Catenanes and Rotaxanes of the Amide Type

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Received January 19, 1996

Introduction

Catenanes and rotaxanes (Figure 1), representing intertwined polymembered rings and interlocked species, are fascinating because they are tied together in an unusual way.[1] They still represent a severe preparative challenge to the synthetic organic chemist: bringing a molecular thread into the eye of a nanoscale needle requires diligent efforts and knowledge of the effects that rule the molecular level.

For a long time catenanes and rotaxanes were only accessible in low yields by statistical or multistep syntheses.[2] Now, however, certain types of these mechanically connected molecules including molecular knots can be produced in preparative amounts[3−10] using noncovalent supramolecular templating effects.[11]

Nature, however, still outruns the ability of today's chemists by far. Proteins forming molecular knots are well known[12] (cf. protein folding[13]). Enzymes transfer DNA rings into intertwined assemblies of intriging complexity. The kinetoplast DNA (kDNA) of trypanosomatid mitochondria for example consists of thousands of DNA mini- and macrocycles topologically interlocked into a giant network compacted by catenation.[14]

By preparing similar yet relatively simple species, e.g., catenanes and rotaxanes, the laboratory chemist makes a first step toward uncovering how nature creates these elegant constructions and what tools it is using to do so.

Amide-Based Catenanes

During work since 1983 on the synthesis of various basket-shaped host molecules,[15] we unexpectedly found an extremely simple one-step catenane synthesis in 1992.[16] Catenane **3** could be prepared from the simple components **1** and **2** in one step (Scheme 1). As byproducts, the dimethoxy-substituted macromonocycle **4** was isolated along with the 72-membered "tetramer" **5**, an isomer of the catenane having the same mass but different chromatographic behavior.[16]

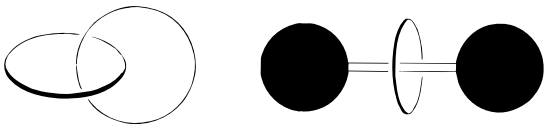

Figure 1. Symbolic formula of a catenane (left) and a rotaxane (right).

While we were waiting for an X-ray analysis of this catenane, the unsubstituted representative was published independently by Hunter et al.[17] on the basis of NMR studies. This prompted us to submit our results a few days later.[16] In 1995 a benzylamide catenane with smaller rings was introduced by Leigh et al.[18] It is reasonable to assume for all three approaches that "orthogonalization", the perpendicular preorganization of the catenane building blocks, is based on three templating effects: (a) steric complementarity, (b) hydrogen bonding between carbonyl oxygen atoms and amide protons, and (c) $\pi-\pi$ interactions between the benzene rings of host and guest subunits. But which are the intermediate intertwining fragments?

Fritz Vögtle, born in 1939 in Ehingen/Donau, South Germany, studied chemistry in Freiburg as well as chemistry and medicine in Heidelberg. There he received his Ph.D. for research with H. A. Staab on the valence isomerization of double Schiff bases. After his training on steric interactions inside cyclic compounds, he was H2/H3 professor in Würzburg from 1969 to 1975. He then accepted a position as full professor and director of the Institut für Organische Chemie und Biochemie in Bonn. Awards obtained include a "literature prize" for his book *Supramolekulare Chemie* (translated in English, Japanese, and Chinese) and the Israeli Lise Meitner-Alexander von Humboldt-Prize. He is interested in the field of supramolecular chemistry and molecular recognition, and after working on topics concerning crown ethers, podands, and siderophores, he has concentrated on compounds with large intramolecular cavities, ligands for supramolecular photochemistry, molecular tweezers, and belt- and tube-shaped molecules. His further areas of research are strained and chiral/helical molecules (cyclophanes), compounds with appealing architectures, and, last but not least, catenanes and rotaxanes.

Thomas Dünnwald was born in Hürth, Germany, in 1968. He obtained his diplom degree in chemistry from Bonn University in 1994 with a thesis on enzyme technology. He is currently working toward his doctoral degree in the research group of Fritz Vögtle in the field of higher [*n*]rotaxanes.

Thomas Schmidt was born in Zülpich, Germany, in 1969. He has been studying chemistry at Bonn University since 1989 and received the diplom degree in 1994. His doctoral research in Fritz Vögtle's group focuses on supramolecular chemistry, particularly on the formation of catenanes and rotaxanes.

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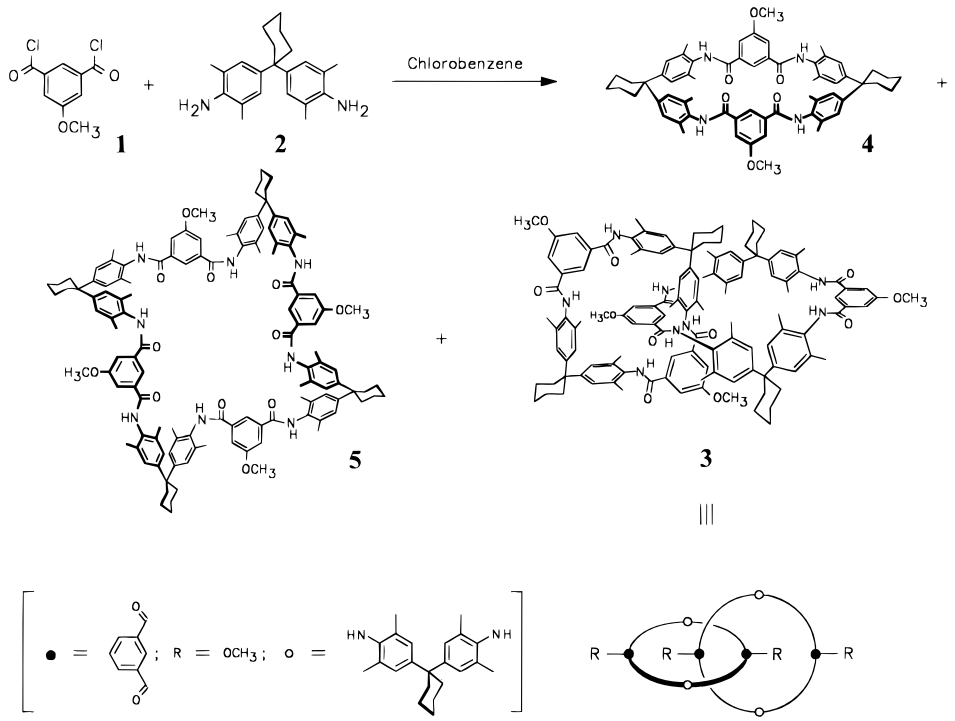
Scheme 1. One-Step Synthesis of the Amide-Based Catenane 3



The selective formation (see Figure 2) of the isomeric disubstituted catenanes **6**−**8** and of the monosubstituted catenane **9** allowed conclusions concerning their mechanism of formation.[19] The synthetic strategy which leads to the monomethoxy-substituted catenane **9** made it possible, for the first time, to obtain lactam catenanes with two different interlocking macrocycles.

