

From rotaxanes to knots. Templating, hydrogen bond patterns, and cyclochirality*

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Abstract: Rotaxanes of the amide type have been accessible in preparative yields by a variety of reactions. Beneath S_N2 - and S_N2_t -mechanisms we developed a synthesis of [2]rotaxanes that comes off a Michael addition. The motif of the attractive interactions between an axle-shaped and a macrocyclic wheel part to form rotaxanes consists of multiple hydrogen bonds in the nonionic strategy (threading), as well as in a new high yield anionic template synthesis (trapping). We introduce new synthetic routes for the preparation of [n]rotaxanes using nonionic as well as anionic templates. Furthermore, we report on the latest results of the statistical synthesis (slipping) by melting together axle and wheel to form rotaxanes. The chiroptical properties of a homologous series of cycloenantiomeric [1]rotaxanes as well as a cyclodiastereomeric [3]rotaxane have been described. The differences in the Cotton effects obtained show that small structural changes have an impact on the chiroptical properties of rotaxanes. The first X-ray structures obtained of cycloenantiomerically chiral amide-based [2]- and [1]rotaxanes as well as of the first topologically chiral amide-based knot compound were solved which show networks of H-bonds between the entities of the rotaxanes and the segments of the knot-shaped molecule. Our investigations in template effects based on hydrogen bonding for the synthesis of supramolecular structures open up a variety of strategies for the preparation of catenanes, rotaxanes and—recently— even molecular knots.

ROTAXANES VIA ANIONIC TEMPLATE ASSISTANCE

S_N reactions

Recently, we reported on a very efficient strategy with near-to-quantitative yields for the synthesis of a phenyl ether [2]rotaxane **6** based on the action of a preorganized supramolecular nucleophile **3**, which is formed from the molecular recognition of a phenolate anion stopper **1** by the tetralactam wheel **2** [1]. We term this synthetic step “trapping” because the nucleophilic blocking group is caught by the wheel like a mouse in a trap. This supramolecular nucleophile **3** can now generate a rotaxane by an S_N reaction with a suitable functionalized electrophilic axle centerpiece **4** as shown in Fig. 1.

We assume that in a first step the dibromide **4** reacts with the phenolate–wheel complex **3a** to form the semiaxle **5** and probably causes subsequent dissociation of the resulting semirotaxane complex. Free **5** then reacts with a second phenolate–wheel complex **3a** to furnish the rotaxane **6**.

It has been demonstrated that a variety of other anionic nucleophiles can be used as axle building blocks alternatively. A series of new rotaxanes was synthesized upon formation of acetal, thioacetal, ester, thioester, sulfide, *N*-tosylamide, and phosphate bonds in their axles. The yields are high (23–81%) which underlines the versatility of this synthetic interlocking concept [2].

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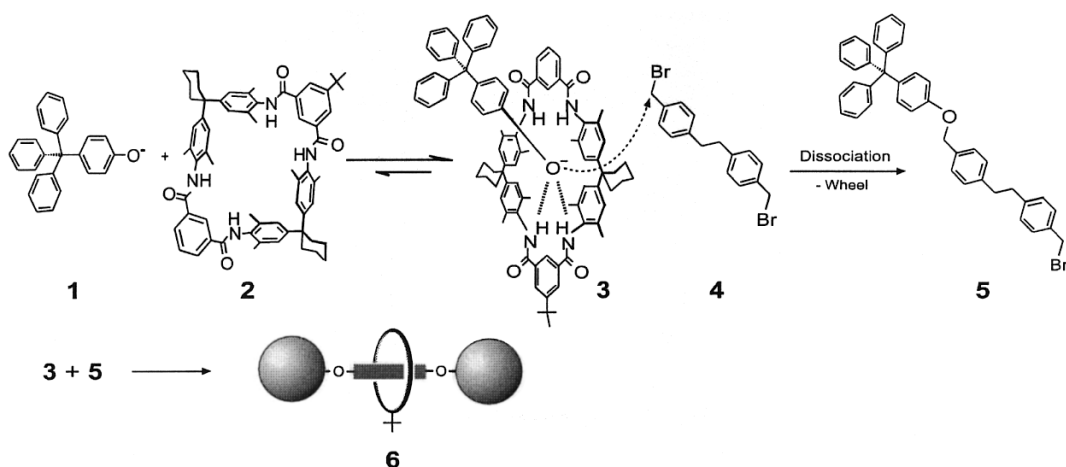


Fig. 1 Synthesis of rotaxanes with ether axles (trapping method).

