Iterative Synthesis of [n]Rotaxanes

Amir Hossain Parham, Roland Schmieder, Fritz Vögtle*

Kekulé-Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard-Domagk-Strasse 1, D-53121 Bonn (Germany)
Fax (+49)228-735662; E-mail: voegtle@uni-bonn.de

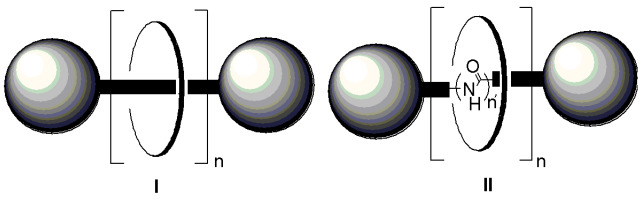
Received 6 September 1999

Abstract: An iterative pathway for the synthesis of higher order [n]rotaxanes is described. Stepwise reactions with repeatedly used building blocks lead to rod-shaped axle parts which form threading hydrogen bond interactions with macrocycles. A followed stoppering enables several molecular wheels to be fixed onto an axle.

Keywords: macrocycle, mechanical bonding, molecular recognition, rotaxane, supramolecular chemistry

The synthesis of mechanically interlocked supramolecular compounds such as rotaxanes can be performed by threading macrocycles onto molecular axles.[1] To avoid disassembly of the molecular components, the axle must have bulky end-groups at both sides, that prevent deslipping of the wheel. The assembly is usually based on a template assistance like the preorganization of building blocks by metal coordination, hydrophobic and donor-acceptor interactions or hydrogen bonding with neutral, cationic or anionic molecules.[2]

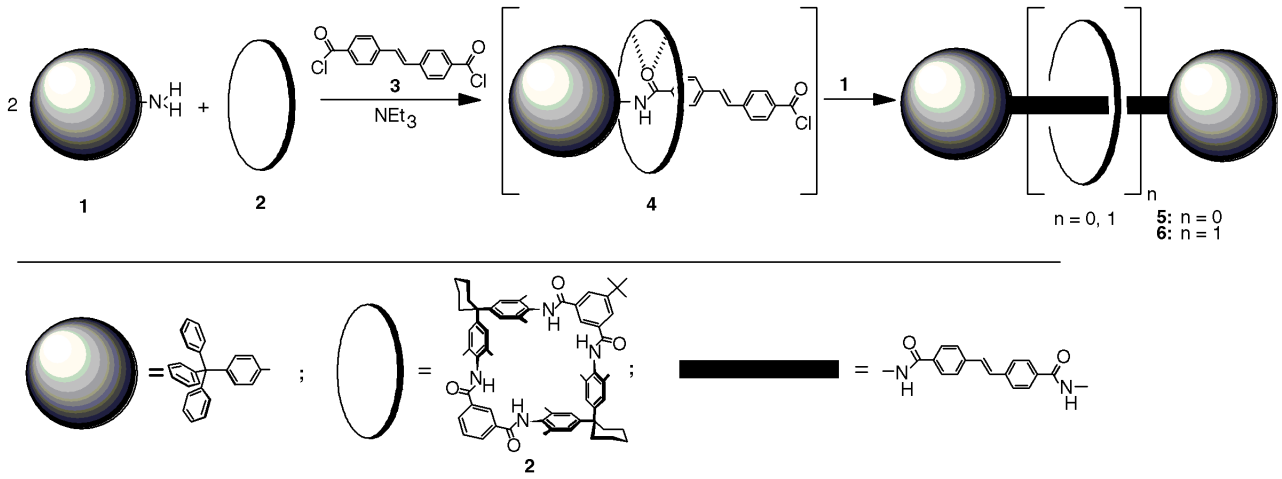
For investigations of basic questions about molecular recognition and interactions between several wheels on an axle it would be desirable to have preparative synthetic access to higher order [n]rotaxanes („[n]„ results from the quantity of assembled molecules: n-1 wheels, 1 axle). Furthermore, [n]rotaxanes, containing wheels with translational and rotational freedom of movement on the axle may open the way for the future preparation of molecular devices and machines.[3] In recent years some [3]rotaxanes of type **I** (n = 2) (Scheme 1), have been realized.[4] Even [4]- and [5]rotaxanes (n = 3, 4) were accessible.[5] Higher order representatives are of the polydisperse type.[6]