The thermally stable isomeric disubstituted [2]-catenanes **6**−**8** were synthesized by alternative routes (Scheme 2). The isomers **6** and **7** were prepared according to route A in which the methoxy-substituted diamine **12** was reacted with isophthaloyl dichloride (**11**). The resulting mixture contained the substituted macromonocycle **14** (cf. Scheme 4) and the corresponding dimethoxy-substituted tetramer (cf. the tetramethoxy-substituted tetramer **5**) besides the isomeric dimethoxy catenanes **6** and **7**. These translational isomers were separated by column chromatography and show characteristic differences in their NMR spectra.

In an attempt to synthesize the third dimethoxy-substituted catenane isomer **8**, we performed the reaction using starting materials with a reversed substitution pattern, i.e., 5-methoxyisophthaloyl dichloride (**1**) and the unsubstituted diamine **13** (route B). Besides

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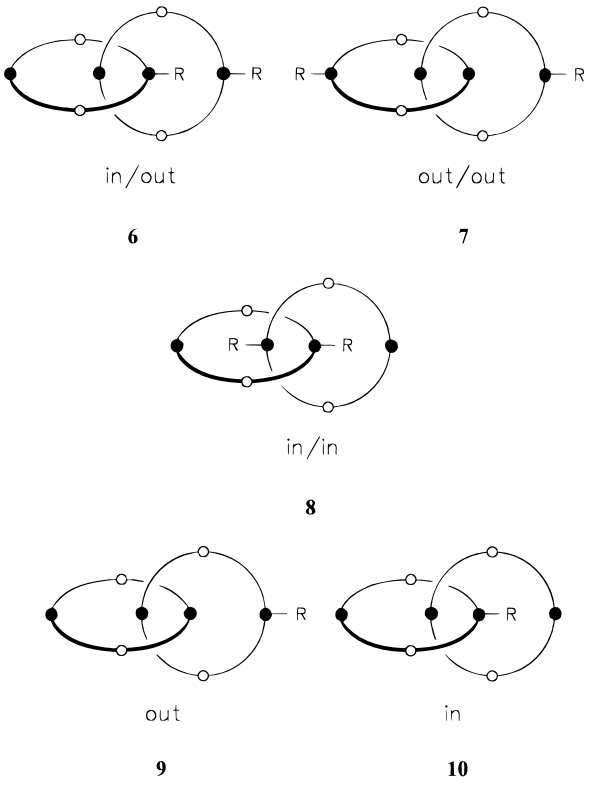

Figure 2. The three possible isomeric disubstituted catenanes **6**−**8** and the two isomeric monosubstituted catenanes **9** and **10**.

the analogous macromonocycles, the catenane isomers **6** and **8** were found exclusively.

The route-dependent, selective formation of the stable isomers **7** and **8** allows conclusions to be drawn about the mechanism of ring interlocking. We assume that the supramolecular template effect, which is responsible for catenation, results from the respective diacid dichlorides **1** and **11** lodging as guests inside the cavity of the host, the intermediate macromonocycle **14**, in such a way that the *m*-phenylene ring of the guest is oriented orthogonally to the ring plane of the host (Scheme 3). However, we do not exclude the possibility that the isophthaloyl dichloride **1** or **11** already forms one amide bond with the corresponding diamine **12** or **13** before lodging inside the host. There are two possible orientations (**I**, **II** and **III**, **IV**, respectively) for each diacid dichloride guest **1** and **11**. Routes A and B thus lead to selective formation of isomers **7** and **8**, respectively, in addition to **6**.

This mechanism provides a qualitative explanation for the significantly different yields of the catenanes obtained in routes A (**6**, 17%; **7**, 23%) and B (**6**, 2.7%; **8**, 1.4%): in the case of route B, the methoxy substituent on the diacid dichloride might cause steric hindrance in the host/guest complexes. Catenanes **6** and **8** in route B should thus be formed in lower yields than **6** and **7** in route A.

No interconversion or equilibrium of the diastereoisomeric catenanes **6**−**8** could be observed even at high temperature (300 °C). The translation (circumrotation) of the rings is hindered by the large cyclohexylidene moieties. A translational barrier built up by the methoxybenzene moieties would lead to enantiomers, which have not yet been found.

To provide further evidence for the hypothesis that the reaction proceeds *via* an intermediate monocycle of type **14**, we carried out a synthesis following route C (Scheme 4). Building blocks **11** and **13** were mixed in the presence of macrocycle **14** obtained as a byproduct in routes A and B. Of the two possible monomethoxy-substituted isomers **9** and **10**, only **9** was formed. The combination of the three reaction components **11**, **13**, and **14** to form a single product is consistent with our proposed orthogonalization and intertwining mechanism. Other mechanisms, in particular the interlocking of two open-chain fragments such as **11** with **12** or **12** with itself, do not appear to be significant.

An advantage of route C lies in the fact that the catenane **9** formed from the macrocycle **14** can be identified unambiguously from the molecular peak in the mass spectrum of the crude product, because the isomeric macromonocycle (identical molecular mass) cannot be formed in route C. Moreover, this intertwining mechanism of an open-chain isophthalic guest through a "dimer" type macromonocycle gives definite chemical proof of the catenane structure, even if X-ray analyses were not possible at that time because of crystal quality.

