Chemical Interconversion of Azo and Hydrazodicarboxamide-based [2]rotaxanes

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Abstract: The synthesis of novel hydrogen-bonded [2]rotaxanes having two pyridine rings into the macrocycle and azo and hydrazodicarboxamide-based templates decorated with four cyclohexyl groups is described. The different affinity of the binding sites for the benzylic amide macrocycle and the formation of programmed non-convalent interactions between the interlocked components have an important effect on the dynamic behavior of these compounds. Having this in mind, the chemical interconversion between the azo and hydrazo forms of the [2]-rotaxane was investigated to provide a chemically-driven interlocked system enable to switch its circumrotation rate as a function of the oxidation level of the binding site.

Keywords: azo compounds, template synthesis, rotaxanes, non-covalent interactions, switchable systems

INTRODUCTION

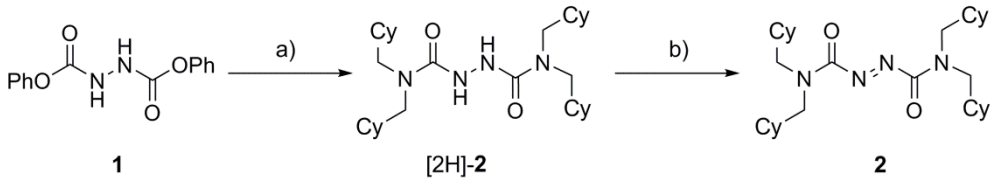
Mechanically interlocked compounds are chemical entities composed by, at least two or more entwined components.[1-3] The lacking of a covalent bond between the subunits of these compounds allows relative large amplitude motions.[4,5] During the last decades, the control of the internal dynamics of these species under different external stimuli allowed the development of smart interlocked devices for a broad range of applications.[6-9]

In this field, some of us reported that azodicarboxamides are able to act as templates for driving the assembly of hydrogen-bond-assembled [2]rotaxanes.[10-12] Moreover, these binding sites can be reversibly and efficiently interconverted with their hydrazo forms through a hydrogenation–dehydrogenation strategy of the nitrogen–nitrogen bond. This type of chemical control was efficiently employed for building stimuli-responsive molecular shuttles.[10] In a different work, it was shown that the rotation dynamics of these particular systems depend on the oxidation level of the nitrogen-based binding site.[11] Simultaneously, we also described how this pirouetting motion can be also affected by the incorporation of different substituents at the nitrogen atoms of a succinamide.[13]

Herein we describe the effect of integrating dicyclohexylmethyl stoppers on a azodicarboxamide template in the preparation of a hydrogen-bond-assembled [2]rotaxane having two pyridine rings into the macrocycle and its interconversion into the corresponding hydrazo surrogate.

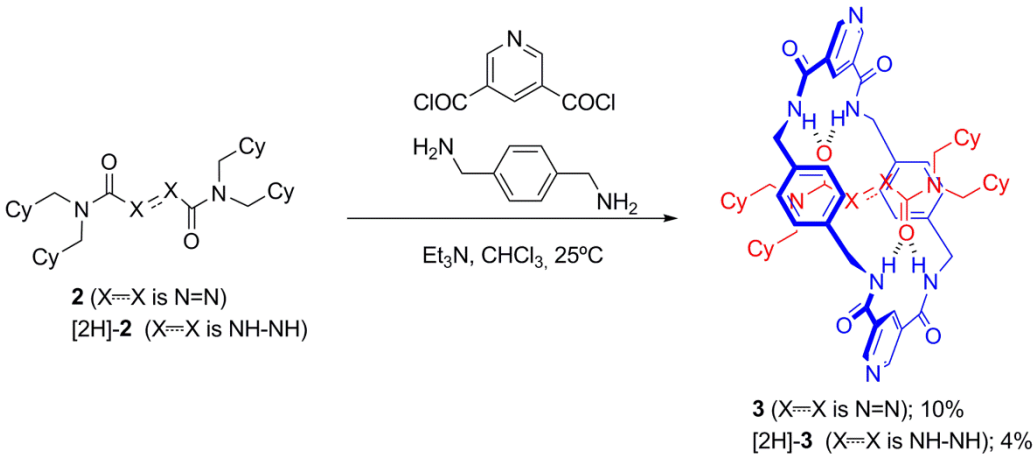
Result and discussion

The reaction of diphenyl hydrazodicarboxylate (**1**) with bis(cyclohexylmethyl)-amine in the presence of two equivalents of triethylamine provided the hydrazodicarboxamide [2H]-**2** in a 51% yield. Next, the oxidation of the hydrazo compound [2H]-**2** was carried out using *N*-bromosuccinamide in the presence of pyridine. This reaction was monitored by IR spectroscopy observing the vanishing of the band ascribed to the NH at 3397 cm^{-1} of hydrazo compound and the shifting of absorption frequency of CO band from 1653 cm^{-1} to 1699 cm^{-1}. After the work-up, the azodicarboxamide **2** was isolated in a 97% yield.



