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Dethreading of Tetraalkylsuccinamide-Based [2]Rotaxanes for Preparing Benzylic Amide Macrocycles

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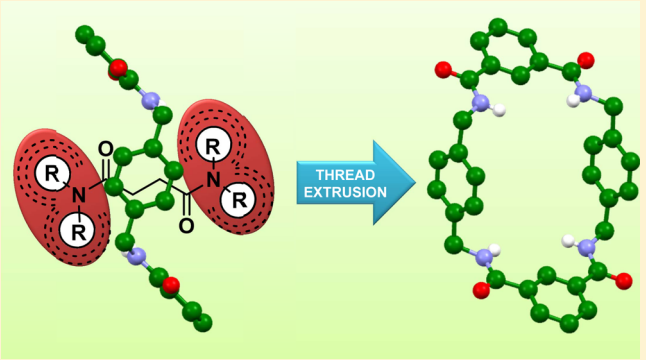
Supporting Information

ABSTRACT: The dethreading of a series of succinamide-based [2]rotaxanes bearing benzylic amide macrocycles is reported herein. These transformations proceeded quantitatively either under flash vacuum pyrolysis, conventional heating, or microwave irradiation. Studying the size complementarity of the stoppers at the ends of the thread and the cavity of the macrocycle allowed us to set up the best substituents for implementing the extrusion of the thread from the interlocked precursors. A variety of ^{1}H NMR kinetic experiments were carried out in order to evaluate the rate constants of the dethreading process, the half-life times of the rotaxanes, and the influence of temperature and solvents on these processes. The use of dibutylamino groups as stoppers yielded the rotaxane precursor in a reasonable yield and allowed the quantitative deslipping of the rotaxane. The overall process, including the rotaxane formation and its further dethreading, has been exploited for preparing benzylic amide macrocycles enhancing, in most cases, the results of the classical (2 + 2) condensation and other reported stepwise syntheses. The kinetics of the dethreading process is fairly sensitive to the electronic effects of the substituents on the isophthalamide unit or to the electronic nature of the pyridine rings through a conformational equilibrium expanding or contracting the cavity of the interlocked precursor.



1. INTRODUCTION

Functional interlocked systems programmed to perform controllable mechanical motions are ideally suited for the design of a broad range of molecular devices.[1−3] In this arena, the ability to achieve the spatial ordering of such switchable compounds at the solid state and the exportation of their properties to the macroscopic world are important for the nanofabrication of molecular devices.[4−6] Among the different types of interlocked molecules integrated at the condensed phase, [2]rotaxanes are clearly considered as one of the most widespread scaffolds for the construction of functional materials.[4] Besides the dumbbell-shaped component, these building blocks contain threaded macrocycles having diverse architectures such as calixarenes, cyclodextrins, crown ethers, cucurbiturils, cyclophanes, pillarenes, or amide-based rings.[6]

Noninterlocked benzylic amide macrocycles have been extensively employed as model compounds when investigating the macroscopic effects of the mechanical bond in materials elaborated with hydrogen-bonded interlocked compounds.[1−6] In much less extension, these tetraamido macrocycles have been used for sensing carbon dioxide[7] and, more recently, glucose.[8,9] Tetralactam rings of this kind are usually obtained in 19−25% yield by means of a (2 + 2) condensation of *p*-xylylenediamine and an aroyl dichloride.[10,11] In fact, the corresponding [2]catenane is also a main product of this approach in which the assembly of this interlocked octaamide is driven by hydrogen-bonded interactions.[10] Moreover, several oligomers are also obtained, making the isolation of the individual macrocycles, which are barely soluble in nonpolar solvents, even more difficult. In order to circumvent this matter, Leigh et al. were pioneers in describing the disassembly of hydrogen-bonded [2]rotaxanes through the transesterification of the stoppers of the thread for affording this type of rings.[7]

Although alternative methods[12] for the preparation of benzylic amide macrocycles have been described in the literature, these procedures usually require multiple synthetic steps,[8,9,13] the previous preparation of templates,[7,14,15] or the use of organo-clay derivatives.[16] Herein, we propose an amenable approach based on the dethreading reaction[17,18] of tetraalkylsuccinamide-based [2]rotaxanes for the synthesis of a broad range of substituted benzylic amide macrocycles in which

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a dumbbell-shaped template can be recovered and indefinitely reused. Different reaction conditions (conventional heating in solution, microwaves, and flash vacuum pyrolysis) were assayed in the deslipping step to efficiently afford the macrocyclic compounds. This study also includes an exploration of the size complementarity between the Leigh-type tetralactam rings and a series of succinamide-based threads having stoppers of diverse spatial demand. The kinetics of the disassembling process is also reported, giving a concise idea of the stability of the mechanical bond of these interlocked compounds at different temperatures in polar and nonpolar solvents such as dimethyl sulfoxide and tetrachloroethane. Overall, this research sets the experimental framework required for the synthesis of benzylic amide macrocycles, including one or two different isophthalamide units as well as for building up a practical use of the metastability of hydrogen-bonded [2]rotaxanes.

2. RESULTS AND DISCUSSION

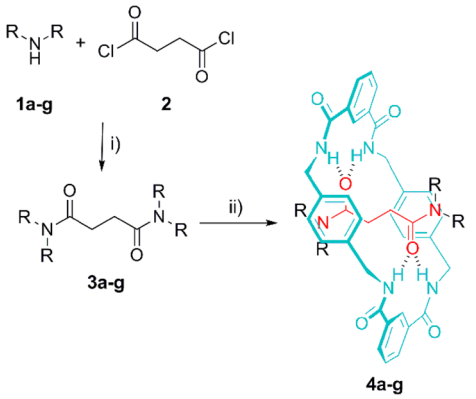
2.1. Synthesis of Tetraalkyl-Substituted Succinamide-Based [2]Rotaxanes. Early studies on the deslipping of Hunter–Vögtle rotaxanes having a tetraanilide-based macrocycle revealed that a proper size complementarity of the macrocyclic cavity and the stoppers is required for guaranteeing their structural integrity and avoiding the dethreading of the axis from the molecule.[19,20] In addition, Schalley et al. also deepened into similar interlocked systems, showing that small structural changes in the thread (including variations on its length, flexibility, or connectivity of their stoppers) have a significant impact on the deslippage process.[21−23] Although the macrocyclic hollow of the benzylic amide ring of the Leigh-type rotaxanes is notably lesser than the aforementioned, a study of the size complementarity has been never accomplished with these compounds.

In order to establish the influence of the steric size[24−26] of the stoppers of succinamide-based rotaxanes[27−29] on the stability of their mechanical bond,[30] we first prepared a series of surrogates, keeping the structure of the benzylic amide macrocycle constant and varying the alkyl substituents at the nitrogen atoms of the succinamide-based template. For this purpose, we assayed the five-component clipping reaction by using the tetraalkyl succinamides **3a−g**, easily prepared from the corresponding secondary amines **1a−g** and succinyl chloride (**2**), as templates and *p*-xylylenediamine and isophthaloyl chloride as precursors of the benzylic amide macrocycle (Table 1).

Our attempts for obtaining the threaded species with tetramethyl- or tetraethylsuccinamide templates were unsuccessful (entries 1 and 2), pointing out that the steric demand of the stoppers on the succinyl-based binding site must be larger than that of the diethylamino substituent in order to kinetically stabilize the mechanical bond between the interlocked components. In addition, although the formation of these (pseudo)rotaxanes[30−32] could be achieved, their thermodynamic equilibria between each one and the corresponding thread and ring must be largely shifted toward the formation of the unthreaded species, most probably due to the high insolubility of the benzylic amide macrocycle (<1 mg/L in chloroform)[7] under the employed reaction conditions.

On the other hand, the yields of the isolated rotaxanes containing linear alkyl substituents, such as propyl and butyl, **4c** and **4e** were 38% and 39%, respectively. These values are clearly acceptable considering that these rotaxanes are the resulting products of five-component clipping reactions.[29,33]

Table 1. Synthesis of the Tetraalkyl-Substituted Succinamide-Based [2]Rotaxanes 4[a]



entry	thread	yield [%][b]	R	rotaxane	yield [%][c]
1	**3a**	81	Me	**4a**	0[d]
2	**3b**	75	Et	**4b**	0[d]
3	**3c**	79	*n*-Pr	**4c**	38
4	**3d**	65	*i*-Pr	**4d**	17
5	**3e**	89	*n*-Bu	**4e**	39
6	**3f**	56	*i*-Bu	**4f**	19
7	**3g**	70	CH_2Cy[e]	**4g**	23[f]

[a]Reagent and conditions: (i) amine **1**, succinyl chloride (**2**), CH_2Cl_2, rt; (ii) succinamide **3**, isophthaloyl chloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, rt. [b]Yield of the thread preparation. [c]Yield of the rotaxane formation. [d]No traces were observed by ESI-MS. [e]Cy = cyclohexyl. [f]See refs 26 and 27.

However, the yield of this protocol drops off by half if the alkyl substituents on the nitrogen atoms of the succinamide are branched, as is the cases of **4d** (17%), **4f** (19%), and **4g** (23%), respectively, bearing isopropyl, isobutyl, and cyclohexylmethyl substituents. The structure determination of the rotaxanes **4c−g** was accomplished by means of their analytical and spectral data (see the Experimental Section).

It is known that the incorporation of a 2,6-pyridinedicarbonyl unit acid diamide into the ring reduces the void of the respective tetraanilide macrocycles due to the incidence of intracyclic hydrogen bonding, and consequently, it affects the deslipping of the corresponding interlocked precursors.[21] Aimed to study how this effect alters the thermal stability of our rotaxanes, we first tested the hydrogen bond directed assembly of rotaxanes **5a−d** using succinamides containing linear alkyl substituents as templates (Table 2). Although the yields of rotaxanes **5** are notably lower (<10%) than those obtained for rotaxanes **4**, the incorporation of two endotopic pyridine rings into the macrocycle tolerates the preparation of **5b** bearing two diethylamino groups as stoppers (entry 2, Table 2), which was proved unfeasible in the attempted preparation of rotaxane **4b** (entry 2, Table 1).