In order to gain further insight into the catenane formation, we were interested in the consequences for the template mechanism arising from replacement of the *m*-phenylene subunits by different units. Therefore, we carried out the synthesis D shown in Scheme 5 by reaction of the diamino-functionalized diamide **13** with the dichloride of 2,5-furandicarboxylic acid (**15**) at high dilution. Here no catenanes could be detected, but the macromonocycle **16** was isolated in 15% yield.

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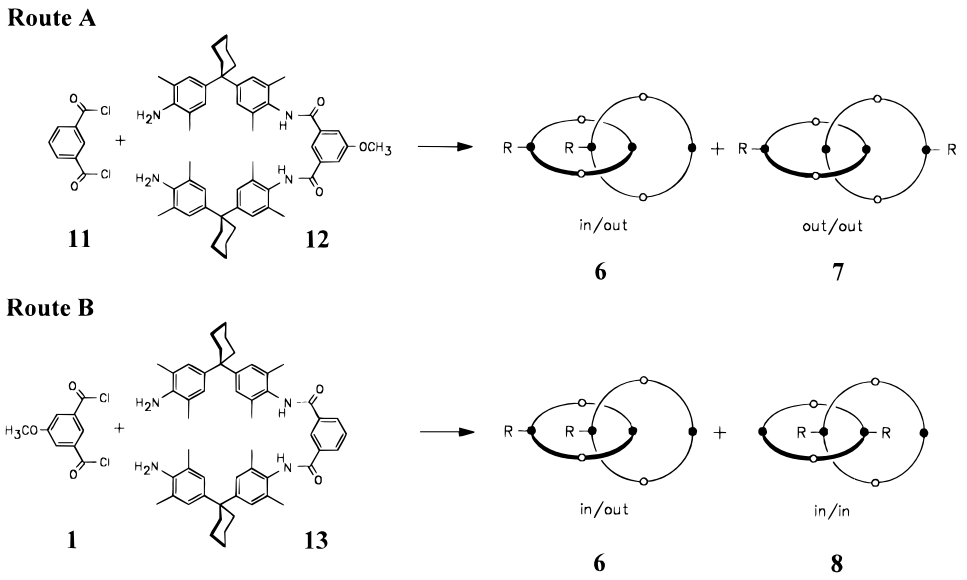
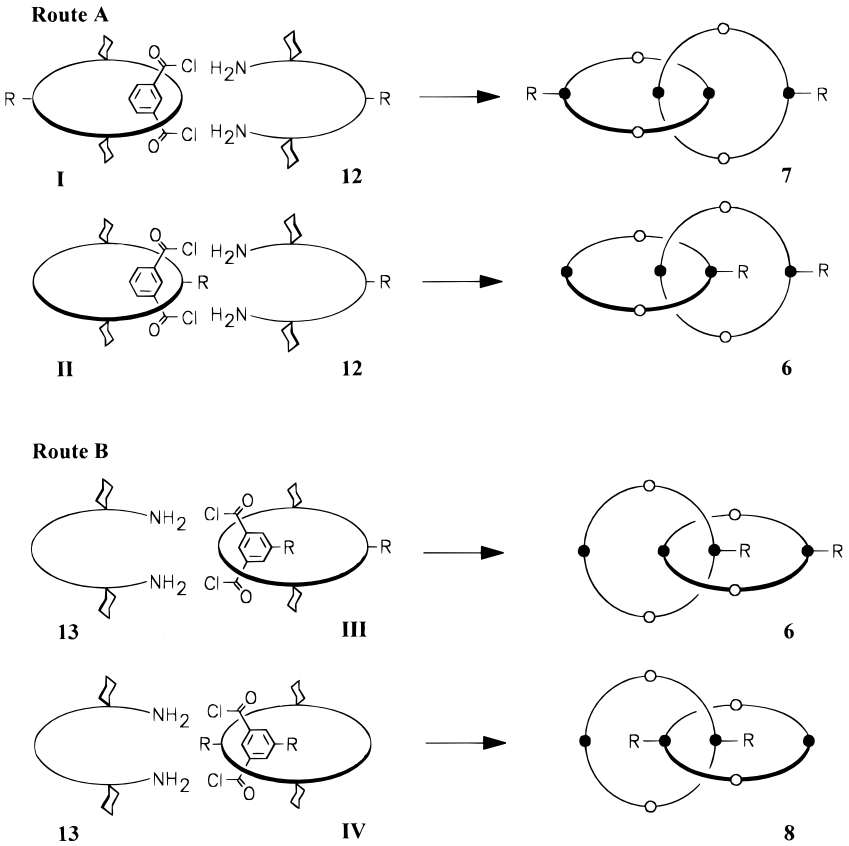
Scheme 2[a]



[a] Route A leads to a different set of dimethoxy-substituted catenanes (**6**, **7**) than route B (**6**, **8**).

Scheme 3[a]



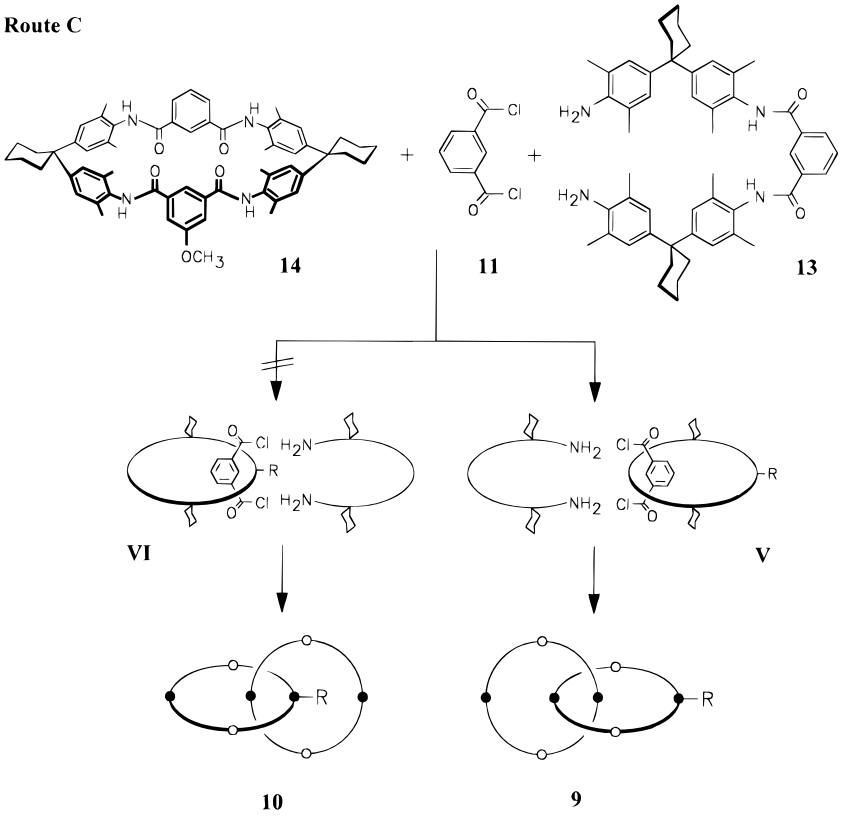
[a] The proposed template and orthogonalization mechanism (cf. **I**–**IV**) provides an explanation for the formation of different catenane isomers (**6**, **7** and **6**, **8**) in routes A and B (cf. Scheme 2).