Scheme 1. Synthesis of the hydrazodicarboxamide [2H]-**2** and its azo derivative **2**. *Reagent and conditions:* a) $(CyCH_2)_2NH$, Et_3N, $CHCl_3$, reflux, 24 h, 51%; b) NBS (*N*-bromosuccinimide), pyridine, CH_2Cl_2, 25 ^oC, 1 h, 97%. (Cy = cyclohexyl, C_6H_{11})

The five-component clipping reaction between *p*-xylylenediamine, 3,5-pyridinedicarbonyl dichloride, the hydrazo template [2H]-**2** and triethylamine provided the hydrazo [2]rotaxane [2H]-**3** in only 4% yield (Scheme 2). The rotaxane formation reaction using the template **2** leads to the interlocked azo compound **3** in a more reasonable 10% yield probing the better templating capability of the azo compound for driving the construction of the tetralactam ring around the thread (Scheme 2).



Scheme 2. Syntheses the azo and hydrazo rotaxanes **3** and [2H]-**3**.

These results are in line with those obtained for the assembly of *N,N,N',N'*-tetrabenzylhydrazodicarboxamide and its corresponding azo derivative.[10] However, the incorporation of two pyridine rings into the tetralactam ring also provokes an noticeable decrease of the yield probably due to the stumpy aggregation between the thread and the intermediate polyamides, precursors of the interlocked tetralactam.[14]

Figure 1 displays the stacked plot of the ^{1}H NMR spectrum of each thread **2** and [2H]-**3** and the corresponding interlocked compounds **3** and [2H]-**3**. Both comparisons prove the interlocked nature of the assembled products. Nevertheless, the shape of the signal of the macrocyclic methylenic protons of these rotaxanes deserves to be highlighted. Whereas the signals ascribed to the macrocyclic methylene protons of [2H]-**3** (Fig. 1B) appears as a slightly broad singlet a 4.56 ppm, the analogue signals of **3** (Fig. 1D) are non-equivalent as result of the different magnetic environments attributed to its equatorial and axial positions in the macrocycle. The peak for the equatorial methylene proton emerges as a doublet of doublets ($^{2}J(H_1,H_2)$ = 14.3 Hz and $^{3}J(H_1,H_D)$ = 7.3 Hz) at 4.96 ppm and the peak for the axial one appears as a doublet ($J(H_1,H_2)$ = 14.1 Hz) at 4.06 ppm. This patent difference is connected with the rotational motion of the ring of single binding site amide-based [2]rotaxanes[13-21] which occurs in a higher spinning rate in [2H]-**3** than in **3**. Moreover, the substantial upfield shift ($\Delta\delta \approx$ 0.5 ppm) corresponding to the signal of the methylenic $H_{d'}$ protons of one of the cyclohexane rings of **3** (Fig. 1C) with respect to the naked thread (Fig. 1C) reveals the establishment of stabilizing CH···π interactions[22,23] which further deaccelerate the rotational motion.[13]

