at the solid state.[25] By contrast, the four methyl groups of rotaxane **10a** are in *pseudoaxial* location and, consequently, their four CO amide groups adopt an *out* disposition. Indeed, this conformation is the most commonly disposition found at the solid state for all the reported *N,N,N',N'*-tetraalkylsubstituted fumaramide-based [2]rotaxanes.[19,26,27] We reasoned that the origin of the observed selectivity could relies on the requirement imposed by the conformational disposition of the α-methyl group determining the *in/out* orientation of the closely amide CO group during the revesible association of the open ring precursors and the fumaramide (see ESI).

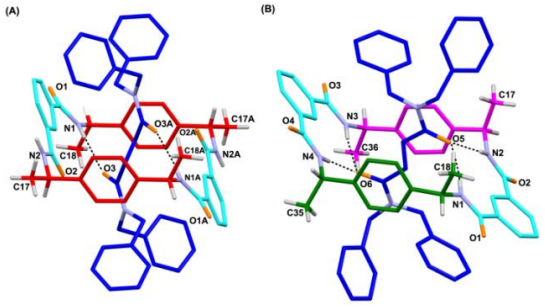


Figure 2 X–ray structures of: **5a** (two axial methyl groups, C18 and C18A, and two equatorial methyl groups, C17 and C17A) (A) and **10a** (four axial methyl groups) (B).

Interestingly, the absence of chirality in the solid state structure of **5a** contrasts with its ^{1}H NMR spectrum of an analytically pure sample in $CDCl_3$ solution showing the formation of a 5:1 mixture of two rotamers, $\mathbf{5a_M}$ and $\mathbf{5a_m}$. The spectrum of the major rotamer, $\mathbf{5a_M}$, reveals a high degree of dissymmetry. The CH_3 groups, magnetically equivalent in the achiral precursor amine *(R,S)*-**1** (Fig. 3A), appear in this interlocked species as inequivalent nuclei displaying four doublets at 1.42, 1.47, 1.48 and 1.52 ppm (Fig. 3C). Intriguingly, the chemical shifts of its also inequivalent CH groups are in two well-differentiated regions, three of these centered at 5.45 ppm corresponding to protons in *pseudoequatorial* position of the cyclic component and the remaining one at 4.89 ppm corresponding to a *pseudoaxial* proton.[28] This particular spatial arrangement of the methyl groups most probably forces the cyclic polyamide to organize three amide CO groups outwards of the cavity for avoiding unfavorable non-bonding interactions. The asymmetry of the ring is spatially transmitted to the thread through the mechanical bond. Thus, the CH groups, equivalents in the fumaramide **3a** (Fig. 3B), are inequivalent in $\mathbf{5a_M}$ appearing as a perturbed AB system (6.24 and 6.31 ppm; J_{AB} = 14.4 Hz) (Fig. 3C) whereas the *cisoid* and *transoid* CH_2 benzylic groups, which emerge as two singlets in **3a** (Fig. 3B), are now splitted into two sets of

perturbed AB systems (Fig. 3C). It also worth nothing the low chemical shift of the only NH_{out} in **5aM**, at 5.7 ppm, compared to that of a NH_{in} (e.g. 7.3 ppm in the unsubstituted derivative[23]). Interestingly, a preferential deteurium exchange[29] of this NH was observed in relative short times (see ESI) corroborating its *in* orientation. A structural analysis by 1D and 2D NMR experiments (see ESI) also confirm the proposed *(out,out,out,in)* conformation for **5a$_M$**. Such spatial arrangement of this rotamer in solution would relieve the repulsive interactions between the ring CO groups pointing to the inner of the macrocyclic void and the CO groups of the template and it would be enthapically stabilized by the formation of one additional hydrogen bond (Fig. 4). The set of low intensity signals also emerging after dissolving **5a** in deuterated chloroform corresponds to a symmetric species that is tentatively assigned to the minor rotamer *(out,in,out,in)*-**5a$_m$**. Interestingly, this rotameric mixture remains unaltered in a broad range of temperature (from +25 to 140 ºC) in deuterated solvents such as $C_2D_2Cl_4$ and DMSO-d_6. In stark contrast with the ^{1}H NMR spectra of **5a$_M$**, that of **10a** (Fig. 3D) shows only one set of signals for the four equivalent CH_3 and CH groups at 1.42 and 5.43 ppm respectively which is coherent with its structure observed in the solid state placing all methyl groups in *pseudoaxial* sites. Comparable spectra were recorded for the rotaxanes **5b** and **10b**.

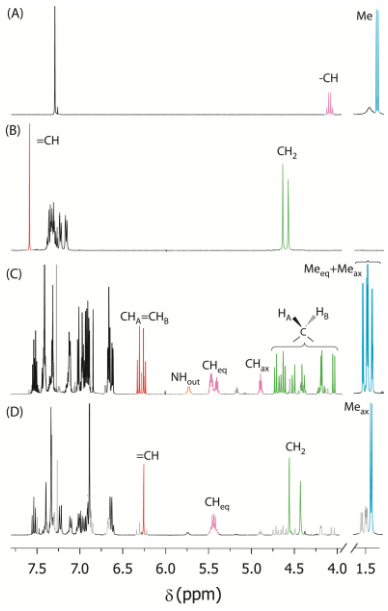


Figure 3 Partial ^{1}H NMR spectra (600 MHz, $CDCl_3$, 298 K) of (a) *α,α'*-dimethyl-*p*-xylylenediamines (*meso*-**1**/*rac*-**1** : 2/3), (b) tetrabenzylfumaramide **3a**, (c) rotaxane **5a$_M$** and its rotamer **5a$_m$** (**5a$_M$**/**5a$_m$** : 5/1), and (d) symmetric rotaxane **10a** (plus a minor amount of **5a**). Signals corresponding to the minor component are in grey color.