2.2. Reaction Conditions for the Dethreading of the Benzylic Amide [2]Rotaxanes 4c and 4e. First, we explored the thermally promoted dethreading of tetraalkylsuccinamides **3c** and **3e** from the benzyl amide macrocycles of rotaxanes **4c** and **4e**. For this purpose, thermogravimetric (TG) experiments with these rotaxanes were carried out (Figure 1). Pleasantly, the resulting thermograms of rotaxanes **4c** and **4e** show a weight loss near 300 °C corresponding to the dethreading of succinamides **3c** and **3e**. Differential scanning calorimetry (DSC) (see the Supporting Information) revealed that the

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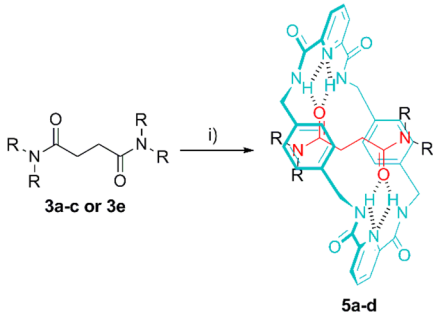
Table 2. Preparation of the Succinamide-Based [2]Rotaxanes 5[a]



entry	rotaxane	R	yield [%][b]
1	**5a**	Me	0[c]
2	**5b**	Et	9
3	**5c**	*n*-Pr	5
4	**5d**	*n*-Bu	3

[a]Reaction conditions: (i) succinamide **3a**–**c** or **3e**, 2,6-pyridinedicarboxylic acid chloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, rt. [b]Yield of isolated product based on **3**. [c]No traces of the [2]rotaxane were observed by ESI-MS.

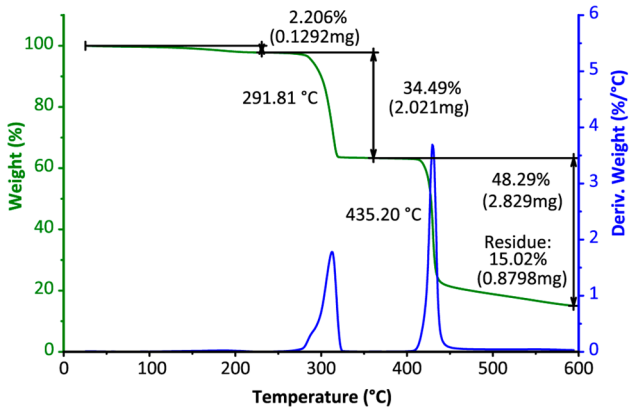
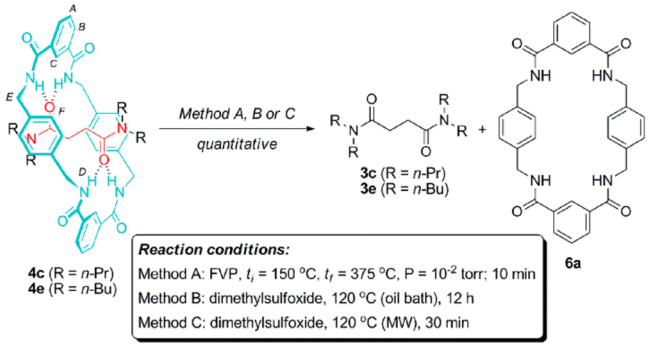


Figure 1. Thermogravimetric analysis of rotaxane **4c** (5 °C/min; N_2 stream).

deslippage processes occur after the melting of the rotaxane. In both cases, a second weight loss at 435 °C, ascribed to the sublimation of the macrocycle, was also observed.

On the basis of these TG–DSC analyses, we assayed the heating of a neat sample of rotaxane **4c** at 300 °C, but we recovered the starting material without any disassembly evidence. Then, we explored the same reaction in a flash vacuum pyrolysis (FVP)[34,35] apparatus by placing a solid sample of rotaxane **4c** in a preheated furnace at 150 °C and heating up to 375 °C during 10 min, keeping a moderate vacuum of 0.01 Torr. The corresponding succinamide **3c** was quantitatively recovered from the cooled U-tube, and the resulting dethreaded macrocycle remained in the initial vial, thus indicating that the complete deslippage had taken place (Scheme 1, Method A) without any evidence of decomposition.[36] An identical efficiency was found in the dethreading of rotaxane **4e**. With the aim of obtaining thermodynamic and kinetic parameters of this deslippage process, we considered the viability of carrying out this reaction in solution. A solution of the rotaxane **4c** or **4e** heated in dimethyl sulfoxide at 120 °C in an oil bath for 12 h (Scheme 1, Method B) quantitatively yielded the corresponding axis **3c** or **3e** and the macrocycle **6a**,

Scheme 1. Synthetic Approaches for the Deslipping of the Benzylic Amide Rotaxanes 4c and 4e



which were easily separated by precipitation of the latter by adding water into the final reaction mixture. Although other solvents such as methanol or tetrachloroethane were assayed for the deslipping of **4e**, the integrity of the mechanical bond persisted unaltered even after a prolonged heating treatment (3 days). Remarkably, in the cases of rotaxanes **4c** and **4e**, the use of microwave irradiation shortened the deslipping time to 30 min when dimethyl sulfoxide is used as solvent (Scheme 1, Method C).

The recovery of the thread by any of the above dethreading methods is quite straightforward. However, whereas Method A only requires the addition of dichloromethane to the U-tube of the FVP apparatus and solvent evaporation to recover quantitatively the resulting thread, Methods B and C need a further liquid–liquid extraction with chloroform and several washings with water and brine for completely removing the DMSO. In these cases, after a drying treatment with magnesium sulfate as desiccant, filtration, and solvent evaporation, more than 95% of the thread was recovered.

The overall yield for the preparation of the macrocycle **6a**, including the clipping reaction (39%) and the dethreading step (100%), compares favorably with other previously described methods,[7,11] proving the suitability of the present protocol. Note that a further amount of the cyclic compound **6a** (18%) is also obtained during the rotaxane formation of **4e**.

2.3. Thermodynamic and Kinetic Parameters of the Dethreading Processes. The deslipping reactions of hydrogen-bonded rotaxanes[19−23] can be easily monitored by ^1H NMR spectroscopy for affording the kinetic parameters of the process. Thus, following the variation of the relative intensity of the signals of the rotaxane and the tetralactam ring, we were able to estimate the rate constant k and the half-life time $t_{1/2}$ of this first-order reaction. This study was first carried out with the rotaxane **4e** by monitoring its ^1H NMR spectra at different times while the temperature was kept at 373 K (Figure 2). The signals of all the aromatic protons and the NH group of the macrocycle **6a** can be clearly distinguished from those of its interlocked precursor **4e** [$\Delta\delta(H_A)$ = +0.11 ppm; $\Delta\delta(H_B)$ = +0.21 ppm; $\Delta\delta(H_C)$ = +0.64 ppm; $\Delta\delta(H_F)$ = −0.13 ppm; $\Delta\delta(H_D)$ = −0.68 ppm]. The presence of the ring has a clear influence on the chemical shifts of the nuclei of the succinamide subcomponent due to the anisotropy originated by the aromatic rings of the tetralactam macrocycle, and so, the lack of the latter restores the chemical shift of the pristine **3e** [$\Delta\delta(H_a)$ = −1.4 ppm].

The decrease of the relative ratio of rotaxane **4e** as a function of time allows us to calculate a rate constant of (7.56 ± 0.19) ×

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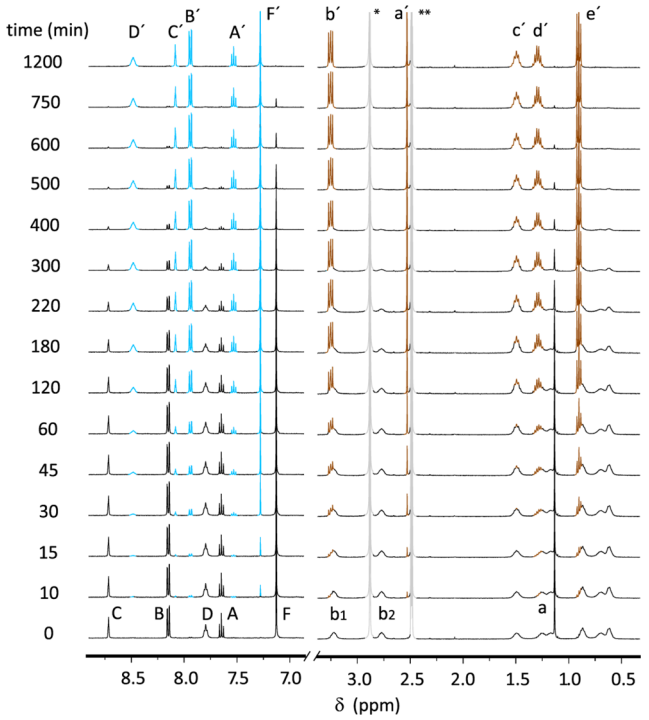

Figure 2. Kinetic experiment with rotaxane **4e** in DMSO-d_6 at 373 K. Stack plot of partial ^{1}H NMR spectra of **4e** over time. Capital letters A–F correspond to the hydrogen atoms of the macrocycle (see Scheme 1 for numbering) and lowercase letters a–e correspond to the hydrogen atoms of the thread: $[C(H_a)_2CONC(H_b)_2C(H_c)_2C(H_d)_2C(H_e)_3]_2$. Prime symbols are used to ascribe the signals of the noninterlocked compounds **3e** and **6a**. Signals marked with an asterisk are residual solvent peaks.

