Rotaxanes

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Small-Molecule Recognition for Controlling Molecular Motion in Hydrogen-Bond-Assembled Rotaxanes**

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In Memory of Alan R. Katritzky

Abstract: *Di(acylamino)pyridines successfully template the formation of hydrogen-bonded rotaxanes through five-component clipping reactions. A solid-state study showed the participation of the pyridine nitrogen atom in the stabilization of the mechanical bond between the thread and the benzylic amide macrocycle. The addition of external complementary binders to a series of interlocked bis(2,6-di(acylamino)pyridines) promoted restraint of the back and forward ring motion. The original translation can be restored through a competitive recognition event by the addition of a preorganized bis(di(acylamino)pyridine) that forms stronger ADA–DAD complexes with the external binders.*

Molecular recognition is a key process for the assembly of the building blocks of vital biological compounds[1] and one of the most important regulatory processes in metabolism.[2] The usefulness of this phenomenon[3] has been efficiently transferred to the construction of artificial molecular architectures focused on mimicking the chemistry of important biological processes. In this regard, mechanically interlocked molecules are playing a prominent role as suitable scaffolds for imitating some of the most important cell functions. Recently, different rotaxane-based systems were reported to act as peptide synthesizers[4] or catalysts of chemical reactions,[5,6] and thus to show activity resembling that of ribosomes and enzymes, respectively. These and similar goals[7] have been reached as a result of the studies of multidisciplinary research teams aimed at taming the Brownian ring motion of the rotaxanes. External control of this translational motion enables reliable access to different thermodynamic states by the use of different stimuli,[8] including chemical, electrochemical, and photochemical stimuli. For this purpose, molecular-recognition processes with ions have been also used in a number of cases to trigger translational motion as a response from rotaxanes.[9] As far as we know, induction of the ring motion by complexation processes with neutral molecules remains unexplored.

Herein we report a tailor-made rotaxane enabled for inducing a response to the addition of small molecules that form a competitive hydrogen-bonded network with a 2,6-di(acylamino)pyridine fragment of the thread. The effect of these recognition events on macrocycle shuttling was tested in a series of rotaxanes bearing two identical binding units tethered by different alkyl chains. The initial states were recovered by competitive association with a preorganized bis(di(acylamino)pyridine) to provide an unprecedented method for reversibly changing the natural population of coconformers of a multistate hydrogen-bond-assembled rotaxane.

Although a variety of templates, including amide,[10] ester,[11] squaraine,[12] phenolate,[13] urea,[14] azodicarboxamide,[15] nitrone,[16] sulfoxide,[17] and organophosphorus[18] motifs, have been used to drive tetraamide-based rotaxane formation, the participation of heterocycles as binding sites remains largely unexplored. On the other hand, the hydrogen-bond (HB) recognition pattern of *N*,*N*′-diacyl-2,6-diaminopyridines (donor–acceptor–donor, DAD) has been exploited for the construction of a number molecular receptors, tuning of the chemical and physical properties of complementary species, or the preparation of assembled materials.[19] We initiated our research by incorporating this supramolecular codon into the thread **1**, readily obtained by a double amide coupling between 3,3-diphenylpropanoic acid and 2,6-diaminopyridine in a single step (see Scheme S1 in the Supporting Information). Thread **1** successfully templated the formation of the [2]rotaxane **2** in 33% yield by means of a five-component clipping reaction[20] involving *p*-xylylenediamine and isophthaloyl chloride in the presence of triethylamine (Scheme 1).

To confirm the contribution of the pyridine nitrogen atom to the intercomponent interactions of the rotaxane, we obtained suitable monocrystals for X-ray diffraction measurements by slow cooling of a solution of **2** in acetonitrile. The resulting interlocked molecular structure of **2** (Figure 1) displays hydrogen bonds between the hydrogen atoms of two NH groups of the macrocycle and two of the three available acceptors of the thread, specifically, with one of the carbonyl oxygen atoms (2.03 Å, 168°) and with the pyridine nitrogen atom (2.20 Å, 171°).[21]

Aiming to study competitive recognition events of suitable neutral guests with the DAD stations and the effect of these recognition events on the shuttling of the Brownian ring