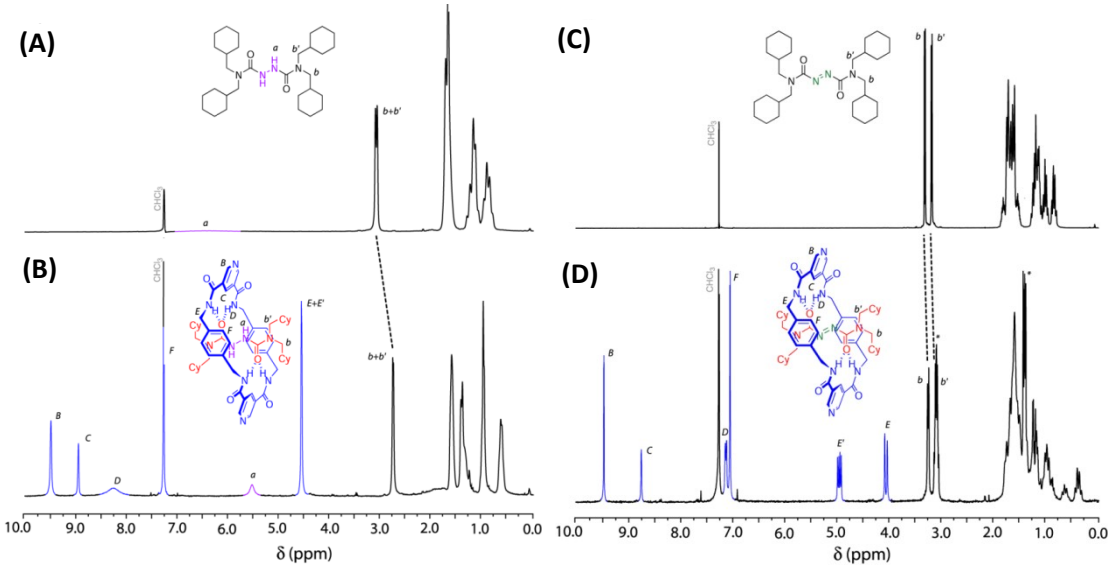
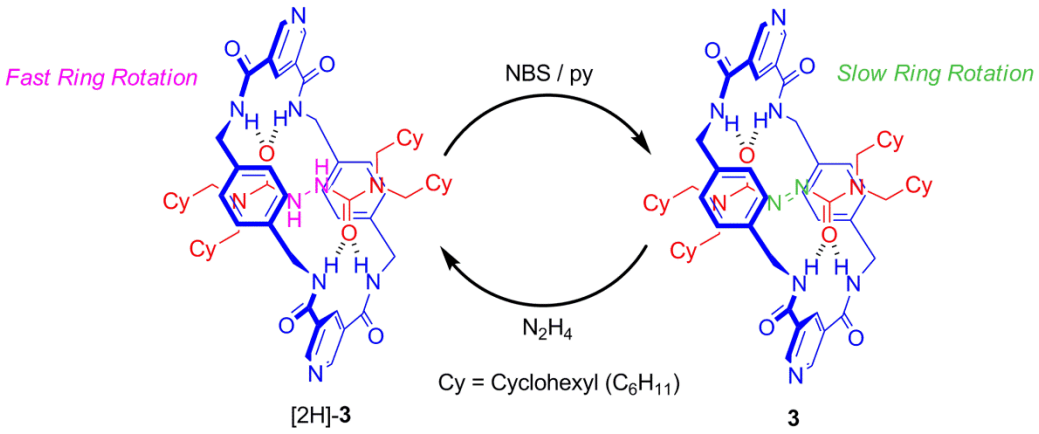


Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) hydrazodicarboxamide thread [2H]-**2**, (b) hydrazodicarboxamide rotaxane [2H]-**3**, (c), azodicarboxamide thread **2** and (d) azodicarboxamide rotaxane **3**.

Taking into account our previous considerations on the spinning rate of the macrocycle of the interlocked systems, by exchanging the oxidation state of the dinitrogenated binding site of this rotaxane we could switch between two different dynamic states. Consequently, we then assayed the chemical interconversion between the two accessible oxidation states of the [2]rotaxane **3**. A reduction of the azo rotaxane **3** with hydrazine quantitatively afforded the [2]rotaxane [2H]-**3** (Scheme 3). In the reverse sense, [2H]-**3** was completely transformed by oxidation with *N*-bromosuccinimide in the presence of pyridine (see Experimental Section).



Scheme 3. Interconversion of the azo and hydrazo rotaxanes **3** and [2H]-**3**.

In this way, we switched from a fast ring rotation state of a rotaxane to a slow ring rotation one, and viceversa, by simple and efficient chemical modifications.

CONCLUSIONS

In summary, we have described the assembly of two hydrogen-bonded [2]rotaxanes having a nitrogenated binding site and two pyridine rings in the macrocycle. A close inspection of their ^{1}H NMR spectra reveals a deep dissimilarity in the dynamic behavior of the cyclic component as consequence of the distinguishable affinity of the binding sites for the macrocycle and the non-covalent interactions between both interlocked components. The chemical interconversion between the azo and hydrazo forms of the [2]-rotaxane facilitated the development of a chemically-switchable interlocked system enable to exchange two different dynamic states as a function of the oxidation level of the binding site of one of the entwined components.