We repeated the reaction with a "reversed pattern" (route E) by reaction of the diamide **17** with isophthaloyl dichloride (**11**).[20] We again obtained **16** (4% yield); however, in addition the catenane isomers **18** and **19** were also produced in 20% and 8% yields, respectively. Whereas in both syntheses D and E the same macrocycle **16** is formed, only in the case of path E does the isophthaloyl dichloride (**11**), after nestling inside it, lead to catenane formation. It is remarkable that the analogous nestling of 2,5-furandicarbonyl dichloride (**15**) (or its open-chain amide derivative) and its subsequent interlocking macrocyclization in the course of path D does not seem to occur to a comparable extent.

Of the three possible difuranocatenane isomers resulting from the hindered circumrotation of the catenane rings, we only observed the formation of **18** (*out/out*) and **19** (*in/out*), in agreement with our proposed template mechanism.

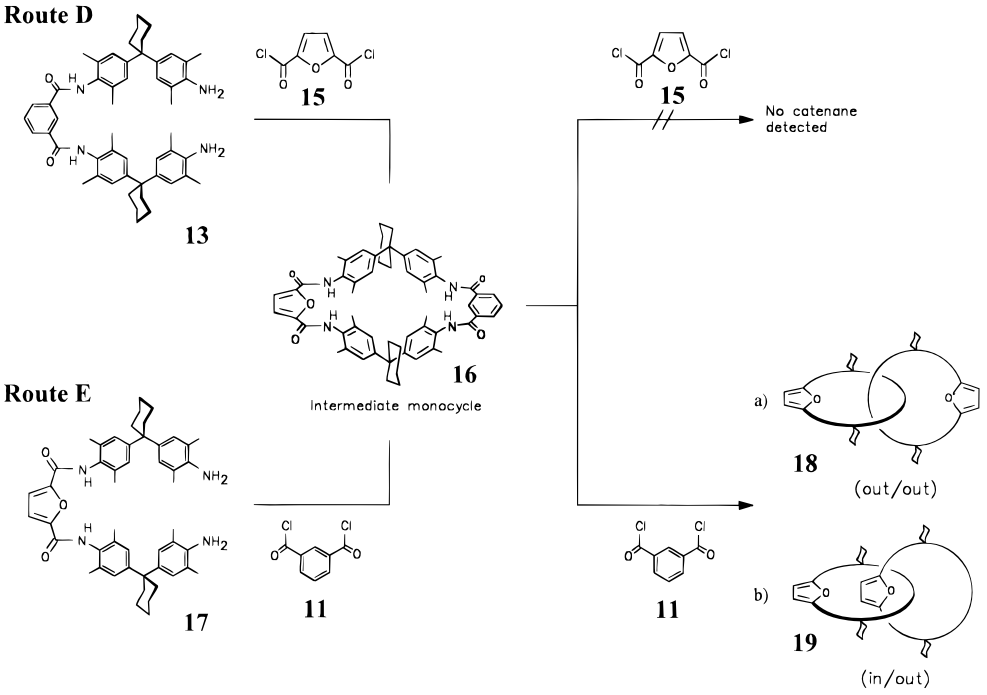
(20) Ottens-Hildebrandt, S.; Nieger, M.; Rissanen, K.; Rouvinen, J.; Meier, S.; Harder, G.; Vögtle, F. *J. Chem. Soc., Chem. Commun.* **1995**, 777.

Scheme 4[a]



[a] The "catenation" of the macrocycle **14** with **11** and **13** leads to the formation only of the catenane isomer **9**. The guest diacid dichloride **11** and the host **14** are locked in an orthogonal arrangement (**V**). The functional groups are fixed and thus preorganized for reaction with the diamine **13**.

Scheme 5. Formation of the Furanocatenane Isomers 18 and 19



The X-ray crystal structure of **18** was solved (Figure 3), the first in this octaamide series.[20] In the crystal of this *out/out* isomer, both 34-membered and structurally identical catenane rings which are composed of rather rigid building blocks show the same conformation and are connected by numerous intra- and intermolecular hydrogen bonds.

The X-ray crystal structure of the *in/out* isomer **19** was also clarified in the meantime and shows similar *exo/endo* conformations and hydrogen-bonding patterns.[21] In Figure 3 the two isomers **18** and **19** are compared.

(21) Vögtle, F.; Ottens-Hildebrandt, S.; Nieger, M.; Schmidt, T. Unpublished work.