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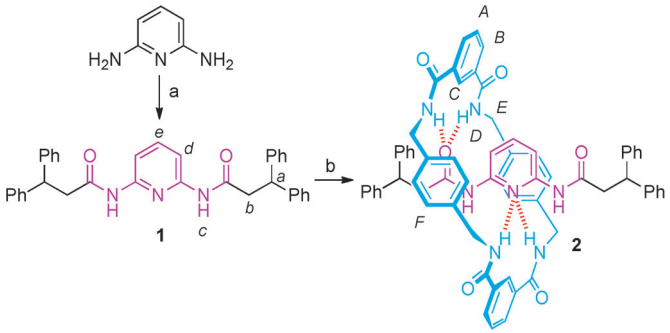


Scheme 1. Synthesis of *N*,*N*′-bis(3,3-diphenylpropanoyl)-2,6-diaminopyridine (**1**) and the hydrogen-bonded [2]rotaxane **2**. Reagents and conditions: a) 3,3-diphenylpropanoic acid (2 equiv), EDCI, DMAP, CH_2Cl_2, 55%; b) isophthaloyl dichloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, 33%. DMAP = 4-dimethylaminopyridine, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

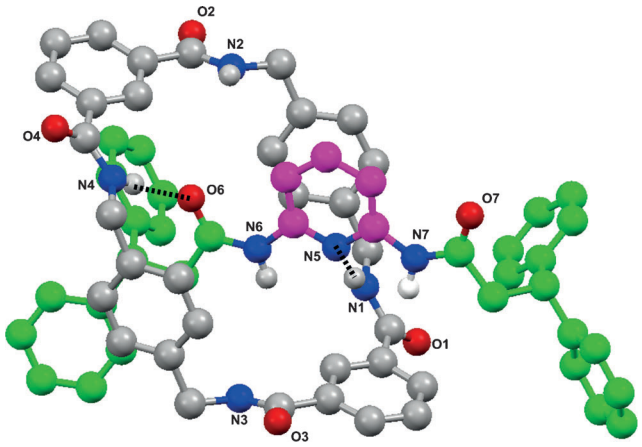
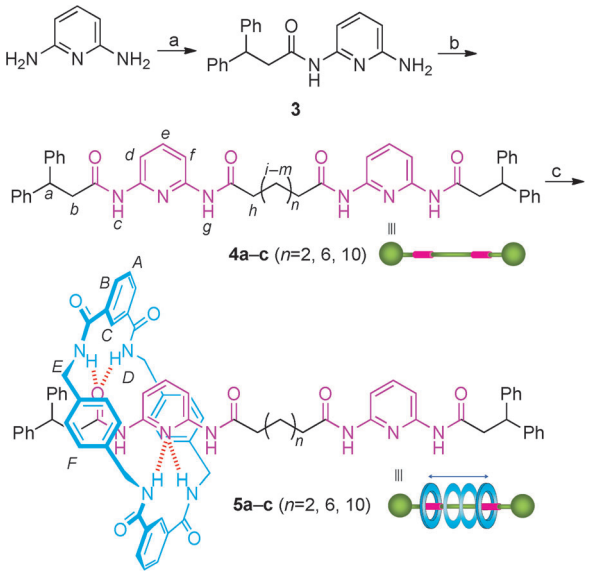


Figure 1. X-ray crystal structure of the 2,6-di(acylamino)pyridine [2]rotaxane **2**. For clarity, carbon atoms of the macrocycle are shown in gray, carbon atoms of the thread in green, and carbon atoms of the pyridine ring in magenta; oxygen atoms are depicted in red, nitrogen atoms are depicted in blue, and selected hydrogen atoms are in white. Intramolecular hydrogen-bond lengths [Å] (and angles [°]): N1–H01–N5 2.20 (170.8); N4–H04–O6 2.03 (168.4).



Scheme 2. Synthesis of the bis(di(acylamino)pyridine) threads **4a–c** and the corresponding [2]rotaxanes **5a–c**. Reagents and conditions: a) 3,3-diphenylpropanoic acid, EDCI, DMAP, CH_2Cl_2, 78%; b) $ClCO-(CH_2)_{n+2}COCl$, Et_3N, THF; **4a** (*n* = 2), 28%; **4b** (*n* = 6), 79%; **4c** (*n* = 10), 50%; c) isophthaloyl dichloride, *p*-xylylenediamine, Et_3N, $CHCl_3$; **5a** (*n* = 2), 14%; **5b** (*n* = 6), 30%; **5c** (*n* = 10), 23%.

