Chiral Amide Rotaxanes with Glucose Stoppers − Synthesis, Chiroptical Properties and Wheel-Axle Interactions

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In this paper we report on amide rotaxanes with tetrabenzoylglucose stoppers. When acetyl groups are used instead of benzoyl groups, merely a pseudo-rotaxane **5** is obtained. The circular dichroism measurements of the rotaxanes **6a** and **6b** differ significantly from that one of the free axle **7**. Similarly, the Cotton effects of the mixtures of achiral wheels **2a** and **2b** and chiral axle indicate intermolecular host-guest interactions, likewise. After an addition of a solution of NaOMe the wheel is slipping off immediately and quantitatively by hydrolysis, as the benzoylglucose stoppers decrease in size by hydrolysis.

Introduction

The importance of non-covalent interactions in biological processes has greatly increased the interest in supramolecular chemistry during the last few years[1]. Furthermore, chirality is of great importance in nature. With the intention of converging aspects of both topics we describe here new rotaxanes with chiral stoppers.

In the synthesis of catenanes and rotaxanes[2] it is possible to vary the properties usually observed in the constituent molecules by forming a mechanical bond. Thus, no covalent substitution is necessary in the molecular construction, e.g. the solubility of a molecular axle[3] or a wheel[4] increases when it is a part of a rotaxane. Moreover, the optical properties like fluorescence[5] or the *E*/*Z* isomerization of azobenzene derivatives[2][6] are influenced by mechanical links.

The involved processes in the synthesis are based on molecular recognition according to Emil Fisher's key/lock principle[7], which is well founded by the necessary demands of steric fit and weak interactions like hydrogen bonding, π-stacking, electrostatic and van der Waals interactions. The incorporation of carbonyl functions in the guest molecule [in our case isophthaloyl dichloride (**1**)], seem to fulfil these requirements[8].

In the course of our investigations into the topological chirality of catenanes and pretzel-shaped molecules as well as cycloenantiomeric rotaxanes[9], the question arose whether the chiroptical properties of a chiral axle-shaped molecule are changed by threading it through an achiral wheel. In analogy to core-chiral dendrimers[10], a wheel on a chiral axle might cover and mask the chiral centres and thus chiroptical properties might decrease in magnitude. On the other hand, a chiral induction from the axle to the achiral wheel may also occur[11].

We recently reported the synthesis of donor/acceptor rotaxanes of the Stoddart-type[2c] with tetraacetylglucose stoppers[12]. However, the circular dichroism (CD) of these materials did not give a definite evaluation due to the small molar ellipticity. Meanwhile, we succeeded in synthesizing the first chiral amide-based rotaxanes, which meet the requirements mentioned above. Like the free axle, the corresponding rotaxanes show a significant CD.

Results and Discussion

For the synthesis of the rotaxanes we firstly extended 2,3,4,6-tetra-*O*-acetylglucosyl bromide with *p*-nitrophenol and subsequently reduced the resulting compound to the amine **3**. In contrast to stoppers reported earlier, there are more possibilities for interactions due to the enlarged π-system. The rotaxane syntheses were carried out by our threading method[2a][13]. The reaction of **3** with macrocycle **2a** and isophthaloyl dichloride (**1**) only yields the pseudorotaxane **5**, the wheel of which slips off in solution. We therefore replaced the acetyl groups in **3** with the bulkier benzoyl groups. Consequently, this stopper prevents the wheel from slipping off. The reaction of **4** with **1** and **2a**, shown in Figure 1, leads to the stable amide rotaxane[2b] **6a** in 9% yield. In the same way the macrocyclic sulfonamide wheel **2b** gave 10% of rotaxane **6b** in the reaction with stopper **4** and dichloride **1**.

The axle **7** could not be isolated in its pure form in this reaction. It was synthesized in the absence of the corresponding macrocycle **2**.