10^{-5} s^{-1} and a half-life of 2.6 h at 373 K by an exponential fitting of the deslipping percentage against time (see the Supporting Information). The progress of this reaction also allowed us to know the required time to reach the maximum conversion (approximately 8 h in the case of the dethreading of **4e**). To obtain further information about this transformation, we performed similar kinetic ^{1}H NMR experiments at different temperatures (358, 368, 373, and 398 K). Thus, the corresponding rate constants at each temperature were determined by plotting $\ln(c/c_0)$ against time (Figure 3). The

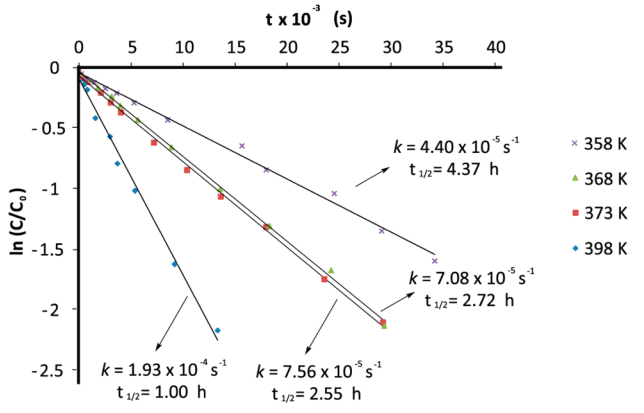

Figure 3. Deslipping of the rotaxane **4e** in DMSO-d_6 at different temperatures. Plot of $\ln(c/c_0)$ versus time for the determination of the half-life times and the rate constants: T (K), $k \times 10^5$ (s^{-1}) = 358, 4.40 ± 0.51; 368, 7.08 ± 0.19; 373, 7.56 ± 0.19; 398, 19.30 ± 1.40.

use of these values in an Eyring plot of $\ln(k/T)$ vs $1/T$ let us calculate the activation parameters of the process, $\Delta H^{\ddagger}$ = 40 kJ·mol^{-1} and $\Delta S^{\ddagger}$ = −218 J·K^{-1}·mol^{-1} (see Figure 4). Like in

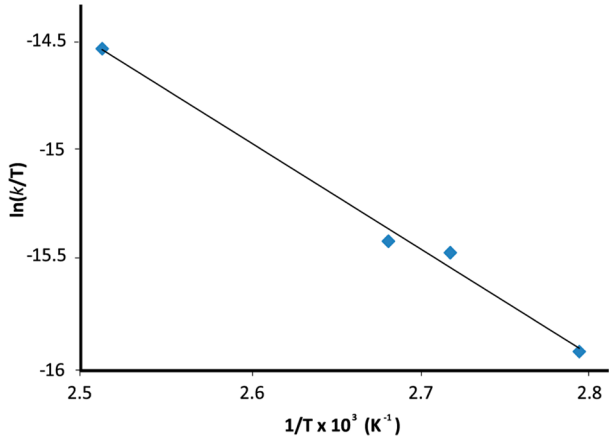

Figure 4. Eyring plot of $\ln(k/T)$ vs $1/T$ for the evaluation of the activation enthalpy, $\Delta H^{\ddagger}$, and the activation entropy, $\Delta S^{\ddagger}$, for the deslipping of the rotaxane **4e**. A good correlation coefficient was obtained for this linear regression (R^2 = 0.992).

other related deslipping processes of amide-based rotaxanes,[21−23] a negative value for the activation entropy of the deslipping of **4e** was expected. The high flexibility of this rotaxane, containing four butyl substituents and a nonrigid template, is vastly reduced, and, therefore, also their freedom degrees, in the transition state of the dethreading process.

It should be noted that the featuring parameters of the dethreading process dramatically depend on the hydrogen bond (HB) acceptor ability of the solvent. In fact, the process does not seem to proceed in very weak HB acceptor solvents, such as tetrachloroethane, but in dimethyl sulfoxide, an excellent HB acceptor, the damage of the intercomponent HB interactions facilitates the egression of the thread through a unimolecular, first-order decomposition.

Previous studies on the dethreading of tetraanilide-based rotaxanes[19−23,26] revealed a noticeable sensitivity of these processes even toward minor modifications in the structure of the interlocked compounds. Thus, variations on the progress of the thermal treatment of the benzylic amide rotaxanes **4c–g** having different alkyl substituents at the N atom of the succinamide should be expected. Aiming to evaluate the magnitude of these variations for best choosing the ideal template in the tetralactam macrocycles synthesis, we performed ^{1}H NMR kinetic experiments with rotaxanes **4c–g** (see the Supporting Information) in order to determine the corresponding rate constants and half-life times at 398 K (Figure 5). In those conditions, the deslipping of **4c** having a dipropylamino group as stopper is so fast that we were unable to obtain suitable data (entry 1, Table 3). As we expected, the dethreading of rotaxane **4d**, with diisopropyl groups as stoppers, occurs notably slower than that of rotaxane **4c**, $t_{1/2}$ (~30 h) (entry 2, Table 3). This value is larger than that of **4e** $t_{1/2}$ (1 h) bearing a less sterically demanding dibutylamino group (entry 3, Table 3). By further increasing the size of the stopper, as in the case of rotaxane **4f**, which possesses diisobutyl groups, the reaction proceeds extremely slow and $t_{1/2}$ rises up to more than 2 weeks (entry 4, Table 3). When di(cyclohexylmethyl)amino groups are used as stoppers, the extrusion of the

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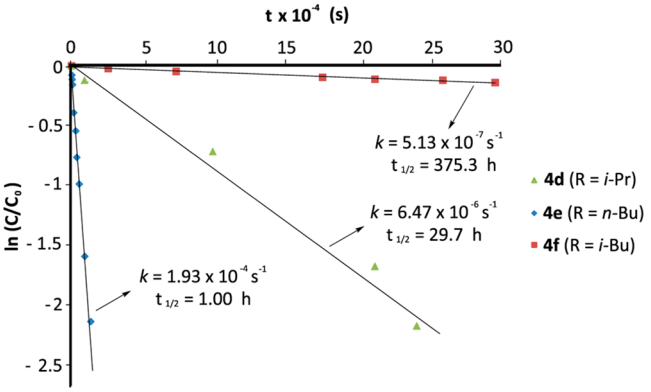

Figure 5. Deslipping of the rotaxanes **4d–f** having different substituents on the succinamide thread in DMSO-d_6 at 398 K. Plot of $\ln(c/c_0)$ versus time for the determination of the rate constants and half-life times.

corresponding succinamide from the rotaxane **4g** did not come about at the selected reaction conditions. Taking into account our purpose of synthesizing tetralactam rings by the deslipping of succinamide-based rotaxanes (see next section), the results summarized in Table 3 seem to point out the convenience of using *N,N,N′,N′*-tetrabutylsuccinamide (**3e**) as a suitable template by considering the intermediate thermal stability of the resulting rotaxane and the yield which is obtained.

In order to get further information about the thread ejection from **4c**, we modified the reaction conditions by using deuterated tetrachloroethane as a nondisrupting hydrogen bond solvent at 373 K for decreasing the deslipping rate and enabling the calculation of the kinetic parameters of this particular process. These modifications allowed us to follow the progress of the dethreading by ^{1}H NMR, featured by a rate constant of $(4.6 \pm 0.7) \times 10^{-5}$ s^{-1} and a half-life time of 4.2 h ($\Delta G^{\ddagger}$ = 123.1 kJ mol^{-1}). We also monitored the reaction at 373 K using a mixture of dimethyl sulfoxide: tetrachloroethane 1:1 (v/v) as solvent to obtain a rate constant of $(6.3 \pm 0.6) \times 10^{-3}$ s^{-1} and a half-life time of 2 min ($\Delta G^{\ddagger}$ = 107.8 kJ mol^{-1}) (see the Supporting Information). The increase of the rate constant in 2 orders of magnitude and the noticeable decrease of the $t_{1/2}$ value highlight the remarkable effect of the hydrogen bond acceptor strength of the solvent on this kind of process.

2.4. Synthesis of Benzylic Amide Macrocycles by Dethreading of Succinamide-Based Rotaxanes. We extended the scope of the synthesis of benzylic amide macrocycles by examining the deslipping of succinamide-based rotaxanes containing different substituents on the macrocycle, such as alkyl, hydroxyl, alkoxy, alkoxycarbonyl, or nitro groups, or incorporating pyridine rings. The syntheses of the interlocked compounds **7a–f** (Table 4) employed for this study were carried out by using the known clipping methodology with *N,N,N′,N′*-tetrabutylsuccinamide (**3e**) as the HB acceptor template,[37] *p*-xylylenediamine, and the corresponding acid dichloride (see the Experimental Section). The deslipping of the rotaxanes **7a–f** was carried out in dimethyl sulfoxide at 373 K to afford the succinamide **3e** and the respective macrocycles **8a–f**. Considering that subtle structural variations in the starting interlocked compound can alter the kinetics of the deslipping process, we extended the reaction time until 24 h for ensuring a 100% conversion (Method B, Table 4). This conversion level is also reached by using microwave irradiation for 1 h (Method C, Table 4). Table 4 includes the yields of the isolated compounds by employing the same direct workup used in the preparation of **6a**. It is worth noting the deslipping of **7b** having a nonsymmetrical ring with only one TBDMSO group, which is converted into a hydroxyl function during the thermal treatment.[38] This deprotection is accelerated by adding water to the reaction medium for affording the appealing macrocycle **8b** (entry 2, Table 4) ready to be further connected to other compounds or attached to materials through its available OH group. In stark contrast with the dethreading of the rotaxanes **7a–f** (entries 1–6, Table 4), which proceeds in a quantitative manner by using any of the proposed protocols, we only could detect traces of **8g** from the deslipping of **5d**, irrespective of using the heating Method B or C (entry 7, Table 4).