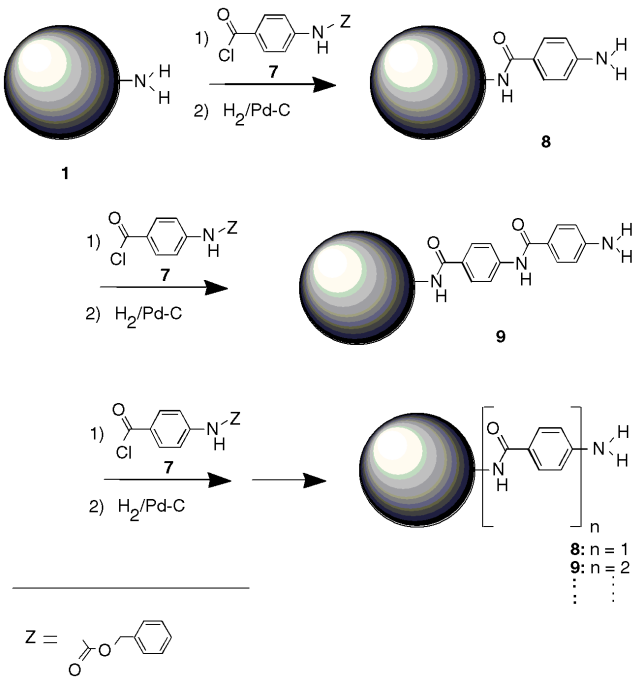
Scheme 1

Rotaxanes of the amide type **II** with more than two threaded macrocyclic wheels have not been described yet.[4h] We report here a methodology for building up such monodisperse higher order rotaxanes based advantageously on an iterative reaction sequence.

It has been shown that tetralactam macrocycles of the type **2** can act as hosts for the inclusion of guest compounds containing secondary amide groups.[7] Thus, the reaction of stopper amine **1** with the diacid dichloride **3** in the presence of macrocycle **2** should result in a semirotaxane **4** which leads to a [2]rotaxane **6** upon reaction with another blocking group **1**. In fact, we isolated [2]rotaxane **6** in 18% yield along with 20% of the free axle **5** (Scheme 2).[8]



Scheme 2



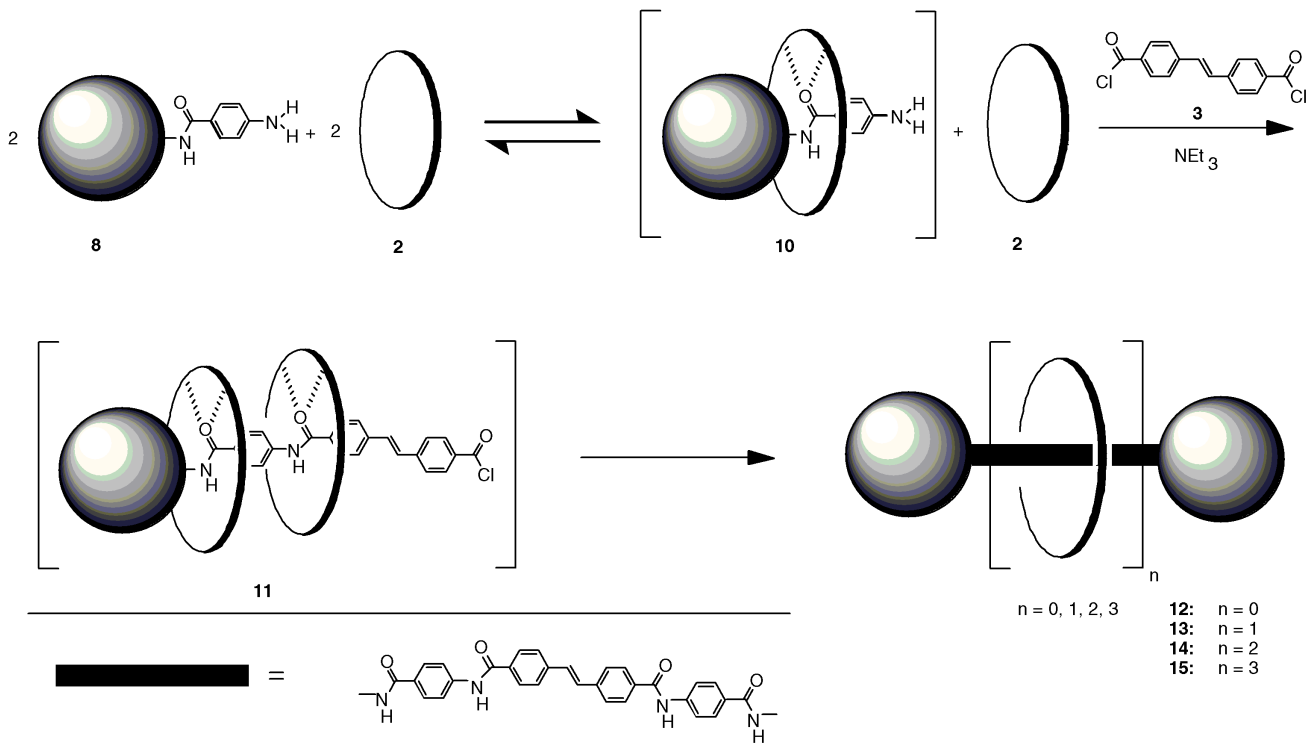
Scheme 3

It should be noted that no [3]rotaxane was formed here. The second amide group is generated with the second bulky stopper and therefore no more macrocycle **2** can be threaded.