Figure 3 shows the circular dichrograms of the free axle **7** with chiral tetrabenzoylglucose stoppers and the corresponding rotaxanes with the tetraamide wheel **2a** and the sulfonamide wheel **2b**, respectively. Both macrocycles cause a significant amplification in the CD of the rotaxanes **6a** and **6b** in comparison to that of **7**. The molar ellipticities

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Figure 1. Synthesis of the pseudo-rotaxane **5** and the rotaxanes **6a** and **6b** by threading

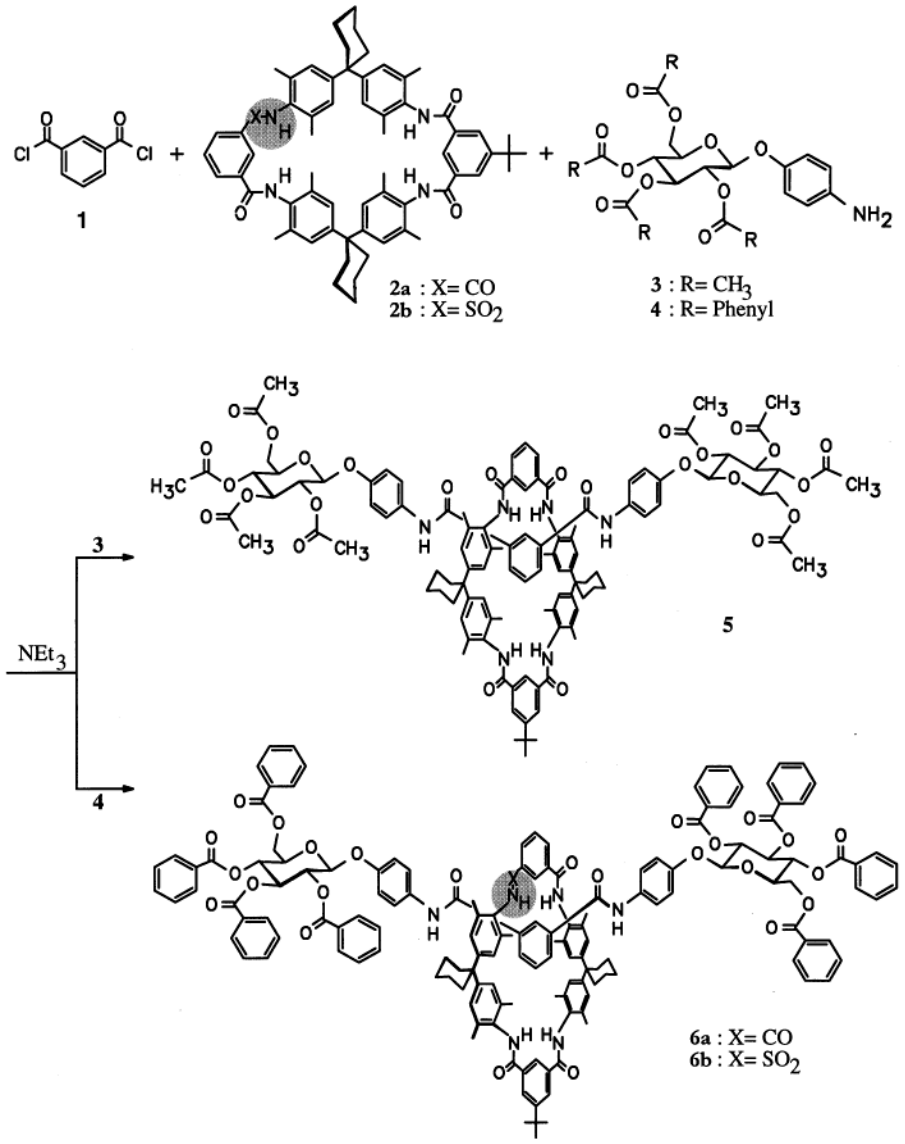
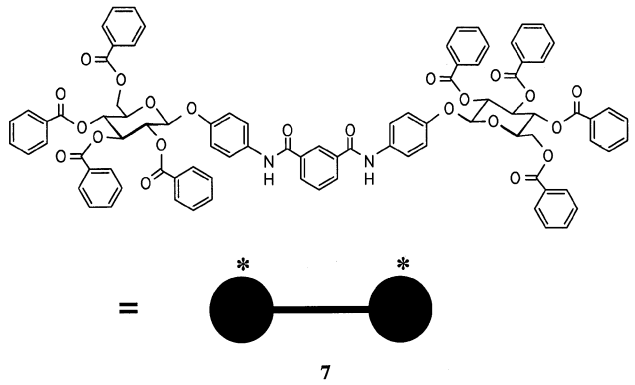


Figure 2. Axle **7** with the same chiral stoppers as in rotaxanes **6a** and **6b**



are distinctly higher than in the free axle. Moreover, the maxima at 198 nm in the CD spectra of **6a** and **6b** are bathochromically shifted in comparison to **7** by 2 nm and 1 nm, respectively.