Table 1: Occupancy of the diacylaminopyridine binding sites of [2]rotaxanes.

Entry	Di(acylamino)pyridine	$\delta(H_e)$ [ppm][a]	$\Delta\delta(H_e)$ [ppm][b]	Occupancy [%]
1	**1**	7.61		
2	**2**	7.36	−0.25	100
3	**4b**	7.65		
4	**5b**	7.57	−0.08	64
5	**4c**	7.65		
6	**5c**	7.53	−0.12	96

[a] ^{1}H NMR spectra were recorded in CD_2Cl_2 at 400 MHz and 298 K. [b] $\Delta\delta(H_e) = \delta(H_e)_{rotaxane} - \delta(H_e)_{thread}$.

motion between two di(acylamino)pyridine stations,[22] we synthesized the hydrogen-bonded rotaxanes **5** (Scheme 2). The two-station threads **4** were obtained in a straightforward manner by a double coupling of readily available *N*-(3,3-diphenylpropanoyl)-2,6-diaminopyridine (**3**; see Scheme S2) with three dicarboxylic acid dichlorides differing in the length of their carbon chain.

To estimate the occupancy of the tetraamide ring over the di(acylamino)pyridine sites in the rotaxanes **5**, we focused our attention on the upfield shift of the ^{1}H NMR signal of the hydrogen atom at the 4-position of the pyridine ring (H_e) following rotaxane formation. These values were compared with the chemical shift of this hydrogen atom in rotaxane **2**, in which the occupation of the binding site is complete (Table 1, entries 1 and 2). Although the insolubility of **5a** in most common solvents that do not disrupt hydrogen bonding precluded the aforementioned analysis, examination of the chemical-shift variations in the ^{1}H NMR spectra of the remaining members of the series revealed that the occupation of the binding stations in **5c** (96%) was notably higher than in **5b** (64%; Table 1), in which the greater participation of the alkyl diamide region as a binding site is supported by the splitting of the resonances of the alkyl chain of this rotaxane.[23] From these results, it became clear that **5c** was the best candidate for examining the competitive binding of an external HB competitor.

Several factors could influence the competitive binding of these HB-forming rotaxanes with external competitors, including the donor–acceptor abilities of the binding units,[24] the strength of the recognition pattern,[25] and even self-association of the involved partners.[26] By monitoring the shift of the ^{1}H NMR signal of the NH hydrogen atoms of **1** at varying concentrations, we determined that its self-association constant is very low (0.15 M^{-1}, measured in CD_2Cl_2 at 25 °C), thus showing its availability to associate with other complementary systems. To explore whether **1** might form triple hydrogen-bonded complexes with different ADA (acceptor–donor–acceptor) systems in dichloromethane, we

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evaluated the induced ^{1}H NMR chemical shifts after the addition of one equivalent of a range of ADA systems (see Figure S6). As we had presumed, barbital (**B**) and *N*-hexylthymine (**T**) showed higher affinities for the di(acylamino)pyridine **1** as compared to other assayed five-membered heterocycles, including succinimide, maleimide, and phthalimide.[27] Although the values of the association constants of similar complexes have been reported previously, the high sensitivity of these values to the side substituents[28] led us to calculate the association constants of **1**·**B** and **1**·**T** in CD_2Cl_2 at 25 °C, which were determined to be 550 and 2846 M^{-1}, respectively.

At this point, we evaluated the effect of the triple hydrogen-bonding complexation of **B** and **T** on the back and forward ring motion of the synthetized molecular shuttles by measuring the association constants of these ADA counterparts with the DAD-based two-station threads **4b** and **4c** and with their corresponding interlocked partners **5b** and **5c**. ^{1}H NMR titration experiments were carried out to assess the stepwise binding constants (K_{11} and K_{12}) of the corresponding assemblies (Table 2).