Although the conversion of the dethreading of rotaxanes **7a–f** was complete, slight fluctuations in the yield of the macrocycles were observed because of their different solubilities in dimethyl sulfoxide:water mixtures.

The templating effect of the thread **3a** in the preparation of macrocycle **8a** was evaluated. In the presence of the template **3a** using 2 equiv of *p*-xylylenediamine and 2 equiv of 5-*tert*-butylisophthaloyl dichloride, **8a** was obtained, after several chromatography purifications, in a 14% yield together with a 22% of the rotaxane **7a**. If the reaction is performed without **3a**, the ring **8a** can also be hardly isolated in a 17% yield. These values prove the important role of the template,[7] allowing the isolation in a 36% yield after the complete deslipping step of the rotaxane, almost more than 20% of the amount obtained by direct condensation.[11] Overall, except for the pyridine-containing tetralactam ring **8g** (see Table 2), the approach herein described for the preparation of benzylic amide macrocycles compares favorably, in terms of yield and amenability, with other reported methodologies.

In order to explore the kinetics of the dethreading of some selected rotaxanes **7**, we monitored over time the heating of their solutions in deuterated dimethyl sulfoxide at 373 K by ^{1}H NMR spectroscopy. The data registered at these conditions were compiled to plot the $\ln(c/c_0)$ versus time (Figure 6). For comparison, the graph corresponding to the deslipping of the rotaxane **4e** has been also included in this representation. The

Table 3. Rate Constants and Half-Life Times for the Deslipping of the Rotaxanes 4c–g in DMSO-d_6 at 398 K

entry	rotaxane	R	$t_{1/2}$ (h)	$k \times 10^6$ (s^{-1})	$\Delta G^{\ddagger}$ (kJ mol^{-1})[a]
1	**4c**	*n*-Pr	[b]		
2	**4d**	*i*-Pr	29.7	6.48 ± 1.01	138.0
3	**4e**	*n*-Bu	1.0	193.23 ± 13.98	126.7
4	**4f**	*i*-Bu	375.3	0.50 ± 0.03	146.4
5	**4g**	CH_2Cy	[c]		

[a]Gibbs free energies of activation were calculated at 398 K. [b]Deslipping of **4c** occurs too rapidly to be monitored by ^{1}H NMR. [c]No deslipping of **4g** was observed under these conditions. Microwave irradiation of this rotaxane did not promote the extrusion of the thread.

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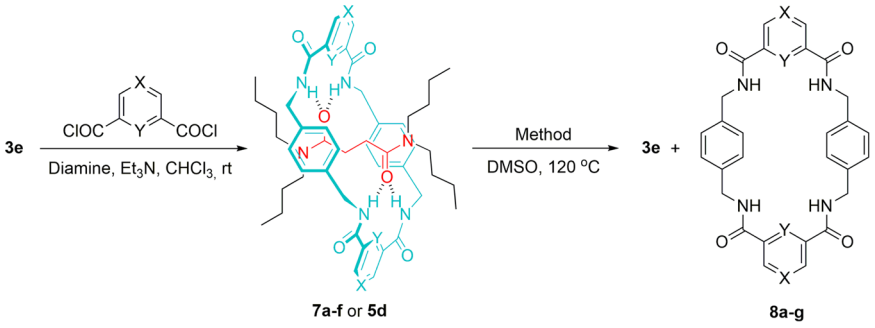
Table 4. Synthesis of Benzylic Amide Macrocycles by Deslipping of Succinamide-Based Rotaxanes[a,b,c]



entry	rotaxane[d]	yield [%][e]	X	Y	macrocycle	yield [%][f]
1	**7a**	25	C-C$(CH_3)_3$	CH	**8a**	77[a]
2	**7b**	37	CH and C-OH[g]	CH	**8b**	84[a]
3	**7c**	38	C-O$(CH_2)_4$CH=CH_2	CH	**8c**	87[a]
4	**7d**	17	C-$COOCH_3$	CH	**8d**	99[b]
5	**7e**	32	C-NO_2	CH	**8e**	99[a]
6	**7f**	27	N	CH	**8f**	95[b]
7	**5d**	3	CH	N	**8g**	traces[a,b]

[a]Method B: conventional heating in oil bath, 24 h. [b]Method C: microwave irradiation, 1 h. [c]A complete conversion was obtained in all cases except for the deslipping of **5d**. [d]For the syntheses of the rotaxanes, *p*-xylylenediamine was used as the diamine component, except for the preparation of **7b** (entry 2), in which N^1,N^3-bis(4-(aminomethyl)benzyl)isophthalamide was employed. [e]Yield of the rotaxane formation. [f]Yield of the dethreading step. [g]The rotaxane precursor **7b** contains a TBDMSO substituent which is converted into a hydroxy group during the thermal treatment. This deprotection was accelerated by adding water to the reaction mixture.

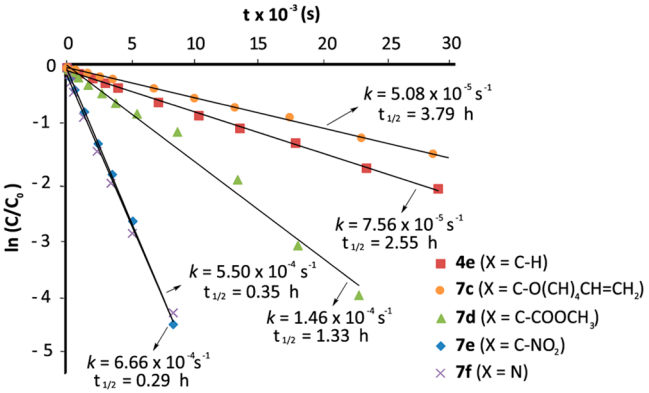


Figure 6. Deslipping of the rotaxanes **4e** and **7c–f** having different substituents at the benzylic amide macrocycle in DMSO-d_6 at 373 K. Plot of $\ln(c/c_0)$ versus time for the determination of the rate constants and half-life times.

thermally activated expulsion of **3e** from **4e** has a Gibbs free energy of activation of 121.5 kJ mol^{-1} ($k = 7.6 \times 10^{-5}$ s^{-1}; $t_{1/2}$ = 2.6 h). This energy value decreases, and also the half-life time (entries 2–4, Table 5), if the benzylic amide macrocycle of the rotaxane precursor has two ester or nitro functional groups as in **8d** or **8e**, respectively, or incorporates two pyridine rings as in **8f**. However, if the ring of the rotaxane contains alkoxy substituents, as in **8c** (entry 1, Table 5), the deslipping takes place more slowly than that of the rotaxane **4e** lacking of substituents.

In nondisrupting hydrogen bond solvents, the incorporation of electron-withdrawing groups in the isophthalamide-based macrocycles enhances the donating ability of their amide groups and, therefore, bind the carbonyl groups of the threaded component more strongly.[29,39] However, the dethreading of the rotaxanes **7c–f** in DMSO seems to follow an inverse trend. In such a competitive solvent, the intercomponent interactions should be less important than the intermolecular ones with the DMSO molecules. In this scenario, these latter interactions with the cyclic component would promote conformational changes of the tetralactam ring such as the outward turning of the amide groups.[40−42] These changes, modulated by the electronic effects of the substituents at the isophthalamide units or the electronic nature of the pyridine units, modify the cross dimensions of the size of the cavity,[43] leading to a faster deslipping of the rotaxanes with electron-poor macrocycles and a slower deslipping of those with electron-rich macrocycles in comparison with that of the rotaxane **4e** (Figure 6, Table 5). Molecular mechanics calculations (see the Supporting Information) pointed out that electron-withdrawing groups at the 5-position of the isophthalamide moiety stabilize the conformation (B) represented in Figure 7, in which one of the carbonyl groups of the macrocycle adopts an *inner* disposition. This conformation of the macrocycle, further stabilized by the

Table 5. Rate Constants and Half-Life Times for the Deslipping of the Rotaxanes 7c–f in DMSO-d_6 at 373 K

entry	rotaxane	X	$t_{1/2}$ (h)	$k \times 10^6$ (s^{-1})	$\Delta G^{\ddagger}$ (kJ mol^{-1})[a]
1	**7c**	C-O$(CH_2)_4$CH=CH_2	3.8	50.86 ± 1.60	122.7
2	**7d**	C-$COOCH_3$	1.3	146.37 ± 9.48	119.4
3	**7e**	C-NO_2	0.4	549.73 ± 19.81	115.3
4	**7f**	N	0.3	665.95 ± 48.04	114.7

[a]Gibbs free energies of activation were calculated at 373 K.

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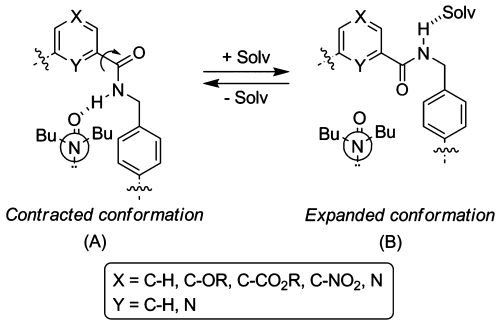

Figure 7. Conformational equilibrium of the partially represented rotaxanes via rotation of the amide group of the macrocycle promoted by the competitive binding with an excellent HB acceptor solvent (Solv).

competitive formation of hydrogen bonds of this NH amide group with DMSO (Solv in Figure 7), expands its cavity, when compared with conformation (A), thus facilitating its dethreading. Remarkably, electron donor substituents such as an alkoxy group stabilize the conformation (A) of Figure 7 in which the carbonyl groups of the macrocycle adopt an *outer* disposition, favoring the intercomponent interactions and keeping a contracted shape of the ring that makes its dethreading difficult.