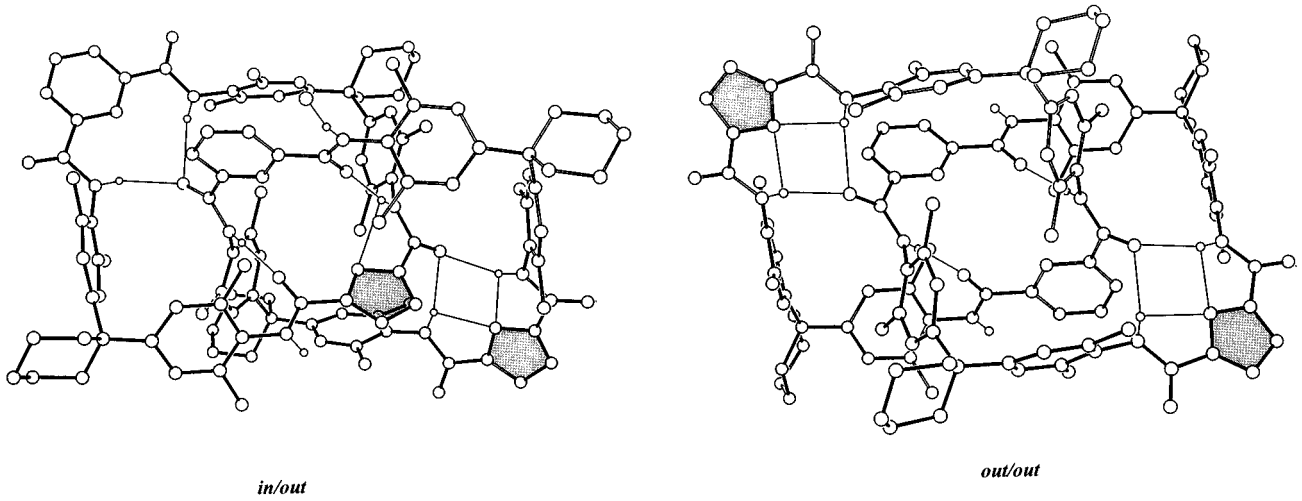
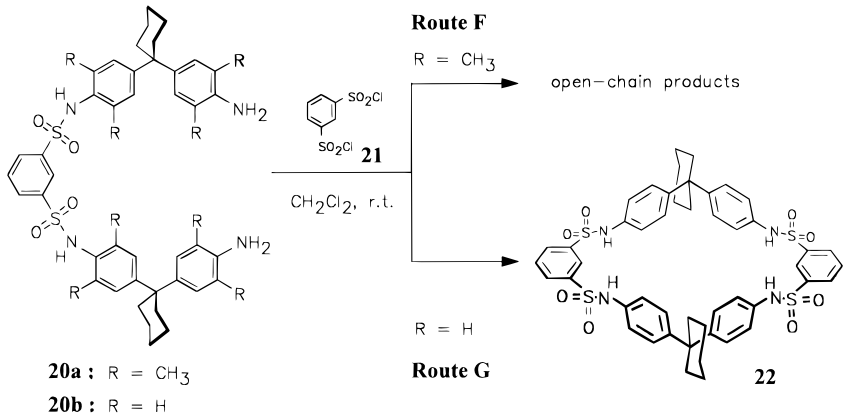


Figure 3. X-ray crystal structures of **19** (left) and **18** (right).

Scheme 6[a]



[a] Route F: No cyclic products were obtained. The formation of SO_2−NH bonds is apparently sterically hindered by the methyl substituent in the macrocyclization step of **20a** and **21**. Route G: Conversion of the corresponding non-methylated compound **20b** with **21** gives macromonocycle **22**. Catenanes, though, could not be detected.

Hunter et al. reported the X-ray crystal structure of the unsubstituted form of catenane **3**.[22] It shows features similar to those of the furanocatenanes **18** and **19**. The third X-ray analysis of an amide catenane was achieved by Leigh et al. for a catenane with a lower ring member number.[18]

Sulfonamide-Based Catenanes

The synthesis of topologically chiral catenanes of type **25** bearing sulfonamide units allowed further conclusions as to the mechanism of the intertwining process.[23] C═O···H−N hydrogen bonds have been shown to exist in catenanes, and they are probably of importance in the templating effect, too. Thus, we were interested in examining whether the carbonamide units could be replaced by sulfonamide units. Since the steric, electronic, and hydrogen-bonding donor/acceptor properties of sulfonamides differ from those of carbonamides, such an exchange should effect molecular recognition and the templating effect.[24] However, carrying out synthesis F (Scheme 6) under this aspect, we obtained neither catenanes nor monocycles but only open-chain condensation products. Apparently the formation of SO_2−NHR bonds is sterically hindered in the macrocyclization step by the methyl substituents in the *ortho*-position of diamine **20a**. In contrast, the corresponding conversion G with the nonsubstituted diamine **20b** at least gave the tetrasultam **22**. The latter, however, seems not to be a suitable template for the threading procedure in the next step, as no subsequent catenane formation occurs.

We then decreased the number of sulfonamide groups that seemed to disturb the catenane formation, by reaction of the cyclization precursor **23** with only one sulfonamide group, with diacid dichloride **1** under dilution conditions (route H, Scheme 7). Two products could be isolated after workup by column chromatography: macrocycle **24** and the *in/out* catenane isomer **25**.[23]

According to the proposed mechanism of the catenane formation (*vide supra*), macromonocycle **24** should be formed in the first reaction steps. The diacid dichloride **1** (or the corresponding monoamide of **23** and **1**) can then nestle down in the macrocycle in two possible orientations. Finally, the reaction with diamine **23** followed by ring closure of the host/guest complex could lead to the formation of the catenane isomer **25** or **26**, respectively, depending on the pathway (Figure 4). Remarkably, of two possible isomers **25** and **26** only the *in/out* species **25** was

(22) Adams, H.; Carver, F. J.; Hunter, C. A. *J. Chem. Soc., Chem. Commun.* **1995**, 809.
(23) Ottens-Hildebrandt, S.; Schmidt, T.; Harren, J.; Vögtle, F. *Liebigs Ann. Chem.* **1995**, 1855.
(24) König, B.; Möller, O.; Jones, P. G.; Ahrends, B. *Liebigs Ann. Chem.* **1995**, 1575.