When the magnitudes of the association constants for rotaxanes **5** are compared with those obtained for their respective threads **4** (Table 2), it becomes clear that the competitive linking of the tetraamide ring with the DAD sites of the thread leads to a measurable decrease in the corresponding association constants with external ADA binders. This reduction largely depends on the strength of the assembly DAD–ADA. Thus, whereas the K_{12} constant decreased from 178 M^{-1} for the formation of a 1:2 complex between **4c** and **B** to 108 M^{-1} for the formation of a 1:2 complex between **5c** and **B**, the corresponding value fell from 405 to 156 M^{-1} in the experiments carried out with **T** (Figure 2). As expected, the difference in the K_{11} constant for the same ADA array involving the thread **4b** (higher K_{11} value) or rotaxane **5b** (lower K_{11} value) was less owing to the larger competitive participation of the alkyl diamide region as a binding site.

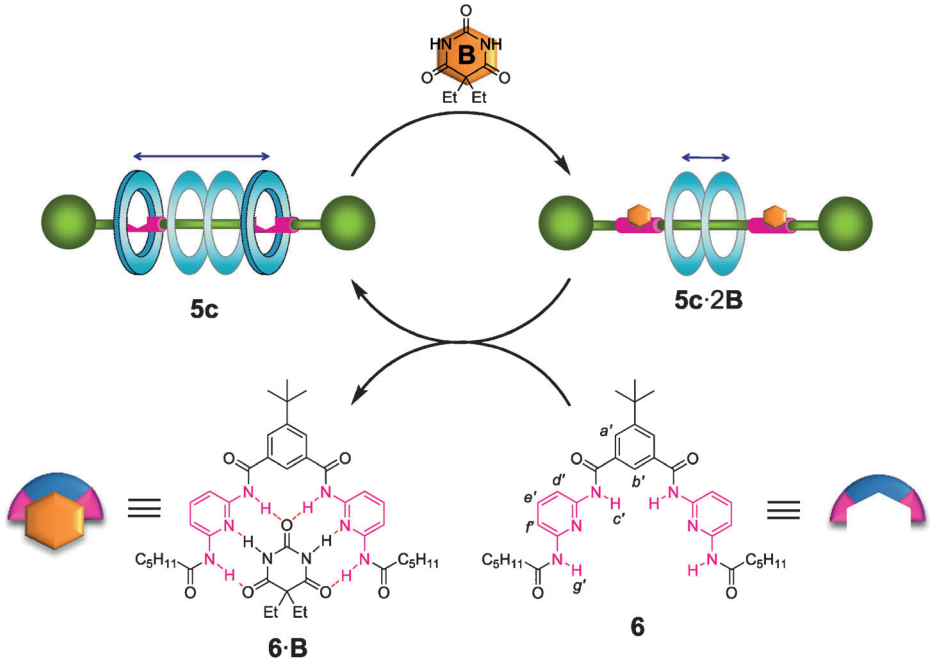
In the absence of an external ADA binder, the motion of the ring along the track between the two binding sites is unrestricted. Progressive saturation of the DAD units of the interlocked compounds with these binders prevents the ring from sitting over the stations, thus narrowing its location to the central alkyl chain. As expected, this constraint of the amplitude of the translational motion causes the downshifting of the ^{1}H NMR resonances of the CH_2 and CH hydrogen atoms at the stoppers (e.g. **5c**→**5c**·2**T**: $\Delta\delta(H_a) = +0.11$; $\Delta\delta(H_b) = +0.27$ ppm) and the upshifting of the ^{1}H NMR signals of the alkyl chain ($\Delta\delta(H_{j+k+l+m}) \approx -0.30$ ppm; see Figure 2).

Table 2: Association constants, K_{assoc}, for $(DAD)_n$·*n*ADA arrays ($n = 1$ and 2).[a]

Entry	$(DAD)_n$	ADA	*n*	K_{assoc} [M^{-1}][b]	
				K_{11}	K_{12}
1	**1**	**B**	1	550	–
2	**1**	**T**	1	2846	–
3	**4c**[c]	**B**	2	994	178
4	**4c**[c]	**T**	2	3267	405
5	**5c**	**B**	2	787	108
6	**5c**	**T**	2	2044	156
7	**4b**	**T**	2	3703	456
8	**5b**	**T**	2	3545	145

[a] The association constants were determined in CD_2Cl_2 at 25 °C with $[(DAD)_n] = 2$ mM and [ADA] = 0–40 mM. [b] The K_{assoc} values were calculated by monitoring the NH ^{1}H NMR signals of the di(acylamino)pyridine units.[29] [c] Self-association constant: 0.60 M^{-1} (CD_2Cl_2, 25 °C).