The phenomenon of a decrease of chiroptical properties in core chiral dendrimers[10] mentioned above is not observed here in rotaxanes like **6a** and **6b**. The macrocycles seem to be too small to cover the stereogenic centres. In contrast, **6a** and **6b** show a remarkable amplification of Cotton effects. Clearly, the threading of a wheel on the chiral axle **7** influences their conformation due to electronic and steric factors. The chiral environment of the enantiomerically pure glucose stopper, with its large benzoyl groups, changes. On the other hand, the remarkable difference in the CD spectra could be explained by a chiral induction from the stoppers onto the achiral wheel, which faces the nearby stereogenic centres. The Cotton effect of the rotaxane may also be influenced by the *intra*molecular hydrogen bonds between the amide groups in the wheel and the amide and ester groups in the axle. This phenomenon chal-

Figure 3. Circular dichroism spectra of **6a** and **6b** compared to those of the axle **7** [c(**6a**) = $1.24 \cdot 10^{-4}$ mol l^{-1}, c(**6b**) = $2.21 \cdot 10^{-4}$ mol l^{-1}, c(**7**) = $1.73 \cdot 10^{-4}$ mol l^{-1}, all spectra were measured in TFE]

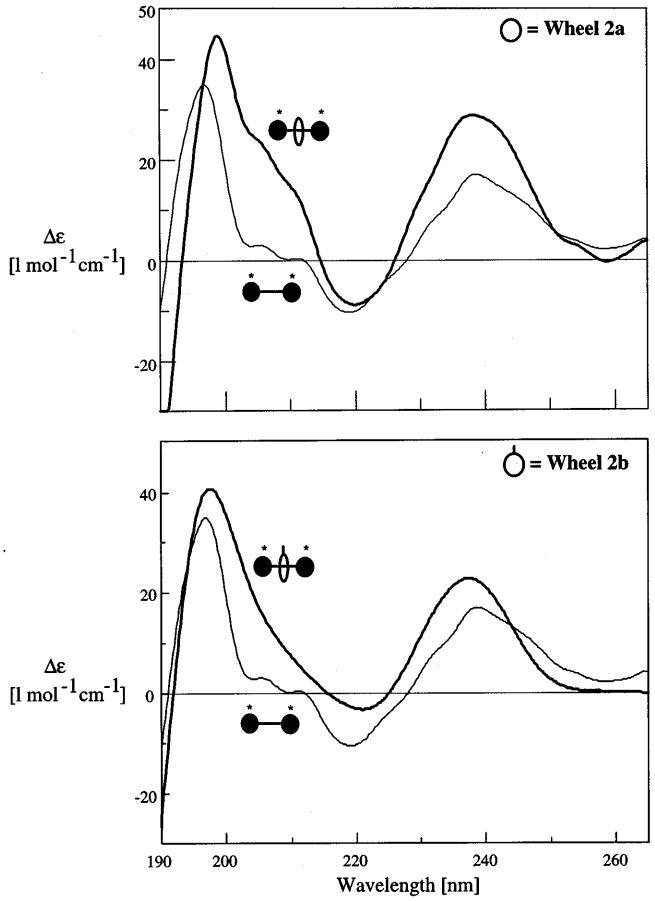
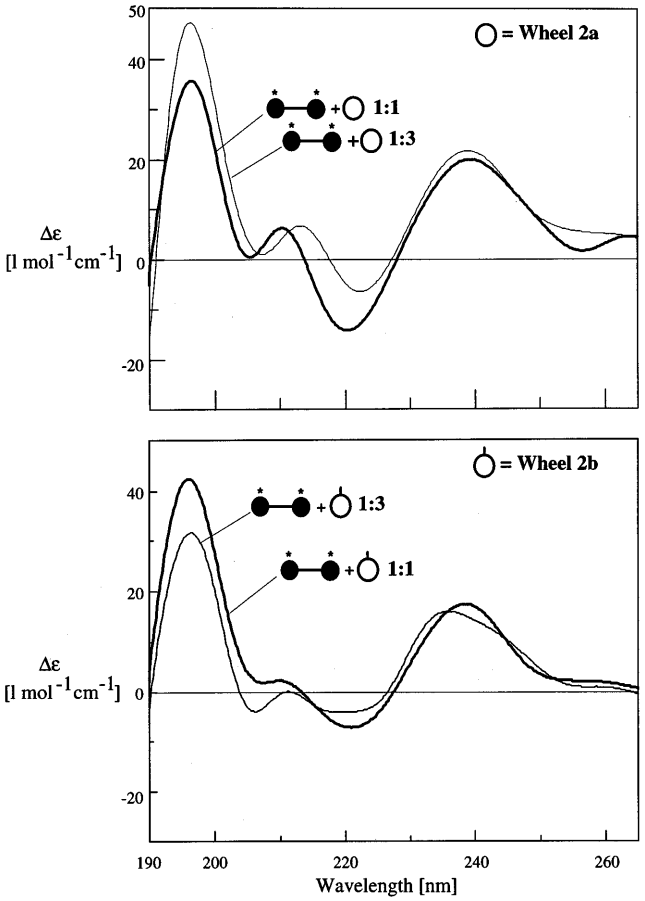