To build up higher order rotaxanes in this way, semiaxles have to be synthesized that contain more amide groups, one for each wheel to be bound and then threaded. By the reaction of the stopperamine **1** with the Boc-protected *p*-aminobenzoyl chloride **7** and subsequent deprotection of the carbonamide group, the elongated semiaxle amide amine **8** is obtained (Scheme 3). Repetition of the same reaction sequence led to the semiaxle diamide **9**.[9] Further iterative synthetic steps with **7** should lead to even higher order tailor made stopper amines (beyond n = 2) that would allow to obtain rotaxanes with a predetermined maximum number of macrocycles.

Compounds **8** and **9** are semiaxles that contain one or two amide groups and are thus enabled to complex one or two tetralactams **2**, respectively. The terminal amino group may then serve as reactive site to be connected with the diacid dichloride **3** used as axle centre piece. As a matter of fact, [2]- to [4]rotaxanes **13**-**15** have been isolated along with the free axle **12**. At first, the stopper amine **8** can interact with one wheel to give **10**. Upon the reaction with **3** another amide group is formed, which can fix a second wheel under formation of the semi[3]rotaxane **11**. This finally reacts with another semirotaxane **10** to yield [4]rotaxane **15** (Scheme 4).

A decomplexation equilibrium of the semiaxle and the macrocyclic lactam is responsible for the formation of the mixture of all possible [n]rotaxanes **13**-**15** as well as of the free axle **12**.[8] Compounds **12**-**15** were unequivocally characterized by ^{1}H, ^{13}C NMR and mass spectroscopy. The yields (Table) decrease with the increasing number of



Scheme 4

wheels which is also caused by the difficulty of the chromatographical separation of each rotaxane on account of very similar retention times. Additionally, the recognition sites on the axle face close together and thus some macrocycles could have minor access to interact.

Table Yields of [n]rotaxanes and free axles.

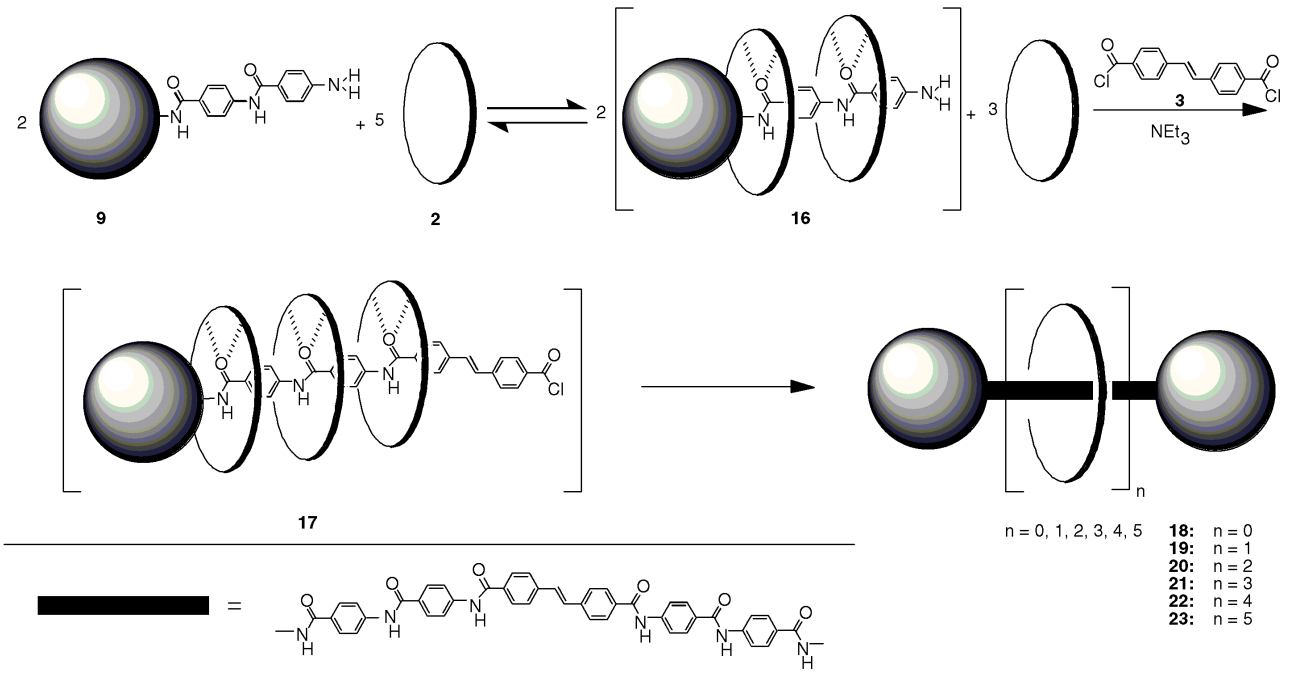
Compound	Numbers of wheels	Yield (%)
5	0	20
6	1	18
12	0	15
13	1	8
14	2	6
15	3	4
18	0	15
19	1	3*
20	2	2*
21	3	<1*
22	4	<1*
23	5	<1*