At this point, we wondered whether the original ring motion of the interlocked counterpart of the aggregate **5c**·2**B** could be restored. In this regard, we reasoned that a new association event with a preorganized bis(di(acylamino)pyridine) could deconvolute this assembly by sequestering the barbital molecules through the formation of a new hydrogen-bonded complex, thus delivering the free rotaxane **5c** and restoring its original translational motion (Scheme 3). Taking into account the known high stability of complexes between Hamilton-type receptors and barbiturate surrogates,[30] we prepared the *N*,*N*′-bis(hexanoylaminopyridinyl)isophthalamide **6** (see Scheme S3) for the removal of the **B** ADA binder molecules from the aggregate **5c**·2**B**. We monitored



Scheme 3. Reversible control of the amplitude of the translational motion in the interlocked bis(di(acylamino)pyridine) **5c** by the formation of a stronger ADA–DAD array.

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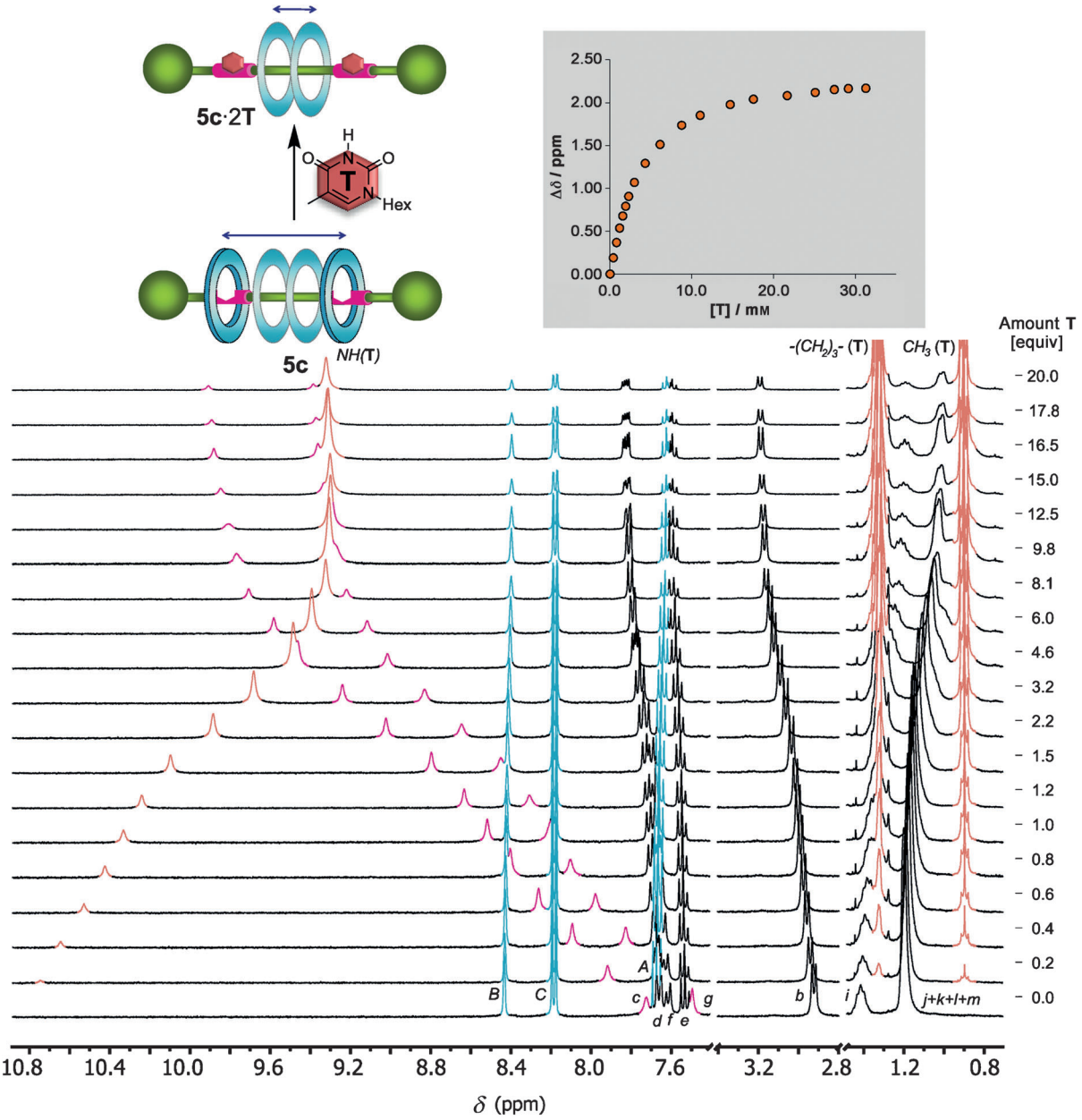