Figure 4. Circular dichroism spectra of the 1:1 and 1:3 mixtures of the chiral axle **7** with the macrocycles **2a** and **2b**, respectively [**2a** + **7**: c(**7**; 1:1) = $7.97 \cdot 10^{-4}$ mol l^{-1}, c(**7**; 1:3) = $1.26 \cdot 10^{-4}$ mol l^{-1}; **2b** + **7**: c(**7**; 1:1) = $5.21 \cdot 10^{-4}$ mol l^{-1}, c(**7**; 1:3) = $1.08 \cdot 10^{-4}$ mol l^{-1}]



lenged a comparison to the corresponding *inter*molecular interactions. We therefore measured the CD spectra of two mixtures of axle **7** and the macrocycles **2a** and **2b**, respectively.

As shown in Figure 4, the two equimolar mixtures of axle **7** and the wheels **2** show a pronounced Cotton effect at 210 nm. With regard to the molar ellipticities and position of the Cotton effects at 198 nm, the spectra are quite similar to that of the axle **7**. A threefold excess of the wheels leads to a small bathochromic shift of the new maxima, in comparison to the 1:1 mixture, of 2 nm (**2a**) and 1 nm (**2b**). Surprisingly, the intensity of the Cotton effect at 198 nm in the 3:1 mixture of the sulfonamide wheel **2b** and **7** ($\Delta\varepsilon$ = 32 l mol^{-1} cm^{-1}) is lower than that of the mixture of **2a** and **7** ($\Delta\varepsilon$ = 48 l mol^{-1} cm^{-1}). In the equimolar mixture this trend is reversed (**2a** + **7**: $\Delta\varepsilon$ = 36 l mol^{-1} cm^{-1}; **2b** + **7**: $\Delta\varepsilon$ = 43 l mol^{-1} cm^{-1}). The exchange of an amide by a sulfonamide moiety in the macrocycle **2b** consequently leads to modified intermolecular interactions. This could be due to the larger cavity formed by the sulfonamide macrocycle and to the SO_2NH group, enabling different conformations and hydrogen bonding.

The positions of the Cotton effects at 210 nm in the axle/wheel mixtures are similar to the wide shoulders in the spectra of the corresponding rotaxanes **6**. The larger absorption and the maximum at 238 nm may be caused by the mechanical bonds, which lead to more intense intramolecular interactions in the rotaxane. In any case, both macrocycles turn out to be *intra*- and *inter*molecular receptors for amides[14].

The UV spectra of rotaxanes **6a** and **6b** and of the axle **7** show the expected absorption maxima at the same wavelengths as seen in the CD spectra. The rotaxane bands are slightly more intense than the axle band. The measurement of the specific optical rotation at different wavelengths yielded smaller values for the two rotaxanes compared to the free axle, with **6b** exhibiting larger values than **6a** (Table 1).