Finally, we were still intrigued by the synthesis of macrocycle **8g**, unviable by the deslipping of rotaxane **5d** (entry 7, Table 4) having a dibutylamino group at the ends of the stoppers. Hence, we explored the thermal treatment of the dipyridine rotaxanes **5b,c** with the less sterically demanding stoppers diethylamino and dipropylamino groups, respectively. Likewise to the case of **5d**, the heating of a DMSO solution of **5c** at 373 K was still unable to promote the desired dethreading. Note that macrocycles with endotopic pyridine rings stabilize the tight conformation (A) shown in Figure 7 by the formation of a strong network of intracyclic hydrogen bonds capable of surviving even in hot dimethyl sulfoxide.[11] This fact would explain the strong resistance of these rotaxanes to the dethreading process. Satisfyingly, the macrocycle **8g** was quantitatively obtained by the thermal deslipping of the rotaxane **5b** in DMSO at 373 K for 1.5 h or in tetrachloroethane at 353 K for 3 h. Interestingly, we also found that this particular process occurred at room temperature using a mixture of dimethyl sulfoxide:tetrachloroethane 1:1 (v/v) after 14 h.

3. CONCLUSIONS

In summary, we have described the synthesis of a complete series of tetraalkylsuccinamide-based [2]rotaxanes bearing a benzylic amide macrocycle. Three different protocols have been established for the dethreading of these interlocked species in a quantitative fashion by either flash vacuum pyrolysis, conventional heating, or microwave irradiation. Varying the steric demand of the dialkylamino stoppers on the succinamide template of the interlocked species allowed the examination of the size complementarity with the benzylic amide macrocycle void to establish the most appropriate substituent for implementing a practical preparation of tetralactam macrocycles by extrusion of the thread of the rotaxanes. The kinetic and thermodynamic parameters of this process were thoroughly evaluated, including temperature and solvent effects. Decreasing the size of the stoppers reduces the Gibbs free energy of activation of the dethreading, which is also favored in good hydrogen bond acceptor solvents. These studies determined that the incorporation of dibutylamino groups as stoppers in the succinamide template allowed the preparation of the interlocked precursor in a reasonable yield and the quantitative deslipping by any of the protocols established in this work. Moreover, a deep exploration of the effect of the substituents at the ring of the interlocked precursor on its deslipping in solution revealed that electron-withdrawing groups speed up the egression of the thread. The formation of intracyclic hydrogen bonds due to the incorporation of two endotopic pyridine rings into the macrocycle requires a noticeable decreasing of the steric demand of the lids on the succinamide to efficiently undergo deslippage to afford the cyclic target.

4. EXPERIMENTAL SECTION

4.1. General Methods. Unless stated otherwise, all reagents were purchased from commercial suppliers and used without further purification. HPLC grade solvents were dried in a solvent purification system by passing it through an activated alumina column before use. Column chromatography was carried out using silica gel (60 Å, 70−200 μm) as stationary phase, and TLC was performed on precoated silica gel on aluminum cards (0.25 mm thick, with fluorescent indicator 254 nm) and observed under UV light. All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. In the case of the main part of the rotaxanes, decomposition was observed above 275 °C due to the deslipping pathway. ^{1}H and ^{13}C NMR spectra were recorded at 298 K on 200, 300, and 400 MHz spectrometers. ^{1}H NMR chemical shifts are reported relative to Me_4Si and were referenced via residual proton resonances of the corresponding deuterated solvent, whereas ^{13}C NMR spectra are reported relative to Me_4Si using the carbon signals of the deuterated solvent. Abbreviations of coupling patterns are as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. Coupling constants (J) are expressed in Hz. High-resolution mass spectra (HRMS) were obtained using a time-of-flight (TOF) instrument equipped with electrospray ionization (ESI). The experiments using microwave irradiations were performed in a Discover CEM MW with simultaneous cooling. The power of the equipment was established at 200 W. A microwave vessel (10 mL) equipped with a standard cap (vessel commercially furnished by Discover CEM) and a level of internal pressure maximum of 250 psi was used.

4.2. Materials. Threads **3a**,[44] **3b**,[45] and **3g**[28] and rotaxane **4g**[29] were prepared as previously reported.

4.3. General Procedure for the Synthesis of the Succinamide-Based Threads 3b−g. To a solution of the corresponding amine **1b−g** (16 mmol) in CH_2Cl_2 (50 mL) was added succinyl dichloride **2** (4 mmol) in CH_2Cl_2 (10 mL) droppwise at 0 °C. The reaction mixture was stirred for 20 h at room temperature under a N_2 atmosphere. After this time, the solution was washed with 1 M NaOH (2 × 30 mL), 1 M HCl (2 × 30 mL), and brine (2 × 30 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The reaction residue was subjected to column chromatography on silica gel using a $CHCl_3$/MeOH (99/1) mixture as eluent to give the corresponding thread.

Thread ***3a***[44] was prepared from a solution of dimethylamine **1a** (40% in water, 2.58 mL, 16 mmol) and succinyl chloride **2** (616 mg, 4 mmol). Colorless oil (466 mg, 81%). This compound was synthesized as described in ref 44 and showed identical spectroscopic data as those reported therein.

Thread ***3b***[45] was prepared from diethylamine **1b** (1.17 g, 16 mmol) and succinyl chloride **2** (616 mg, 4 mmol). Colorless oil (684 mg, 75%). This compound was synthesized as described in ref 45 and showed identical spectroscopic data as those reported therein.

Thread ***3c*** was prepared from dipropylamine **1c** (1.62 g, 16 mmol) and succinyl chloride (**2**, 616 mg, 4 mmol). Yellow oil (900 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20−3.26 (m, 8H), 2.64 (s, 4H), 1.65−1.45 (m, 8H), 0.87 (t, J = 7.4 Hz, 6H), 0.82 (t, J = 7.4 Hz, 6H);

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$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 49.7 (CH_2), 47.9 (CH_2), 28.5 (CH_2), 22.2 (CH_2), 21.05 (CH_2), 11.4 (CH_3), 11.3 (CH_3); HRMS (ESI+) m/z for $C_{16}H_{33}N_2O_2$ $[M + H]^+$ 285.2537, found 285.2542.

Thread **3d** was prepared from di(isopropyl)amine **1d** (1.62 g, 16 mmol) and succinyl chloride **2** (616 mg, 4 mmol). Colorless oil (741 mg, 65%); ^1H NMR (200 MHz, $CDCl_3$) δ 4.20−4.00 (m, 2H), 3.51−3.34 (m, 2H), 2.64 (s, 4H), 1.34 (d, J = 6.8 Hz, 12H), 1.14 (d, J = 6.7 Hz, 12H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 171.1 (C), 48.3 (CH), 45.7 (CH), 30.3 (CH_2), 20.84 (CH_3), 20.77 (CH_3); HRMS (ESI+) m/z for $C_{16}H_{33}N_2O_2$ $[M + H]^+$ 285.2537, found 285.2533.

Thread **3e** was prepared from dibutylamine **1e** (2.06 g, 16 mmol) and succinyl chloride **2** (616 mg, 4 mmol). Yellow oil (1.21 g, 89%); ^1H NMR (400 MHz, $CDCl_3$) δ 3.28−3.20 (m, 8H), 2.63 (s, 4H), 1.57−1.40 (m, 8H), 1.33−1.19 (m, 8H), 0.90 (t, J = 7.3 Hz, 6H), 0.86 (t, J = 7.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.7 (C), 47.8 (CH_2), 46.02 (CH_2), 31.1 (CH_2), 30.0 (CH_2), 28.4 (CH_2), 20.3 (CH_2), 20.2 (CH_2), 13.9 (CH_3), 13.88 (CH_3); HRMS (ESI+) m/z calcd for $C_{20}H_{41}N_2O_2$ $[M + H]^+$ 341.3163, found 341.3172.

Thread **3f** was prepared from di(isobutyl)amine **1f** (2.06 g, 16 mmol) and succinyl chloride **2** (616 mg, 4 mmol). Yellow oil (763 mg, 56%); ^1H NMR (400 MHz, $CDCl_3$) δ 3.20−3.13 (m, 8H), 2.70 (s, 4H), 2.03−1.90 (m, 4H), 0.91 (d, J = 6.7 Hz, 12H), 0.84 (d, J = 6.7 Hz, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.5 (C), 55.4 (CH_2), 53.4 (CH_2), 28.9 (CH_2), 27.8 (CH), 26.5 (CH), 20.1 (CH_3), 20.0 (CH_3); HRMS (ESI+) m/z calcd for $C_{20}H_{41}N_2O_2$ $[M + H]^+$ 341.3163, found 341.3171.

Thread **3g**[28] was prepared from bis(cyclohexylmethyl)amine **1g** (3.34 g, 16 mmol) and succinyl chloride **2** (616 mg, 4 mmol). White solid (1.40 g, 70%). The title compound showed identical spectroscopic data as those reported in ref 28 (see the Supporting Information for a ^1H NMR spectrum).

4.4. General Procedure for the Synthesis of the Succinamide-Based [2]Rotaxanes 4, 5, and 7. The thread (1 equiv) and Et_3N (24 equiv) in anhydrous $CHCl_3$ (300 mL) were stirred vigorously while 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 5 h using motor-driven syringe pumps. After a further 4 h, the resulting suspension was filtered through a Celite pad and washed with water (2 × 50 mL), a solution of 1 M HCl (2 × 50 mL), a saturated solution of $NaHCO_3$ (2 × 50 mL), and brine (2 × 50 mL). The organic phase was then dried over $MgSO_4$, and the solvent was removed under reduced pressure. The resulting solid was subjected to column chromatography (silica gel) to yield unconsumed thread, [2]rotaxane, and [2]catenane.