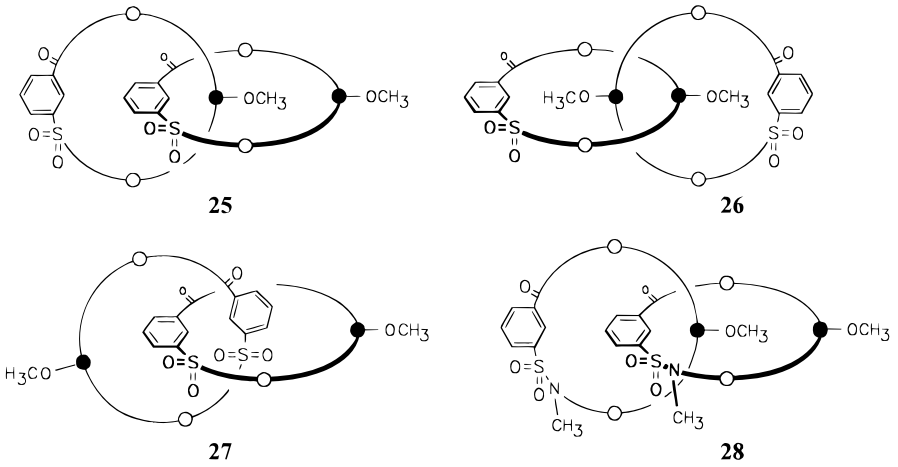
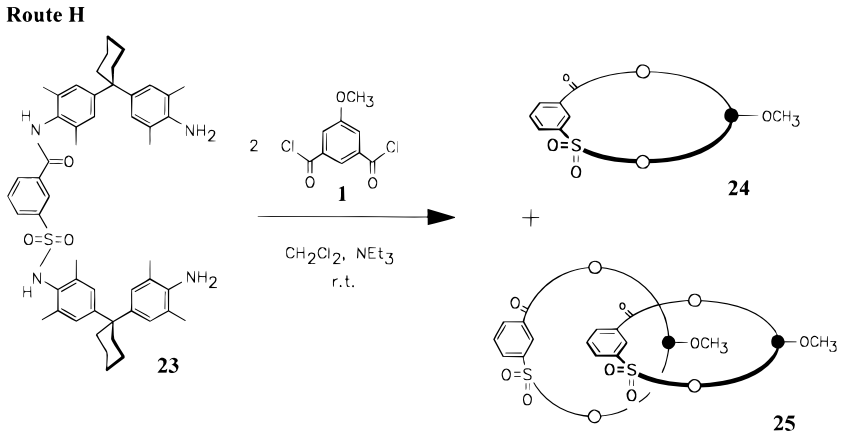


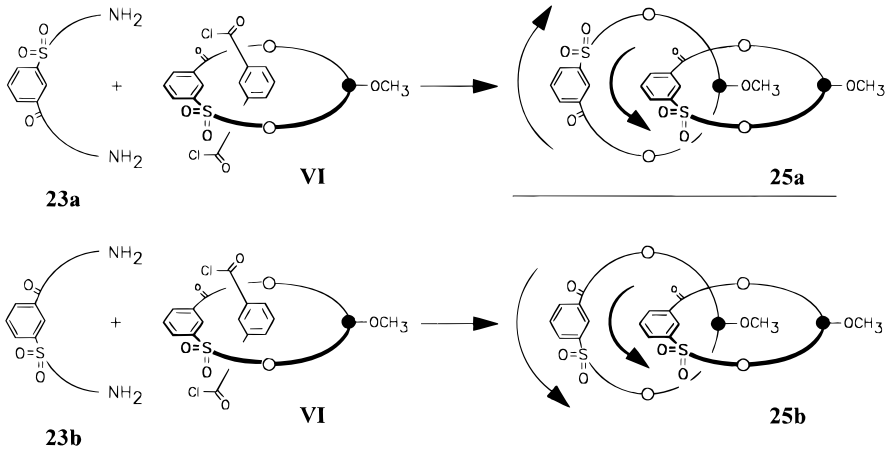
Figure 4. The three possible isomeric disubstituted sulfonamide catenanes **25**–**27** and the methylated sulfonamide catenane **28**.

Scheme 7[a]



[a] The reaction of cyclization precursor **23** with diacid dichloride **1** leads to the formation of macromonocycle **24** and to the *in*/*out* catenane isomer **25**.

Scheme 8[a]



[a] Depending on the orientation of diamine **23** (**23a** or **23b**), one of the topologically chiral catenane isomers **25a** and **25b** is formed. **25a** and **25b** are mirror images of each other.

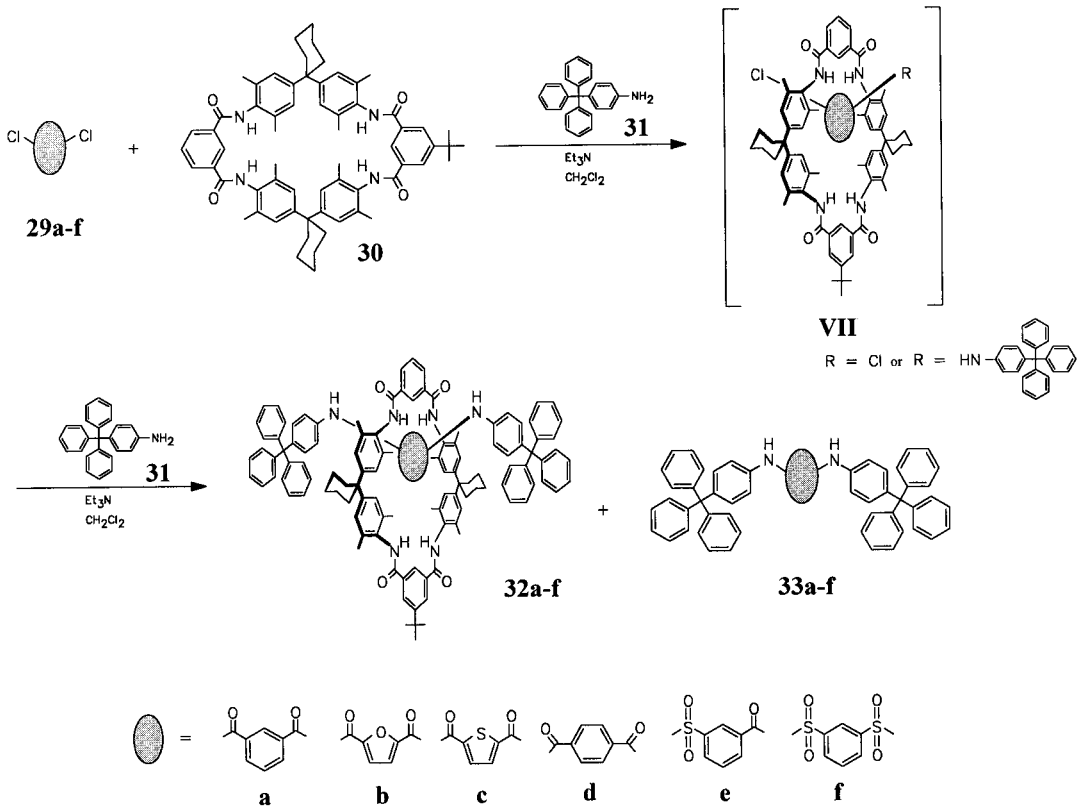
found in detectable amounts. In a corresponding reaction pathway starting with mono-SO_2-N-methylated **23** we also obtained the methylated catenane **28** in similar yields.[23]