EXPERIMENTAL SECTION

Preparation of N^1,N^1,N^2,N^2-tetrakis(cyclohexylmethyl)-1,2-hydrazodicarboxamide ([2H]-2)

To a solution of diphenyl hydrazodicarboxylate (**1**) (1.65 g, 6.06 mmol) in chloroform (50 mL) was added bis(cyclohexylmethyl)amine (2.80 g, 13.37 mmol) followed by triethylamine (1.69 mL, 12.16 mmol). The reaction mixture was stirred for 15 hours at

reflux temperature after which time the reaction was concentrated under reduced pressure and purified by column chromatography on silica gel using a $CHCl_3$/MeOH (99/1) mixture as eluent to give the title product as a white solid ([2H]-**2**, 1.53 g, 51%). M.p. 249-251 ^oC; IR (Nujol): 3627 (w), 3575 (w), 3397 (w), 3019 (w), 2925 (w), 1653 (w), 1449 (w), 1215 (vs), 1046 (w), 758 (vs), 699 (s). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.34 (s ancho, 2H, NH), 3.09 (d, *J* = 6.9 Hz, 8H,NC*H*$_2$), 1.82-1.53 (m, 24H, H_{Cy}), 1.34-1.05 (m, 12H, H_{Cy}), 1.02-0.75 (m, 8H, H_{Cy}).; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.96 (CO), 54.34 (CH_2N), 36.79 (CH), 30.90, 26.38, 25.85; HRMS (ESI) calcd for $C_{30}H_{55}N_4O_2$ $[M + H]^+$ 503.4325, found 503.4329.

Preparation of *N*^{1},*N*^{1},*N*^{2},*N*^{2}-tetrakis(cyclohexylmethyl)-1,2-azodicarboxamide (2)

To a solution of the 1,2-hydrazodicarboxamide [2H]-**2** (2.87 g, 5.71 mmol) in dichloromethane (50 mL) were added pyridine (0.6 mL, 6.85 mmol) and *N*-bromosuccinimide (1.12 g, 6.28 mmol). The resulting orange solution was stirred at room temperature for 1 h. Then the reaction mixture was diluted with dichloromethane (100 mL) and sequentially washed with water (100 mL), 5% aqueous solution of $Na_2S_2O_3$ (75 mL) and saturated solution of $NaHCO_3$ (2 x 75 mL). The organic phase was dried with anhydrous $MgSO_4$, and concentrated *in vacuo* to afford a crude material which was purified by column chromatography on silica gel eluting with a $CHCl_3$/MeOH (98/2) mixture as eluent to give the title product as an orange solid (**2**, 2.77 g, 97%). M.p. 187-189 °C; IR (Nujol): 3019 (m), 2928 (w), 1699 (m), 1450(w), 1216 (vs), 1047 (w), 759 (vs), 699 (m). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.32 (d, *J* = 7.4 Hz, 4H, NCH), 3.19 (d, *J* = 7.2 Hz, 4H, NCH), 1.89-1.48 (m, 22H, HCy), 1.31-0.95 (m, 18H, HCy), 0.92-0.78 (m, 4H, HCy); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.27 (CO), 54.17 (CH2N), 37.98, 36.77, 27.24, 27.07, 26.66, 26.64; HRMS (ESI) calcd for $C_{30}H_{53}N_4O_2$ $[M + H]^+$ 501.4169, found 501.4170.

General procedure for the preparation of [2]rotaxanes 3 and [2H]-3

The thread (1 mmol), **2** or [2H]-**2**, and Et_3N (3.4 mL, 24 mmol) in $CHCl_3$ (250 mL) were stirred whilst solutions of *p*-xylylenediamine (1.63 g, 12 mmol) in $CHCl_3$ (40 mL) and 3,5-pyridinedicarbonyl dichloride (2.45 g, 12 mmol) in $CHCl_3$ (40 mL) were simultaneously added over a period of 3.5 h using a motor-driven syringe pump. Afterwards the resulting suspension was filtered through a Celite pad and the solvent removed under reduced pressure. The resulting solid was subjected to column chromatography (silica gel) to yield unconsumed thread, [2]rotaxane, [2]catenane and, in some cases, [3]rotaxane.