Michael addition

These results encouraged us to extend this template effect to other essential reactions in organic chemistry. The application of the anion template effect to the classical Michael addition of heteronucleophiles to various Michael acceptors was successful (Fig. 2) [3].

First, we synthesized the semiaxles based on acrylic and propiolic acid motifs **7** which were then to be reacted with a phenolate **3a** or thiophenolate **3b** “supranucleophile” (wheeled nucleophile, see Fig. 1). Neither of the supranucleophiles **3** yielded a Michael adduct with the acrylic acid derivatives **7**, while reaction of both **3a** and **3b** formed the [2]rotaxanes **8a–c** in 13–35% yield with the more electrophilic propiolate semiaxles **7a,b**. In analogy to the base-catalyzed hetero-Michael addition described in the literature, the addition of the oxygen nucleophile **3a** to propiolate **7a,b** resulted mainly in (E)-**8a**, while with the sulfur nucleophile **3b** (Z)-adducts **8b,c** were preferably formed.

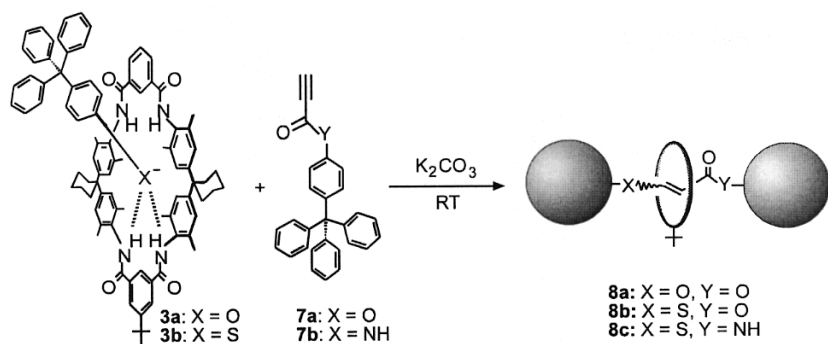


Fig. 2 Rotaxanes via Michael addition (trapping method).

Higher-order [n]rotaxanes via nonionic template effect

Recently, we developed a method for the synthesis of monodisperse higher-order rotaxanes of the amide type based advantageously on an iterative reaction sequence [4]. Up to five wheels could be threaded on one axle **13**. 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. Therefore, we elongated a bulky stopper group in a repetitive reaction sequence that led to the diamide **9**, which is a

semi-axle **9** allows two tetralactams **2** to complex with and gives **10**. Additionally, the reaction with the diacid dichloride **11** enables to bind one more wheel **2** on the axle on account of the additional amide group. The semi[4]rotaxane **12** can now react with the semi[3]rotaxane **10**, that leads even to the formation of the [6]rotaxane **13** (Fig. 3).

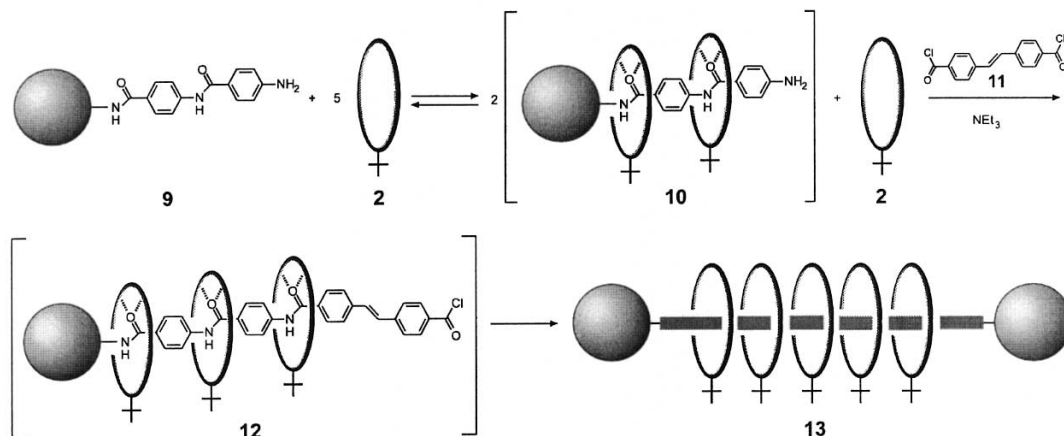


Fig. 3 Synthesis of oligo[n]rotaxanes (iterative threading method).