The catenanes **25** and **28** show another interesting aspect: depending on the orientation of the sulfonamide group of diamine **23** (orientations **23a** and **23b**), two mirror-image stereoisomers, **25a** and **25b**, are possible. Both should be formed in equal amounts. **25a** and **25b** belong to the rare group of compounds exhibiting topological chirality.[25] This is a result of the different constitution of the linked rings which gives the catenane rings a preferred direction (see the bent arrows in Scheme 8).

To give a hint as to the chirality of **25**, the compound was titrated with the chiral NMR shift reagent Eu-

(25) Walba, D. M. *Tetrahedron* **1985**, *41*, 3161; Mitchell, D. K.; Sauvage, J.-P. *Angew. Chem.* **1988**, *100*, 985; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 930. Cf. Chambron, J.-C.; Dietrich-Buchecker, C. O.; Sauvage, J.-P. *Top. Curr. Chem.* **1993**, *165*, 131.

Scheme 9. Synthesis of Rotaxanes 32a−f



[(+)-thc]$_3$. Signal splitting, usually characteristic for the presence of enantiomers, was observed in the NMR spectrum in both the aromatic and aliphatic regions.[23] Enantiomer separation by means of HPLC and column chromatography has not yet been successful.

Further investigations focus on the selective substitution of sulfonamide protons in the presence of carbonamide protons. This allows the use of catenane **25** as a starting compound in chemical reactions. Different substituents, for example, will influence the mobility of the macrocyclic rings. In addition, "pretzel"-shaped molecules (by bridging of the two SO_2NH groups in **25** with a bishalide) are accessible by this procedure for the first time (see below).

Amide-Based Rotaxanes

On the basis of our above-described hypothesis of the intertwining mechanism, the syntheses of the first amide-based rotaxanes were successfully accomplished. Their (supramolecular template) syntheses turned out to be strikingly simple. The central part of the "axle" **29** is added as its diacid dichloride to the "wheel" **30** and subsequently capped. The macromonocycle (wheel) provides the receptor cavity for the axle, and the *p*-(triphenylmethyl)aniline stoppers (**31**) confirm the mechanical bond between the wheel and axle (Scheme 9).[26]

Indeed, by using this method, all rotaxanes could be isolated with yields up to 41%, each with a different axle center.[27] The host/guest complex **VII** seems to be remarkably tolerant toward changing the structure of the guest and so acts as a "friendly" concave template.[11]

In the ^{1}H NMR spectra of the rotaxanes **32**, the H-atoms of the axle center show a high-field shift compared to the free axle **33**; e.g., the terephthaloyl protons in the pure axle **33d** give a singlet at 7.85 ppm whereas the same protons of the axle incorporated in the rotaxane **32d** show a singlet at 6.55 ppm due to the influence of the benzene rings of the host cycle **30**. Temperature dependent NMR studies (−80 to +20 °C) of the rotaxanes **32b**,**d**,**e** revealed that rotaxane isomers which could have theoretically been formed by docking to the differently substituted isophthaloyl subunits of the host cycle **30** are not present.[27]

It is remarkable that the sulfonyl chlorides **29e**,**f** also nestle inside the concave template (cf. **VII**) similar to the analogous carbonyl chlorides **29a**−**d**. The tolerance of the nonionic concave template toward modification of the axle structure introduces a whole new variety of topological variations to the chemistry of these rotaxanes.