Rotaxane **4c** was obtained using the described method from thread **3c** (500 mg, 1.75 mmol). The resulting residue was subjected to column chromatography (silica gel) using a $CHCl_3$/MeOH (98/2) mixture. The solvent was removed under reduced pressure to give the title product as a white solid (544 mg, 38%); mp > 250 °C (decomp.); ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 2H), 8.35 (d, J = 7.7 Hz, 4H), 7.71 (t, J = 5.4 Hz, 4H), 7.65 (t, J = 7.7 Hz, 2H), 7.09 (s, 8H), 5.34 (br s, 4H), 3.77 (br s, 4H), 3.25−3.14 (m, 4H), 2.72−2.60 (m, 4H), 1.60−1.50 (m, 4H), 1.26−1.16 (m, 8H), 1.04 (s, 4H), 0.90 (t, J = 7.4 Hz, 6H), 0.21 (t, J = 7.3 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.1 (C), 165.5 (C), 139.0 (C), 133.6 (CH), 132.5 (C), 129.7 (CH), 129.1 (CH), 122.5 (CH), 50.3 (CH_2), 48.9 (CH_2), 43.4 (CH_2), 28.3 (CH_2), 21.9 (CH_2), 21.5 (CH_2), 11.7 (CH_3), 10.6 (CH_3); HRMS (ESI+) m/z calcd for $C_{48}H_{61}N_6O_6$ $[M + H]^+$ 817.4647, found 817.4649.

Rotaxane **4d** was obtained using the described method from thread **3d** (500 mg, 1.75 mmol). The resulting residue was subjected to column chromatography (silica gel) using a $CHCl_3$/MeOH (98/2) mixture. The solvent was removed under reduced pressure to give the title product as a white solid (243 mg, 17%); mp > 250 °C (decomp.); ^1H NMR (400 MHz, $C_2D_2Cl_4$) δ 8.75 (s, 2H), 8.36 (d, J = 7.9 Hz, 4H), 7.73−7.62 (m, 6H), 7.10 (s, 8H), 5.35 (br s, 4H), 3.70 (br s, 4H), 3.32−3.24 (m, 2H), 3.00−2.90 (m, 2H), 1.38 (d, J = 6.7 Hz, 12H), 1.24 (s, 4H), 0.79 (d, J = 6.5 Hz, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $C_2D_2Cl_4$) δ 171.9 (C), 164.8 (C), 138.8 (C), 132.9 (CH), 132.0 (C), 129.5 (CH), 128.5 (CH), 122.1 (CH), 48.6 (CH), 45.6 (CH), 43.0 (CH_2), 29.8 (CH_2), 20.6 (CH_3), 19.8 (CH_3); HRMS (ESI+) m/z calcd for $C_{48}H_{61}N_6O_6$ $[M + H]^+$ 817.4647, found 817.4661.

Rotaxane **4e** was obtained using the described method from thread **3e** (500 mg, 1.46 mmol). The resulting residue was subjected to column chromatography using a $CHCl_3$/MeOH (99/1) mixture as eluent to give the title product as a white solid (497 mg, 39%); mp > 250 °C (decomp.); ^1H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 2H), 8.35 (dd, J = 7.8, 1.5 Hz, 4H), 7.72 (t, J = 5.2 Hz, 4H), 7.65 (t, J = 7.8 Hz, 2H), 7.10 (s, 8H), 5.33 (br s, 4H), 3.75 (br s, 4H), 3.27−3.18 (m, 4H), 2.76−2.66 (m, 4H), 1.56−1.45 (m, 4H), 1.36−1.10 (m, 8H), 1.05 (s, 4H), 0.93 (t, J = 7.3 Hz, 6H), 0.65−0.45 (m, 10H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.8 (C), 165.4 (C), 138.8 (C), 133.4 (CH), 132.4 (C), 129.6 (CH), 129.1 (CH), 122.6 (CH), 48.3 (CH_2), 46.7 (CH_2), 43.4 (CH_2), 30.8 (CH_2), 30.4 (CH_2), 28.2 (CH_2), 20.4 (CH_2), 19.8 (CH_2), 14.0 (CH_3), 13.8 (CH_3); HRMS (ESI+) m/z calcd for $C_{52}H_{68}N_6O_6$ $[M + H]^+$ 873.5273, found 873.5291.

Rotaxane **4f** was obtained using the described method from thread **3f** (500 mg, 1.46 mmol). The resulting residue was subjected to column chromatography using a $CHCl_3$/MeOH (99/1) mixture as eluent to give the title product as a white solid (242 mg, 19%); mp > 300 °C (decomp.); ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 2H), 8.36 (d, J = 7.8 Hz, 4H), 7.67−7.59 (m, 6H), 7.11 (s, 8H), 5.19 (br s, 4H), 4.00 (br s, 4H), 3.11 (d, J = 7.2 Hz, 4H), 2.62 (d, J = 7.8 Hz, 4H), 1.99−1.88 (m, 2H), 1.62−1.52 (m, 2H), 1.12 (s, 4H), 0.94 (d, J = 6.7 Hz, 12H), 0.41 (d, J = 6.5 Hz, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.2 (C), 165.4 (C), 138.9 (C), 133.6 (CH), 132.6 (C), 129.8 (CH), 129.1 (CH), 122.3 (CH), 57.2 (CH_2), 56.0 (CH_2), 43.2 (CH_2), 28.8 (CH_2), 28.0 (CH), 27.6 (CH), 21.0 (CH_3), 19.8 (CH_3); HRMS (ESI+) m/z calcd for $C_{52}H_{68}N_6O_6$ $[M + H]^+$ 873.5273, found 873.5288.

Rotaxane **4g**[29] was obtained using the described method from thread **3g** (500 mg, 1 mmol). The resulting residue was subjected to column chromatography using a $CHCl_3$/MeOH (95/5) mixture as eluent to give the title product as a white solid (237 mg, 23%). This compound was synthesized as described in ref 29 and showed identical spectroscopic data as those reported therein.

Rotaxane **5b** was obtained using the described method from thread **3b** (500 mg, 2.19 mmol). The resulting residue was purified by column chromatography on silica gel using a $CHCl_3$/MeOH (97/3) mixture as eluent to give the title product as a white solid (150 mg, 9%); mp > 250 °C (decomp.); ^1H NMR (200 MHz, $CDCl_3$) δ 9.46 (d, J = 9.2 Hz, 4H), 8.49 (d, J = 7.8 Hz, 4H), 8.10 (t, J = 7.8 Hz, 2H), 7.16 (d, J = 8.1 Hz, 4H), 6.88 (d, J = 7.9 Hz, 4H), 5.53 (dd, J = 14.1 Hz, 10.6 Hz, 4H), 3.60 (dd, J = 14.1 Hz, 2.0 Hz, 4H), 3.30 (q, J = 6.9 Hz, 4H), 2.62 (q, J = 7.0 Hz, 4H), 1.17 (t, J = 6.9 Hz, 6H), 0.69 (s, 4H), 0.43 (t, J = 7.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.5 (C), 163.8 (C), 149.3 (C), 139.2 (C), 138.9 (CH), 128.7 (CH), 128.2 (CH), 125.5 (CH), 42.7 (CH_2), 41.9 (CH_2), 40.7 (CH_2), 28.1 (CH_2), 13.7 (CH_3), 13.2 (CH_3); HRMS (ESI) m/z calcd for $C_{42}H_{51}N_8O_6$ $[M + H]^+$ 763.3926, found 763.3964.

Rotaxane **5c** was obtained using the described method from thread **3c** (500 mg, 1.75 mmol). The resulting residue was purified by column chromatography on silica gel using a $CHCl_3$/MeOH (97/3) mixture as eluent to give the title product as a white solid (40 mg, 5%); mp > 250 °C (decomp.); ^1H NMR (300 MHz, $CDCl_3$) δ 9.54 (d, J = 8.5 Hz, 4H), 8.48 (d, J = 7.8 Hz, 4H), 8.07 (t, J = 7.8 Hz, 2H), 7.15 (dd, J = 8.0 Hz, 1.3 Hz, 4H), 6.88 (dd, J = 8 Hz, J = 1.5 Hz, 4H), 5.53 (dd, J = 14.3 Hz, 10.4 Hz, 4H), 3.60 (dd, J = 14.3 Hz, 2.2 Hz, 4H), 3.23−3.14 (m, 4H), 2.61−2.53 (m, 4H), 1.66−1.54 (m, 4H), 1.20−1.04 (m, 4H), 0.94 (t, J = 7.4 Hz, 6H), 0.72 (s, 4H), 0.01 (t, J = 7.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.9 (C), 163.8 (C), 149.4 (C), 139.0 (C), 138.9 (CH), 128.8 (CH), 128.4 (CH), 125.6 (CH), 50.0 (CH_2), 48.8 (CH_2), 42.7 (CH_2), 28.3 (CH_2), 21.8 (CH_2), 21.5 (CH_2), 11.8 (CH_3), 10.3 (CH_3); HRMS (ESI+) m/z calcd for $C_{46}H_{59}N_8O_6$ $[M + H]^+$ 819.4552, found 819.4520.

Rotaxane **5d** was obtained using the described method from thread **3e** (1.0 g, 2.92 mmol). The resulting residue was purified by column chromatography on silica gel using a $CHCl_3$/MeOH (98/2) mixture as

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eluent to give the title product as a white solid (80 mg, 3%); mp > 250 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, J = 8.4 Hz, 4H), 8.48 (d, J = 7.8 Hz, 4H), 8.08 (t, J = 7.8 Hz, 2H), 7.15 (dd, J = 7.9 Hz, 1.5 Hz, 4H), 6.88 (dd, J = 7.9 Hz, 1.6 Hz, 4H), 5.53 (dd, J = 14.4 Hz, 10.3 Hz, 4H), 3.59 (dd, J = 14.4 Hz, 2.2 Hz, 4H), 3.25−3.19 (m, 4H), 2.65−2.59 (m, 4H), 1.60−1.50 (m, 4H), 1.34 (dq, J = 14.6 Hz, 7.3 Hz, 4H), 1.15−1.05 (m, 4H), 0.95 (t, J = 7.3 Hz, 6H), 0.72 (s, 4H), 0.56 (t, J = 7.3 Hz, 6H), 0.35−0.24 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.8 (C), 163.8 (C), 149.4 (C), 138.9 (C), 138.7 (CH), 128.9 (CH), 128.4 (CH), 125.6 (CH), 48.1 (CH_2), 46.7 (CH_2), 42.7 (CH_2), 30.9 (CH_2), 30.5 (CH_2), 28.4 (CH_2), 20.5 (CH_2), 19.8 (CH_2), 14.1 (2 × CH_3); HRMS (ESI+) m/z calcd for $C_{50}H_{67}N_8O_6$ $[M + H]^+$ 875.5178, found 875.5201.