Rotaxane [2H]-3: 4% yield; white solid M.p. > 300 °C; IR (Nujol): 3579 (w), 3354 (w), 3019 (s), 2921 (w), 1658 (m), 1527 (m), 1429 (w), 1215 (vs), 1045 (w), 758 (vs), 699 (s). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.49 (s ancho, 4H, CH_B), 8.95 (s ancho, 2H, CH_C), 8.26 (s ancho, 4H, NH_D), 7.26 (s, 8H, CH_F), 5.53 (s ancho, 2H, NH_a), 4.56 (s ancho, 8H, CH_E), 2.76

(d, J = 5.7 Hz, 8H, CH_b), 1.67-1.54 (m, 12H, H_{Cy}), 1.46-1.31 (m, 12H, H_{Cy}), 1.04-0.93 (m, 12H, H_{Cy}), 0.70-0.57 (m, 4H, H_{Cy}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.89 (CO_{thread}), 157.42 ($CO_{macrocycle}$), 149.12, 136.73 (*q*), 131.66, 129.90 (*q*), 129.54, 54.22 (CH_2N), 45.29 ($ArCH_2N$), 36.75 (CH), 30.93, 26.25, 25.84. HRMS (ESI) calcd for $C_{60}H_{81}N_{10}O_6$ $[M + H]^+$ 1037.6341, found 1037.6344.

Rotaxane 3: 10% yield; orange solid, M.p. > 220 °C (decomp.); IR (Nujol): 3385 (m), 3022 (m), 2933 (s), 2850 (m), 2118 (m), 1670 (s), 1545 (m), 1445 (m), 1296 (m), 1224 (s), 1145 (w), 1121 (w), 765 (vs), 672 (vs). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.46 (d, J = 1.5 Hz, 4H, CH_B), 8.75 (s ancho, 2H, CH_C), 7.13 (d ancho, J = 7.7 Hz, 4H, NH_D), 7.06 (s, 8H, CH_F), 4.96 (dd, J = 14.3 Hz, J = 7.3 Hz, 4H, $CH_{E'}$), 4.06 (d, J = 14.1 Hz, 4H, CH_E), 3.26 (d, J = 6.7 Hz, 4H, CH_b), 3.11 (d, J = 7.5 Hz, 4H, $CH_{b'}$), 1.82-1.47 (m, 18H, H_{Cy}), 1.25 (s, 4H, CH_b), 1.22-1.14 (m, 8H, H_{Cy}), 1.07-0.84 (m, 12H, H_{Cy}), 0.71-0.59 (m, 2H, H_{Cy}), 0.47-0.30 (m, 4H, H_{Cy}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.95 (CO_{thread}), 159.53 ($CO_{macrocycle}$), 149.69, 136.49 (*q*), 132.78, 131.14, 129.06, 126.63 (*q*), 56.46 (CH_2N), 56.23 (CH_2N), 44.46 ($ArCH_2N$), 37.45 (CH), 37.16 (CH), 31.62, 30.84, 29.67, 25.79, 25.17. HRMS (ESI) calcd for $C_{60}H_{79}N_{10}O_6$ $[M + H]^+$ 1035.6184, found 1035.6189.

Chemical exchange of [2]rotaxanes 3 and [2H]-3

Reduction Protocol: To a solution of the [2]rotaxane **3** (55 mg, 0.05 mmol) in chloroform (5 mL) was added hydrazine monohydrate (5 μL) in one go. The orange solution was transformed to a colourless solution in less than 5-10 min. The reaction mixture was dried with a high vacuum pump to afford the [2]rotaxane [2H]-**3** (54 mg, 0.05 mmol) as a colorless solid. *Oxidation Protocol:* To a solution of the [2]rotaxane [2H]-**3** (39 mg, 0.04 mmol) in dichloromethane (5 mL) were added pyridine (4 μL) and *N*-bromosuccinimide (7 mg, 0.04 mmol). The resulting orange solution was stirred at 25 ^{o}C for 30 min. Then the reaction mixture was diluted with dichloromethane (10 mL) and sequentially washed with water (25 mL), 5% aqueous solution of $Na_2S_2O_3$ (20 mL) and saturated solution of $NaHCO_3$ (2 x 20 mL). The organic phase was dried with $MgSO_4$, and concentrated *in vacuo* to afford the [2]rotaxane **3** (37 mg, 0.04 mmol) as an orange solid.

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