In the case of the kinetically stable pseudorotaxanes **5c** and **10c**, obtained from the tetrabutylfumaramide **3c,** we were able to resolve the mixture by adsorption chromatography. The isolated major rotaxane **5c** was prone to quickly disassemble into its non-interlocked components in $CDCl_3$ solution at room temperature. We reasoned that the *in-out* equilibration of the amide CO groups could facilitate the enlargement of the macrocyclic void[30] accelerating the thread release in this species. This behavior clearly contrasts with the larger relative stability of **10c** which enabled the monitoring of its disassembly by ^{1}H NMR spectroscopy (see Fig S11).[31] This study

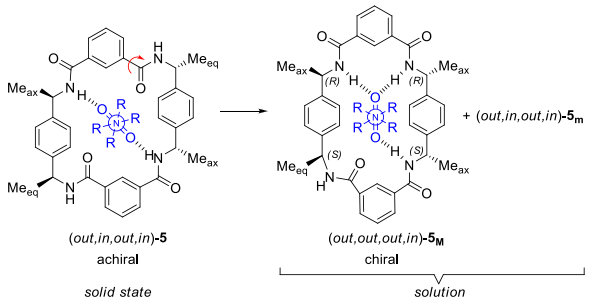
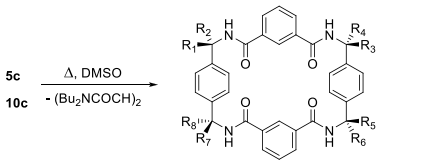


Figure 4 Proposed conformational change of the (*out,in,out,in*)-**5** into (*out,out,out,in*)-**5** promoted by the *in-out* isomerization of an amide CO carbonyl group. M and m subscripts refers to the major and minor components of the rotamers mixture.

allowed to estimate a half-life time of 2.3 hours at 100 ºC (373 K) in $C_2D_2Cl_4$ ($k_{dethreading}$ = 8.5 x 10^{-5} s^{-1}). Note that the lack of the four methyl groups in the parent rotaxane prevents the dethreading of the macrocycle under the same reaction conditions.[32] Heating of solutions of **5c** or **10c** in DMSO quantitatively yielded the macrocycles **11** and **12** (Scheme 2), respectively, which were easily isolated by precipitation after adding water to the reaction mixture.



11 (R_1=R_4=R_6=R_7= CH_3; R_2=R_3=R_5=R_8= H); 98%

12 (R_1=R_3=R_6=R_8= CH_3; R_2=R_4=R_5=R_7= H); 97%

Scheme 2 Preparation of the macrocycles **11** and **12** by thermal dethreading.

Although we were unable to grow suitable crystals of **11** for SCXRD we succeeded to obtain monocrystals of the tetramethyl macrocycle **12** from a DMSO solution thus allowing their structural determination at the solid state. A perspective view of **12** is shown in Figure 5. As in the reported structure of the unsubstituted macrocycle (UJUNOC) (Figure 5B),[26a] the amide CO groups are pointing inwards to the ring void stabilized by the intermolecular hydrogen bonding between the four amide NH groups and four DMSO molecules[33] (see Fig. S17). The four methyl groups of **12** occupy *pseudoequatorial* sites in a C_{2h} chair-like conformation of the tetralactam ring. Thus the solid structure of **12** confirms the $(CH_3)_{eq}$ / CO_{in} relationship found in the former rotaxanes **5**, as well the conformational conversion from the rotaxane **10c** [four pairs $(CH_3)_{ax}$ / CO_{out})] to the isolated ring **12** [four pairs $(CH_3)_{eq}$ / CO_{in})].

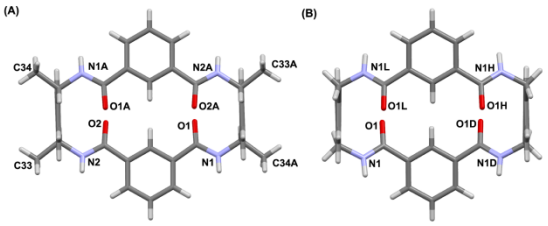


Figure 5 X-Ray structures of **12** (A) and the non-substituted analogue UJUNOC[26a] (B).

In summary, the assembly of [2]rotaxanes through a fumaramide-templated clipping reaction using α,α'-dimethyl-*p*-xylylenediamines selectively occurs to provide two out of seven

possible interlocked isomers thanks to a marked preference of the methyl groups for driving the relative *in* or *out* disposition of the close amide CO groups. In the solid state both rotaxanes present achiral structures but in solution the *out,in,out,in* rotaxane undergoes an *in-out* equilibration of one amide CO group mainly providing a chiral *out,out,out,in* rotamer. This process is also the cause of a noticeable difference in the mechanical stability of the tetramethyl rotaxanes having a tetrabutylfumaramide thread. We believe that this study would open the door to the design of stereochemically programmed rotaxanes and macrocycles through the amplification of the effects originated by the incorporation of stereogenic centers at the ring.

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