Rotaxane **7a** was obtained using the described method from thread **3e** (500 mg, 1.46 mmol). The resulting residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to give the title product as a white solid (340 mg, 25%); mp > 250 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 2H), 8.40 (d, J = 1.2 Hz, 4H), 7.70 (t, J = 5.7 Hz, 4H), 7.09 (s, 8H), 5.38 (br s, 4H), 3.72 (br s, 4H), 3.28−3.16 (m, 4H), 2.74−2.64 (m, 4H), 1.55−1.45 (m, 4H), 1.41 (s, 18H), 1.35−1.10 (m, 8H), 1.05 (s, 4H), 0.92 (t, J = 7.3 Hz, 6H), 0.59 (t, J = 7.1 Hz, 6H), 0.55−0.40 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.8 (C), 165.8 (C), 153.2 (C), 138.9 (C), 133.2 (CH), 129.5 (C), 129.0 (CH), 120.1 (CH), 48.3 (CH_2), 46.7 (CH_2), 43.3 (CH_2), 35.4 (C), 31.4 (CH_3), 30.8 (CH_2), 30.4 (CH_2), 28.2 (CH_2), 20.3 (CH_2), 19.7 (CH_2), 14.0 (CH_3), 13.8 (CH_3); HRMS (ESI+) m/z calcd for $C_{60}H_{85}N_6O_6$ $[M + H]^+$ 985.6525, found 985.6552.

Rotaxane **7c** was obtained using the described method from thread **3e** (339 mg, 1.19 mmol). The resulting residue was purified by column chromatography on silica gel using a CH_2Cl_2/AcOEt (80/20) mixture as eluent to give the title product as a white solid (376 mg, 38%); mp 203−206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 2H), 7.86 (s, 4H), 7.68 (t, J = 5.7 Hz, 4H), 7.08 (s, 8H), 5.84 (ddt, J = 16.9 Hz, 10.2 Hz, 6.7 Hz, 2H), 5.35 (br s, 4H), 5.08−4.95 (m, 4H), 4.10 (t, J = 6.4 Hz, 4H), 3.72 (br s, 4H), 3.30−3.15 (m, 4H), 2.75−2.65 (m, 4H), 2.15 (dd, J = 14.3 Hz, 7.2 Hz, 4H), 1.90−1.80 (m, 4H), 1.66−1.46 (m, 12H), 1.36−1.25 (m, 4H), 1.25−1.12 (m, 4H), 1.02 (s, 4H), 0.94 (t, J = 7.3 Hz, 6H), 0.66−0.52 (m, 10H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.8 (C), 165.3 (C), 160.4 (C), 138.8 (C), 138.6 (CH), 135.0 (C), 129.0 (CH), 118.3 (CH), 115.0 (C), 114.8 (CH), 68.5 (CH_2), 48.3 (CH_2), 46.7 (CH_2), 43.4 (CH_2), 33.5 (CH_2), 30.9 (CH_2), 30.4 (CH_2), 28.7 (CH_2), 28.2 (CH_2), 25.4 (CH_2), 20.4 (CH_2), 19.9 (CH_2), 14.0 (CH_3), 13.9 (CH_3); HRMS (ESI+) m/z calcd for $C_{64}H_{89}N_6O_8$ $[M + H]^+$ 1069.6736, found 1069.6709.

Rotaxane **7d** was obtained using the described method from thread **3e** (500 mg, 1.46 mmol). The resulting residue was purified by column chromatography on silica gel using a $CHCl_3$/MeOH (98/2) mixture as eluent to give the title product as a white solid (222 mg, 17%); mp > 250 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04−8.96 (m, 6H), 7.72 (t, J = 5.6 Hz, 4H), 7.11 (s, 8H), 5.31 (br s, 4H), 4.00 (s, 6H), 3.85 (br s, 4H), 3.26−3.18 (m, 4H), 2.76−2.68 (m, 4H), 1.55−1.45 (m, 4H), 1.35−1.15 (m, 8H), 1.04 (s, 4H), 0.93 (t, J = 7.3 Hz, 6H), 0.62−0.50 (m, 10H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.9 (C), 166.0 (C), 164.5 (C), 138.7 (C), 134.1 (C), 133.4 (C), 132.2 (CH), 129.1 (CH), 126.4 (CH), 52.7 (CH_3), 48.4 (CH_2), 46.8 (CH_2), 43.5 (CH_2), 30.8 (CH_2), 30.4 (CH_2), 28.2 (CH_2), 20.4 (CH_2), 20.0 (CH_2), 14.0 (CH_3), 13.8 (CH_3); HRMS (ESI+) m/z calcd for $C_{56}H_{73}N_6O_{10}$ $[M + H]^+$ 989.5388, found 989.5402.

Rotaxane **7e** was obtained using the described method from thread **3e** (500 mg, 1.46 mmol). The resulting residue was washed with Et_2O and filtered, giving the title product as a white solid (450 mg, 32%); mp > 250 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (m, 6H), 7.75 (t, J = 5.2 Hz, 4H), 7.12 (s, 8H), 5.30 (br s, 4H), 3.86 (br s, 4H), 3.29−3.20 (m, 4H), 2.80−2.68 (m, 4H), 1.56−1.44 (m, 4H), 1.36−1.16 (m, 8H), 1.04 (s, 4H), 0.92 (t, J = 7.3 Hz, 6H), 0.64−0.56 (m, 10H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.9 (C), 163.1 (C), 149.6 (C), 138.4 (C), 135.6 (C), 129.2 (CH), 127.6 (CH), 127.0 (CH), 48.4 (CH_2), 46.9 (CH_2), 43.7 (CH_2), 30.7 (CH_2), 30.3 (CH_2), 28.2 (CH_2), 20.3 (CH_2), 20.0 (CH_2), 14.0 (CH_3), 13.7 (CH_3); HRMS (ESI+) m/z calcd for $C_{52}H_{67}N_8O_{10}$ $[M + H]^+$ 963.4975, found 963.4948.

Rotaxane **7f** was obtained using the described method from thread **3e** (500 mg, 1.46 mmol). The resulting residue was purified by column chromatography on silica gel using a $CHCl_3$/MeOH (98/2) mixture as eluent to give the title product as a white solid (349 mg, 27%); mp > 250 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (d, J = 1.9 Hz, 4H), 9.14 (t, J = 1.9 Hz, 2H), 7.54 (t, J = 5.5 Hz, 4H), 7.10 (s, 8H), 4.52 (br s, 8H), 3.26−3.18 (m, 4H), 2.76−2.67 (m, 4H), 1.54−1.42 (m, 4H), 1.35−1.12 (m, 8H), 1.04 (s, 4H), 0.91 (t, J = 7.3 Hz, 6H), 0.68−0.55 (m, 10H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.7 (C), 163.9 (C), 153.3 (CH), 138.4 (C), 130.2 (C), 129.2 (CH), 127.8 (CH), 48.3 (CH_2), 46.8 (CH_2), 43.4 (CH_2), 30.7 (CH_2), 30.3 (CH_2), 28.1 (CH_2), 20.3 (CH_2), 19.9 (CH_2), 13.9 (CH_3), 13.7 (CH_3); HRMS (ESI) m/z calcd for $C_{50}H_{67}N_8O_6$ $[M + H]^+$ 875.5178, found 875.5156.

4.5. Synthesis of Rotaxane 7b. Thread **3e** (200 mg, 0.60 mmol), Et_3N (14.4 mmol), and N^1,N^3-bis(4-(aminomethyl)benzyl)-isophthalamide[46] (1.46 g, 2.43 mmol) in anhydrous $CHCl_3$ (300 mL) were stirred vigorously while a solution of 5-(*tert*-butyldimethyl-siloxy)isophthaloyl dichloride[47] (0.81 g, 2.42 mmol) in anhydrous $CHCl_3$ (20 mL) was added over a period of 5 h using a motor-driven syringe pump. After a further 4 h, the resulting suspension was filtered through a Celite pad and washed with water (2 × 50 mL), a saturated solution of $NaHCO_3$ (2 × 50 mL), and brine (2 × 50 mL). The organic phase was then dried over $MgSO_4$, and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to give the title product as a white solid (**7b**, 220 mg, 37%); mp 235−236 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.41 (s, 1H), 8.35 (d, J = 7.8 Hz, 2H), 7.79 (s, 2H), 7.76−7.70 (m, 5H), 7.09 (s, 8H), 5.35 (br s, 4H), 3.72 (br s, 4H), 3.26−3.19 (m, 4H), 2.76−2.68 (m, 4H), 1.55−1.45 (m, 4H), 1.35−1.15 (m, 8H), 1.04 (s, 4H), 1.02 (s, 9H), 0.93 (t, J = 7.3 Hz, 6H), 0.66−0.50 (m, 10H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.8 (C), 165.4 (C), 165.2 (C), 157.1(C), 138.84 (C), 138.76 (C), 135.0 (C), 133.4 (C), 132.4 (CH), 129.6 (CH), 129.1 (CH), 123.8 (CH), 122.6 (CH), 115.5 (CH), 48.3 (CH_2), 46.7 (CH_2), 43.3 (CH_2), 30.8 (CH_2), 30.4 (CH_2), 29.8 (C), 28.2 (CH_2), 25.8 (CH_3), 20.4 (CH_2), 19.9 (CH_2), 14.0 (CH_3), 13.8 (CH_3), −4.3 (2 × CH_3); HRMS (ESI+) m/z calcd for $C_{58}H_{83}N_6O_7Si$ $[M + H]^+$ 1003.6087, found 1003.6084.