Table 1. Optical rotation (α_{25} in $CHCl_3$) of the axle **7** (c = $1.19 \cdot 10^{-3}$ mol/l) and the rotaxanes **6a** (c = $8.96 \cdot 10^{-4}$ mol/l) and **6b** (c = $5.39 \cdot 10^{-3}$ mol/l) at different wavelengths

λ [nm]	α(axle **7**) [°]	α(**6a**) [°]	α(**6b**) [°]
589	+45	+13	+25
578	+47	+14	+27
546	+51	+16	+30
436	+108	+29	+57
365	+215	–	+111

When a small amount of NaOMe/MeOH is added to a solution of the rotaxanes **6** in $CHCl_3$, the wheel slips off immediately and quantitatively[3][15]. This process can easily be observed by thin layer chromatography.

Conclusions and Outlook

The use of protected glucose units as stopper components provides optically active rotaxanes. On account of their properties, both rotaxanes mentioned represent a very simple model compound for chiroselective "drug targeting". A mechanically linked macrocycle on an axle containing specific chiral information could be carried to a suitable receptor. Once in place, the rotaxane could be decomposed into its constituent fragments by reducing the stopper size or completely removing the stopper. For this to work it would be necessary to develop wheels with physiological activity while the corresponding rotaxane is inactive. Furthermore, the stopper must have a molecular recognition unit, which would enable the decomposition to take place in the receptor area only.

This work illustrates the importance of synthesizing different types of chiral rotaxanes in the future. Moreover, the study of steric and electronic effects and the chiral or chiroselective interactions between wheel and axle, both *intra*- and *inter*molecular, is of future interest. Due to the various possibilities of incorporating chirality into rotaxanes, e.g. the combination of euclidic and cycloenantiomeric chirality[6][9b][16] within one rotaxane molecule, such interactions can be studied in mechanically linked supramolecular structures.

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Experimental Section

General: Chemicals were purchased from Fluka and Aldrich. Chloroform, dichloromethane and ethyl acetate were distilled and dried over 4-Å molecular sieves before use. Thin layer chromatography was carried out on aluminium sheets precoated with silica gel 60 F_{254} (Merck 1.05554). The TLC plates were inspected by UV light (λ = 254 nm). Column chromatography was carried out on silica gel 60 (Merck 15101). Melting points were determined with a Kofler microscope heater (Reichert, Vienna) and are not corrected. Microanalyses were performed by the Microanalytical Department at the Kekulé-Institut für Organische Chemie und Biochemie der Universität Bonn. Fast atom bombardment mass spectra (FABMS) were obtained with a Kratos Concept 1H spectrometer (Kratos, Manchester, UK) and the matrix used was *m*-nitrobenzyl alcohol. MALDI-TOF spectra were recorded with a micromass TOF specE (Micromass, Manchester, UK) and the matrix used was 2,5-dihydroxybenzoic acid (2,5-DHB). Optical rotation was measured with a Perkin Elmer Polarimeter 341, and the CD/UV spectra with a J-720 spectropolarimeter (Jasco, Japan). The ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AM 400 [400 MHz (^{1}H)] and a Bruker AM 250 [62.9 MHz (^{13}C)]. Abreviations: ar.: aromatic; cy.: cyclohexylidene; aliph.: aliphatic.

Stopper [(4-Aminophenyl)-2,3,4,6-tetra-O-benzoyl-β-D-glucopyranoside] (**4**): 2.00 g of 4-nitrophenyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside[17] (2.8 mmol) was dissolved in 30 ml of ethyl acetate and 55 ml of ethanol and stirred for 2 h with 200 mg of Adams catalyst for hydrogenation. After filtration and removal of the solvent in vacuo, the amine was obtained: 1.80 g (48% yield), m.p. 96°C. $[\alpha]_D$ = 31°, R_f = 0.49 (CH_2Cl_2/CH_3OH, 98:2, v/v). – ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ = 3.25 (s, 2 H, NH_2), 4.19 (m, 1 H, 3-H), 4.45 (dd, ^3J = 6.2 Hz, ^3J = 12.1 Hz, 1 H, 2-H), 4.59 (dd, ^3J = 12.1 Hz, ^2J = 2.9 Hz, 1 H, 1-H), 5.15 (d, ^3J = 7.9 Hz, 1 H, 4-H), 5.59–5.72 (m, 2 H, 6-H), 5.89 (t, ^3J = 9.6 Hz, 1 H, 5-H), 6.38 (d, ^3J = 8.9 Hz, 1 H, ar. H), 6.76 (d, ^3J = 9.0 Hz, 1 H, ar. H), 7.25–7.6 (m, 12 H, ar. H), 7.8–8.15 (m, 8 H, ar. H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, 20°C): δ = 63.27 (CH_2), 69.76, 71.82, 72.43, 72.92, 101.24 (aliph. CH), 115.86, 119.27, 128.38, 128.45, 128.46, 128.50, 129.83, 129.86, 129.91, 133.23, 133.36, 133.59 (ar. CH), 128.70, 128.77, 129.20, 129.61, 142.61, 149.97 (C_q), 165.17, 165.31, 165.85, 166.12 (C=O). – MALDI-TOF-MS (2,5-DHB); *m/z*: 710.4 [M^+ + Na], 726.4 [M^+ + K]. – $C_{40}H_{33}NO_{10}$ (687.7): calcd. C 69.86, H 4.87, N 2.04; found C 69.52, H 4.98, N 1.86.