Figure 2. Titration of rotaxane **5c** with *N*-hexylthymine (**T**). Selected N–H and C_{alkyl}–H signal regions of the ^{1}H NMR spectra (400 MHz, CD_2Cl_2, 298 K) acquired during the titration (see Scheme 2 for signal assignments).

the NH resonances during this recognition process by comparing the ^{1}H NMR spectrum resulting from the addition of **6** to the aggregate **5c**·2**B** to give two equivalents of **6**·**B** ($K_{assoc} = 1.2 \times 10^5\,M^{-1}$; see Figure S17) and the rotaxane **5c** with the ^{1}H NMR spectra of both complexes and with those of the bis(di(acylamino)pyridine)s **6** and **5c** (Figure 3). The recovery of all chemical shifts of **5c** after the sequential binding process demonstrates the recovery of the original ring motion. Interestingly, the role of barbital in the controlled modulation of the amplitude of the ring motion (Scheme 3) resembles that of a cofactor in the regulation of the biological activity of an enzyme, for example, that of flavin derivatives (FAD or FMN) in a plethora of catalyzed biological processes by means of a previous binding event through noncovalent interactions.[31]

In conclusion, herein we have disclosed the ability of di(acylamino)pyridines to template the formation of novel hydrogen-bonded rotaxanes through five-component clipping reactions in reasonably good yields. In the solid state, the intramolecular hydrogen-bond pattern between this binding site and the benzylic amide macrocycle revealed the participation of the pyridine nitrogen atom in the stabilization of the mechanical bond. In rotaxanes of this kind with two binding sites, competitive association with external binders containing a complementary array of HB donor and acceptor sites dynamically blocks the binding sites of the thread and, consequently, restricts the amplitude of the ring motion.

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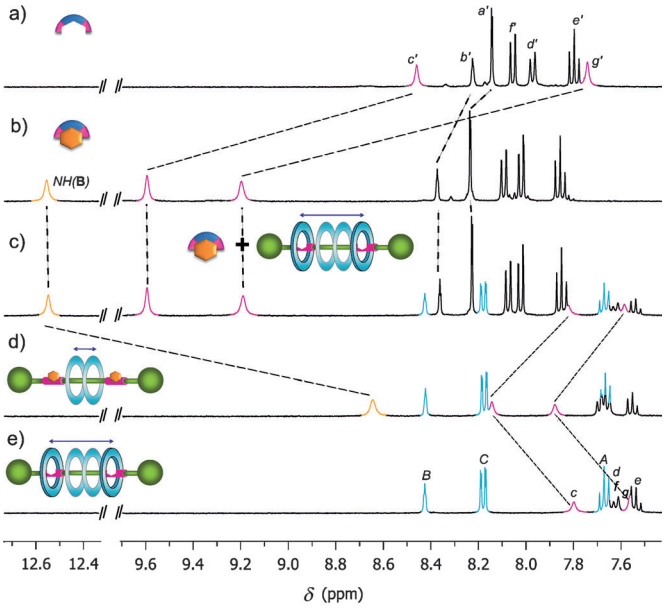

Figure 3. ^{1}H NMR spectra (400 MHz, CD_2Cl_2, 298 K) of a) Hamilton-type receptor **6**, b) complex **6**·2**B**, c) rotaxane **5c** plus complex **6**·2**B**, d) complex **5c**·2**B**, and e) rotaxane **5c** (see Schemes 2 and 3 for signal assignments).

Interestingly, the original state can be restored through a new recognition event by the addition of a preorganized bis(di-(acylamino)pyridine) that forms stronger ADA–DAD complexes with the external HB blockers. We believe that this unprecedented control of the molecular Brownian motion of interlocked molecules could inspire the design and synthesis of novel (biomimetic) complex devices and capture the attention of those researchers involved in the control and design of novel supramolecular catalysts.

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