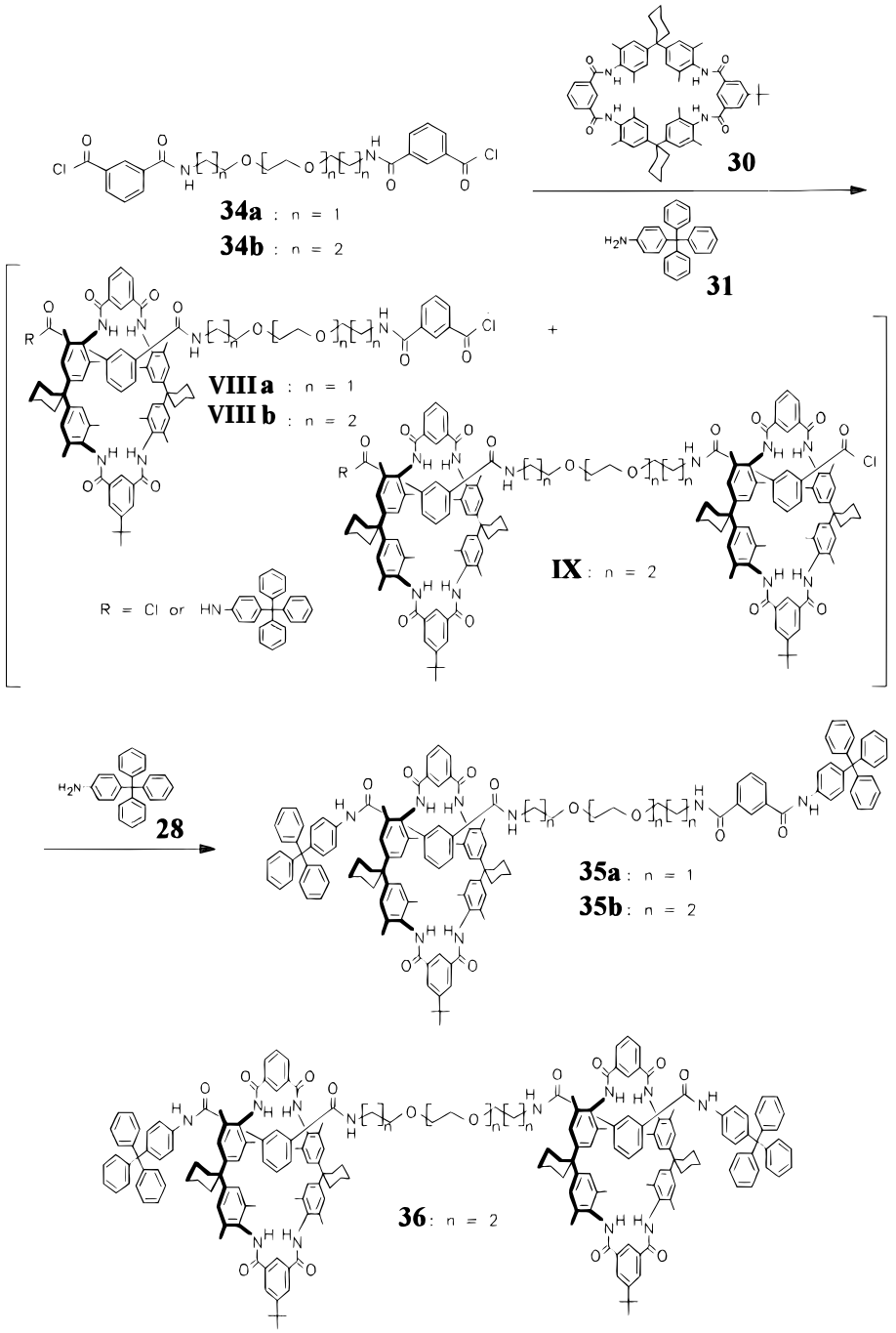
Scheme 10 shows the structural elements we used in the synthesis of the first [3]rotaxane **36** of the amide type.[28] The synthetic strategy took into account that, as in the synthesis of **32**, host/guest interactions are active in the course of the template effect (cf. **34** + **30** → **VIII**, **IX**). In the synthesis of [3]rotaxane **36** we used the center part **34b** of the axle as the starting material and gave it the chance to thread through the wheel **30**[26] once or twice, with the wheel forming the electrically uncharged, concave template. It should

(26) Vögtle, F.; Händel, M.; Meier, S.; Ottens-Hildebrandt, S.; Ott, F.; Schmidt, T. *Liebigs Ann. Chem.* **1995**, 739. Cf. Lindoy, L. F. *Nature* **1995**, *376*, 293.

(27) Vögtle, F.; Jäger, R.; Händel, M.; Ottens-Hildebrandt, S.; Schmidt, W. *Synthesis* **1996**, 353.

(28) Vögtle, F.; Dünnwald, T.; Händel, M.; Jäger, R.; Meier, S; Harder, G. *Chem. Eur. J.* **1996**, *2*, 640.

Scheme 10. Synthesis of the [3]Rotaxane 36 and the [2]Rotaxanes 35a,b



then be feasible to react the host/guest complexes **VIII** (the arrangement shown in Scheme 10 is arbitrarily selected; the wheel can also complex with the right isophthaloyl unit) and **IX** with the "stopper" **31** to give [2]- and [3]rotaxanes **35b** and **36**.

Difficulties occurred, however, when we used the double isophthalic acid dichloride **34a** as the center part of the axle. Instead of the corresponding [3]-rotaxane, only the [2]rotaxane **35a** was formed. When the thread is elongated even more ($n = 2$), [3]rotaxane **36** can be isolated besides [2]rotaxane **35b**. We rationalize this by assuming that the axle is too short in the case of **35a**, possibly resulting in repulsive steric interactions between the two wheels **30** in **VIII**.[28]

We also made an attempt to use dynamic ^{1}H NMR spectroscopy for both of the [2]rotaxanes. The room temperature spectra show the chemical identity of the two isophthalic units in the axle, so we presume that the wheel can shuffle from one isophthalic unit to the other. At low temperatures (−20, −60 °C) we observed only a broadening of the signals, but no coalescence point was found. These results point out that the rotation and shuffling processes of the wheel on the axle are not remarkably hindered at these temperatures.[28]

Conclusions and Outlook

This new approach to connecting mechanical bonds seems to be one of the most simple and most general. Whereas other approaches need phenanthroline units acting as Cu^+ template[4] or 4,4′-bipyridinium tetracationic units leading to salt structures,[5] the amide-

based system is electrically neutral and does not need special complexing building blocks. The structural modifications carried out so far indicate that this system is very tolerant to exchanges of structural units. This means that many more [*n*]rotaxanes, and even knots, may appear in the future especially since yields will undoubtably be optimized. Recently we were successful in synthesizing symmetrical and unsymmetrical [2]rotaxanes with porphyrin blocking groups which have an additional supramolecular functionality.[29] The sulfonamide rotaxanes and catenanes show another interesting aspect: due to their greater acidity sulfonamide protons can be selectively abstracted by mild bases even in the presence of carbonamide groups and then can be substituted with suitable iodo compounds. Therefore, we were able to obtain intra- and intermolecularly covalently linked rotaxanes.[30] In the case of a sulfonamide catenane with one sulfonamide unit in each of its rings, a new topological species, a pretzel-shaped molecule, was formed.[31] It might even be possible to unite building (and especially templating) units of these main approaches into one mechanically bound system.

AR950200T

(29) Vögtle, F.; Ahuis, F.; Baumann, S.; Sessler, J. L. *Liebigs Ann. Chem.* **1996**, 921.

(30) Jäger. R.; Händel, M.; Harren, J. Rissanen, K.; Vögtle, F. *Liebigs Ann. Chem.* **1996**, 1201.

(31) Jäger. R.; Schmidt, T.; Karbach, D.; Vögtle, F. *Synlett*, in press.