4.6. Synthesis of 5-(Hex-5-enyloxy)isophthalic Acid. To a DMF solution (150 mL) of dimethyl 5-hydroxyisophthalate (13.06 g, 62.18 mmol) was added 6-bromohexene (12.1 g, 74.61 mmol) and K_2CO_3 (9.88 g, 71.61 mmol), and the mixture was heated at 65 °C for 14 h. The reaction mixture was partitioned between H_2O and Et_2O. The aqueous layer was separated and washed with Et_2O. Combined organic layers were washed with 1 M aqueous NaOH and brine, dried ($MgSO_4$), filtered, and concentrated under vacuum. The resulting residue was subjected to column chromatography (silica gel) using a mixture hexane/AcOEt (90/10) as eluent to yield dimethyl 5-(hex-5-enyloxy)isophthalate as a yellow oil (16.84 g, 92%).[48] This oil (5.89 g, 20 mmol) was dissolved in MeOH (50 mL), and NaOH (1.60 g, 40 mmol) was added. The mixture was refluxed overnight, and after this time, the solvent was removed under vacuum. The corresponding residue was filtered and washed with $CHCl_3$ to yield the title compound as a white solid (2.89 g, 53%); mp 192−194 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (br s, 2H), 8.05 (t, J = 1.4 Hz, 1H), 7.61 (t, J = 1.4 Hz, 2H), 5.87−5.75 (m, 1H), 5.06−4.93 (m, 2H), 4.05 (t, J = 6.4 Hz, 2H), 2.07 (q, J = 7.2 Hz, 2H), 1.77−1.66 (m, 2H), 1.55−1.46 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.6 (C), 158.9 (C), 138.6 (CH), 132.7 (C), 122.2 (CH), 119.1 (CH), 115.1 (CH_2), 68.0 (CH_2), 32.9 (CH_2), 28.1 (CH_2), 24.7 (CH_2); HRMS (ESI-) m/z calcd for $C_{14}H_{15}O_5$ $[M - H]^-$ 263.0925, found 263.0932.

4.7. General Procedures for the Preparation of Benzylic Amide Macrocycles. Method A: The rotaxane (0.2 mmol) was placed in a 1 mL vial under high vacuum (0.01 Torr) at 150 °C (T_i). The system was heated at 375 °C (T_f) for 10 min. The corresponding thread was trapped in a U-tube situated at the exit point of the furnace and cooled with liquid N_2. After this time, the corresponding

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macrocycle was obtained quantitatively as a white solid. The addition of dichloromethane (10 mL) to the U-tube allows recovering the pure thread after solvent evaporation. **Method B**: The corresponding rotaxane (0.2 mmol) was dissolved in DMSO (1 mL) and stirred vigorously at 120 °C during 24 h. After this time, the reaction mixture was cooled to room temperature and H_2O (2 mL) was added. The resulting white solid was filtered, washed with water (10 mL) and Et_2O (10 mL), and dried under reduced pressure to give the corresponding macrocycle. Then, the ether was removed from the filtrate by rotatory evaporation, and the resulting solution was extracted with chloroform (3 × 12 mL). The combined organic fractions were washed with water (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, and, finally, concentrated under reduced pressure to recover the corresponding thread as a yellow oil. **Method C**: The corresponding rotaxane (0.2 mmol) was dissolved in DMSO (1 mL) in a 10 mL vessel and stirred vigorously at 120 °C during 30 min under microwave radiation (200 W). After this time, the reaction mixture was cooled to room temperature and H_2O (2 mL) was added. The resulting white solid was filtered, washed with water (10 mL) and Et_2O (10 mL), and dried under reduced pressure to give the corresponding macrocycle. Then, the ether was removed from the filtrate by rotatory evaporation, and the resulting solution was extracted with chloroform (3 × 12 mL). The combined organic fractions were washed with water (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, and, finally, concentrated under reduced pressure to recover the corresponding thread as a yellow oil.

Macrocycle ***6a***[7] was quantitatively obtained as a white solid using method **A**, **B**, or **C** from rotaxane **4c** or **4e**. The title compound showed identical spectroscopic data as those reported in ref 7 (see the Supporting Information for a ^{1}H NMR spectrum).

Macrocycle ***8a*** (104 mg, 77%) was obtained as a white solid using method **B** from rotaxane **7a** (205 mg, 0.21 mmol); mp > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (t, J = 5.6 Hz, 4H), 7.96 (s, 4H), 7.90 (s, 2H), 7.24 (s, 8H), 4.40 (d, J = 5.6 Hz, 8H), 1.34 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.2 (C), 151.1 (C), 138.2 (C), 134.6 (C), 127.8 (CH), 126.6 (CH), 123.2 (CH), 42.7 (CH_2), 34.7 (C), 31.0 (CH_3); HRMS (ESI+) m/z calcd for $C_{40}H_{45}N_4O_4$ [M + H]$^+$ 645.3435, found 645.3411.

Macrocycle ***8b*** (80 mg, 84%) was obtained from rotaxane **7b** (173 mg, 0.17 mmol) as a white solid using method **B**, heating at 120 °C for 24 h in a mixture DMSO: H_2O (9:1); mp > 300 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.93 (t, J = 5.4 Hz, 2H), 8.93 (t, J = 5.3 Hz, 2H), 8.07 (s, 1H), 7.95 (d, J = 7.7 Hz, 2H), 7.57 (t, J = 7.7 Hz, 1H), 7.52 (s, 1H), 7.34 (s, 2H), 7.24 (s, 8H), 4.45−4.35 (m, 4H); ^{13}C{^{1}H} NMR (50 MHz, DMSO-d_6) δ 166.0 (C), 165.9 (C), 157.4 (C), 138.2 (C), 138.1 (C), 136.2 (C), 134.8 (C), 129.9 (CH), 128.6 (CH), 127.9 (CH), 125.8 (CH), 116.8 (CH), 116.4 (CH), 42.7 (CH_2); HRMS (ESI+) m/z calcd for $C_{32}H_{29}N_4O_5$ [M + H]$^+$ 549.2132, found 549.2151.

Macrocycle ***8c*** (59 mg, 87%) was obtained as a white solid using method **B** from rotaxane **7c** (100 mg, 0.0936 mmol); mp > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 4H), 7.67 (s, 2H), 7.47 (s, 4H), 7.23 (s, 8H), 5.90−5.75 (m, 2H), 5.10−4.95 (m, 4H), 4.39 (d, J = 4.6 Hz, 8H), 4.07 (s, 4H), 2.15−2.05 (m, 4H), 1.82−1.70 (m, 4H), 1.58−1.50 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 165.6 (C), 158.5 (C), 138.5 (CH), 138.1 (C), 136.1 (C), 127.8 (CH), 118.1 (CH), 115.7 (CH), 115.0 (CH_2), 67.7 (CH_2), 42.7 (CH_2), 32.8 (CH_2), 28.1 (CH_2), 24.7 (CH_2); HRMS (ESI+) m/z calcd for $C_{44}H_{49}N_4O_6$ [M + H]$^+$ 729.3647, found 729.3657.

Macrocycle ***8d*** (140 mg, 99%) was obtained as a white solid using method **C** from rotaxane **7d** (222 mg, 0.224 mmol); mp > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (t, J = 5.6 Hz, 4H), 8.50 (d, J = 1.5 Hz, 4H), 8.33 (s, 2H), 7.23 (s, 8H), 4.40 (d, J = 5.6 Hz, 8H), 3.91 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 165.4 (C), 164.9 (C), 138.1 (C), 135.4 (C), 130.5 (C), 130.3 (CH), 130.1 (CH), 128.0 (CH), 52.7 (CH_3), 42.9 (CH_2); HRMS (ESI+) m/z calcd for $C_{36}H_{33}N_4O_8$ [M + H]$^+$ 649.2293, found 649.2282.

Macrocycle ***8e*** (64 mg, 99%) was obtained as a white solid using method **B** from rotaxane **7e** (100 mg, 0.104 mmol); mp > 300 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 333 K) δ 8.91 (t, J = 5.4 Hz, 4H), 8.71 (d, J = 1.5 Hz, 4H), 8.51 (t, J = 1.5 Hz, 2H), 7.30 (s, 8H), 4.49 (d, J = 5.4 Hz, 8H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6, 333 K) δ 163.4 (C), 147.7 (C), 137.3 (C), 136.2 (C), 130.9 (CH), 127.5 (CH), 123.4 (CH), 42.6 (CH_2); HRMS (ESI+) m/z calcd for $C_{32}H_{27}N_6O_8$ [M + H]$^+$ 623.1885, found 623.1860.

Macrocycle ***8f***[13] (150 mg, 95%) was obtained as a white solid using method **C** from rotaxane **7f** (258 mg, 0.295 mmol). The title compound showed identical spectroscopic data as those reported in ref 13 (see the Supporting Information for a ^{1}H NMR spectrum).

Macrocycle ***8g***[16] (149 mg, 99%) was obtained as a white solid using method **B** from rotaxane **5b** (216 mg, 0.283 mmol). The title compound showed identical spectroscopic data as those reported in ref 16 (see the Supporting Information for a ^{1}H NMR spectrum).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01651.

Copies of the ^{1}H and ^{13}C NMR spectra of all the new compounds described, TGA analyses, and full kinetics data (PDF)

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Notes

The authors declare no competing financial interest.

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