*The total yield of the purified mixture of [n]rotaxanes **19**-**23** before separation is estimated to be around 15%.

The reaction of compound **9** as the iteratively even more elongated stopper amine with **3** in the presence of the wheel **2** leads to the [2]- to [6]rotaxanes **19**-**23** and the corresponding axle **18**.[8] The yields are also listed in the Table. The semiaxle **9** is able to thread two wheels. Additionally, the reaction with the diacid dichloride **3** enables to bind one more wheel on the axle on account of the additional amide group. The semi[4]rotaxane **17** can now react with the semi[3]rotaxane **16** that leads even to the formation of the [6]rotaxane **23** (Scheme 5) but in a very small amount.

Rotaxane **21**, **22**, **23** are isolated in yields of 0.8 mg 0.6 mg, and 0.4 mg, respectively and therefore only characterized by mass spectrometry. As mentioned above, the sterical difficulties at the recognition sites and the problems in the chromatographical separation of the rotaxanes decrease the yields with increasing number of wheels. By improving the separation and enlarging the distance between the recognition sites this iterative synthetic method will allow to obtain a variety of higher order [n]rotaxanes. The maximum number of molecular wheels in the corresponding rotaxanes is limited by the number of amide bonds within the molecular axle. Using this type of threading synthesis an axle containing n carbon amide groups can lead to a rotaxane with a maximum n-1 wheels because the last formation of an amide group leaves no possibility for threading another wheel.

The preparative scale synthesis of [n]rotaxanes opens up the way for complex supramolecular nano-scale architectures with coexistence of mechanical and covalent elements.[10] For example, the possibility of linking two wheels covalently together in a higher order rotaxane opens up interesting aspects about the translational and rotational movement of the wheels on the axle. Furthermore, interesting stereochemical features can be built up by using oriented wheels to give cycloenantiomerism and -diastereomerism.[11]



Scheme 5

Acknowledgement

We thank Dr. Christian Seel for help and discussion and the Deutsche Forschungsgemeinschaft for financial support (Vo145/47-2).

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(8) **General Synthesis of rotaxanes.** 0.4 mmol *tetralactam **2,** 0.8 mmol 4-tritylaniline **1** or semiaxle **8** or **9,** respectively, and 12 drops triethylamine are dissolved in 100 mL CH_2Cl_2 and cooled to 0 °C. A solution of 0.4 mmol 4,4´-stilbenedicarboxylic acid (**3**) in 100 mL CH_2Cl_2 is added dropwise during 4 h. After stirring for 2 h more the solvent is removed in vacuo, and the crude product is purified by column chromatography [SiO_2; 63-100 µm, eluent: rotaxane **6**, axle **5** dichloromethane : ethyl acetate, 25:1; rotaxane **13-15**, axle **12** THF: petroleum ether (40-60), 6:4; rotaxane **19-23**, axle **18** dichloro-methane : ethyl acetate 4:1].
*__Rotaxane 13-15__:1.2 mmol tetralactam, __Rotaxane 19-23__:2.0 mmol tetralactam.

(9) **Synthesis of semiaxles 8 and 9.** To a solution of 8 drops triethylamine and 379 mg (1.13 mmol) 4-tritylaniline (**1**), respectively, in 50 mL CH_2Cl_2 is added dropwise during 2 h a solution of 360 mg (1.13 mmol) *N*-benzyloxycarbonyl-4-aminobenzoylchloride in 50 mL CH_2Cl_2. After further 2 h the solvent is evaporated. The mixture and 10 mg Pd/C in 40 ml ethanol are shaken under 3 bar H_2 atmosphere for 4 h. After filtration the solvent is evaporated and the residue purified by column chromatography [SiO_2, CH_2Cl_2].

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Article Identifier:
1437-2096,E;1999,0,12,1887,1890,ftx,en;G22399ST.pdf