Rotaxane **6a**: To a solution of 900 mg of macrocycle **2a** (0.94 mmol) in 100 ml of dry dichloromethane were added simultaneously 687 mg of **3b** (1 mmol) with 0.2 ml of NEt_3 and 101 mg of isophthaloyl dichloride (**1**) (0.5 mmol), dissolved in 100 ml of dichloromethane at room temperature over a period of 1 h. Before removing the solvent, the mixture was stirred for 12 h. The residue was purified by column chromatography (SiO_2, dichloromethane/ethyl acetate, 10:1): 110 mg (9% yield), m.p. 210°C. R_f = 0.24. – ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ = 1.33 [s, 9 H, $C(CH_3)_3$], 1.49 (br., 8 H, cy-CH_2), 1.59 (br., 8 H, cy-CH_2), 1.87 (s, 12 H, ar-CH_3), 1.89 (s, 12 H, ar-CH_3), 2.25 (br., 8 H, Cy-CH_2), 4.30 (m, 2 H, 3-H), 4.45 (dd, ^3J = 6.3 Hz, ^3J = 12 Hz, 2 H, 2-H), 4.63 (dd, ^3J = 12 Hz, ^2J = 2.8 Hz, 2 H, 1-H), 5.33 (m, 2 H, 4-H), 5.6–5.8 (m, 4 H, 6-H), 5.95 (m, 2 H, 5-H), 6.70 (d, ^3J = 9 Hz, 2 H, ar. H), 6.92 (s, 4 H, ar. H), 6.96 (s, 4 H, ar. H), 7.3–7.6 (m, 29 H, ar. H), 7.75–8.05 (m, 19 H, ar. H), 8.07 (s, 1 H, ar. H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, 20°C): δ = 18.63, 31.29 (CH_3), 23.15, 26.53, 35.23, 63.13 (aliph. CH_2), 69.63, 71.96, 72.46, 72.89, 100.43 (aliph. CH), 117.77, 123.08, 124.49, 126.43, 128.29, 128.68, 128.75, 128.97, 129.49, 129.83, 129.96, 129.99, 130.39, 130.83, 133.53, 133.69, 133.86 (ar. CH), 35.36, 45.46, 125.60, 127.73, 128.72, 129.39, 129.93, 131.46, 131.50, 134.24, 134.97, 135.33, 135.63, 148.47, 148.58, 153.28, 153.98 (C_q), 165.43, 165.51, 166.10, 166.46, 166.62, 166.78, 166.86 (C=O). – MALDI-TOF-MS (2,5-DHB); *m/z*: 2456.5 [M^+], 2488.4 [M^+ + Na]. – $C_{152}H_{140}N_6O_{26}$ (2456.81): calcd. C 70.90, H 5.75, N 3.26; found C 71.09, H 5.82, N 2.98.

Rotaxane **6b**: The synthesis was carried out in an analogous way to **6a** with 938 mg of the macrocycle **2b** (0.94 mmol): 128 mg (10% yield), m.p. 199°C. R_f = 0.21. – ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ = 1.39 [s, 9 H, $C(CH_3)_3$], 1.4–1.7 (br., 12 H, cy-CH_2), 1.57 (s, 6 H, CH_3), 1.73 (s, 6 H, CH_3), 1.88 (s, 6 H, CH_3), 2.05 (s, 6 H, CH_3), 2.22 (br., 4 H, cy-CH_2), 2.30 (br., 4 H, cy-CH_2), 4.30 (m, 2 H, 3-H), 4.50 (m, 2 H, 2-H), 4.68 (m, 2 H, 1-H), 5.36 (t, ^3J = 8.4 Hz, 2 H, 4-H), 5.65– 5.85 (m, 4 H, 6-H), 5.98 (dt, ^3J = 9.4 Hz, ^3J = 4.3 Hz, 2 H, 5-H), 6.73 (m, 2 H, ar. H), 6.80 (s, 2 H, ar. H), 6.83 (s, 2 H, ar. H), 6.91 (s, 2 H, ar. H), 7.09 (s, 2 H, ar. H), 7.25–7.6 (m, 29 H, ar. H), 7.70–8.05 (m, 19 H, ar. H), 8.11 (d, J = 5.6 Hz, 1 H, ar. H), 8.21 (s, 1 H, amide-H), 8.34 (s, 1 H, amide-H), 8.49 (s, 1 H, amide-H), 8.55 (s, 1 H, amide-H), 8.89 (s, 1 H, amide-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, 20°C): δ = 18.74, 18.79, 19.16, 19.59 (CH_3), 23.26, 23.34, 26.57, 26.73, 35.63, 37.13 (cy-CH_2), 31.62 [$C(CH_3)_3$], 35.36 [$C(CH_3)_3$], 45.38, 45.43 (cy-C), 63.13 (CH_2), 69.74, 72.04, 72.78, 72.98, 100.43 (aliph. CH), 117.90, 123.19, 123.52, 126.15, 128.71, 128.77, 128.80, 128.95, 128.99, 129.30, 129.61, 133.07, 130.14, 130.20, 130.59, 133.61, 133.73, 133.87 (ar. CH) 125.61, 127.43, 128.86, 129.24, 129.61, 130.04,

131.69, 132.33, 134.01, 134.82, 135.55, 138.01, 144.01, 149.50, 151.01, 153.57, 154.26, (ar. C_q), 165.15, 165.29, 165.48, 165.51, 165.54, 166.03, 166.10, 166.42, 166.45 (C=O). − MALDI-TOF-MS (2,5-DHB); *m/z*: 2502.25 [M^+], 2524.07 [M^+ + Na]. − FAB-MS; *m/z*: 2502.8 [M^+], 997.5 [M + H (cycle)].

Axle **7**: A solution of 300 mg of the amine **3b** (0.44 mmol) and 0.1 ml of NEt_3 in 10 ml of dry dichloromethane was added to 44 mg of isophthaloyl dichloride (0.44 mmol), dissolved in 20 ml of dichloromethane at room temperature over a period of 30 min. After stirring for 30 min, the solvent was removed. The residue was dissolved in 50 ml of chloroform and washed twice with water. The organic layer was dried with Na_2SO_4 and then filtered. The solvent was distilled in vacuo: 105 mg (32% yield), m.p. 145°C, R_f = 0.29 (CH_2Cl_2/ethyl acetate, 10:1, v/v). − ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ = 4.30 (m, 2 H, 3-H), 4.48 (dd, ^3J = 6.3 Hz, ^3J = 12 Hz, 2 H, 2-H), 4.65 (dd, ^3J = 12 Hz, ^4J = 2.8 Hz, 2 H, 1-H), 5.32 (m, 2 H, 4-H), 5.6−5.8 (m, 4 H, 6-H), 5.95 (m, 2 H, 5-H), 6.9−7.0 (m, 4 H, ar. H), 7.24−7.54 (m, 27 H, ar. H), 7.8−8.1 (m, 17 H, ar. H), 8.2−8.35 (m, 4 H, ar. H). − ^{13}C NMR (62.9 MHz, $CDCl_3$, 20°C): δ = 63.47 (CH_2), 69.89, 72.07, 72.88, 73.10, 100.43 (aliph. CH), 118.28, 122.24, 125.96, 129.62, 130.13, 130.73, 133.63, 133.67, 133.78, 133.93 (ar. CH), 129.34, 129.62, 135.64, 154.18 (C_q), 165.21, 165.53, 165.61, 166.12, 166.47 (C=O). − MALDI-TOF-MS (2,5-DHB); *m/z*: 1527.1 [M^+ + Na]. − $C_{88}H_{68}N_2O_{22}$ (1505.51): calcd. C 70.21, H 4.55, N 1.86; found C 69.82, H 4.73, N 1.71.

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