Combination of anionic and nonionic template

Applying the trapping (anionic template) synthesis in combination with the threading method (nonionic template) for rotaxanes, we reacted the dibromide **14** with the phenolate **1a** in presence of the wheels **2**, **15**, or an equivalent mixture of **2** and **10** [5]. Besides small amounts of the free axle and the corresponding [2]rotaxanes (up to 10%) the [3]rotaxanes **16a–c** were obtained in yields up to 29% (Fig. 4).

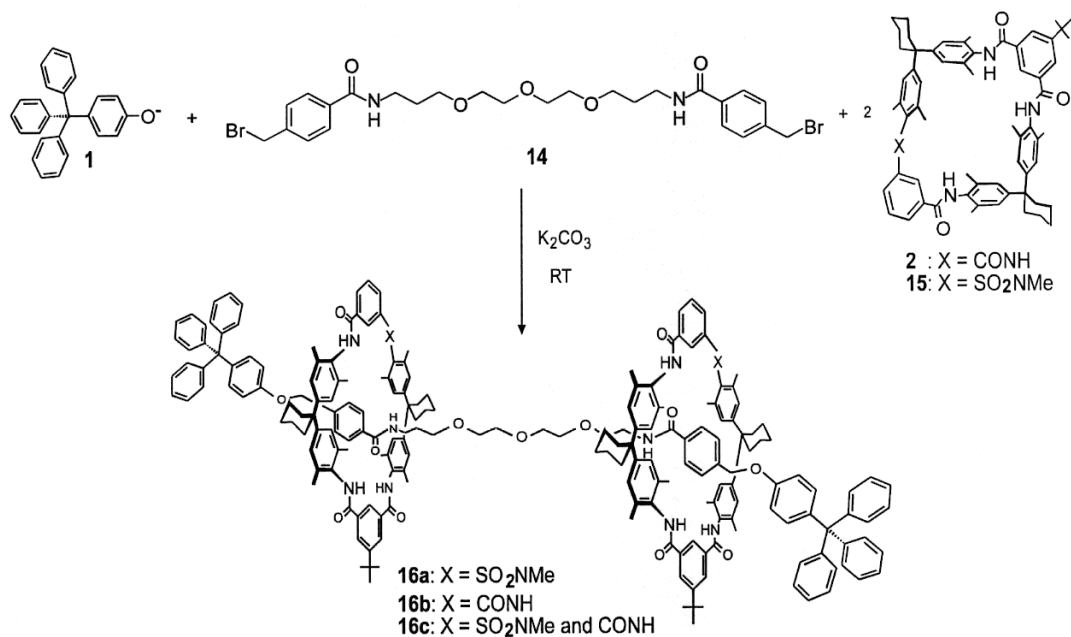


Fig. 4 Synthesis of [3]rotaxanes with ether axles (trapping and threading method).

In the first step, the supramolecular nucleophile is formed, supported by the anion template effect. Thus, a semirotaxane is formed which is stabilized by the presence of the nearby amide group in the axle. In the second step, another “supranucleophile” reacts with the other benzylbromide unit of **14** to finally fix mechanically both wheels on the axle. In all cases, the isolation of the [3]rotaxanes **16** could easily be carried out by column chromatography.

CYCLOCHIRALITY

The design of mechanically interlocked molecules such as rotaxanes, catenanes, and knots presents a range of novel structural and chiroptical properties and non-classical types of chiralities [6]. Cycloenantiomerism of such molecules was foreseen theoretically by Frisch and Wassermann in 1961 [7] and Schill described in 1971 the stereochemistry of rotaxanes as being closely related to that of catenanes [8]. The first topologically chiral catenane [9] and molecular knot [10], however, were not synthesized before the late 1980s. Our group reported in 1996 on the first completely enantio-separated, cycloenantiomeric [2]rotaxane [11].

Cycloenantiomerism of rotaxanes occurs when both its components, the wheel and the axle, contain a sequence information in their molecular scaffolds. One enantiomer has a clockwise orientation of the wheel with respect to the axle, whereas the other enantiomer is arranged anti-clockwise. The covalent connection of the wheel and the axle of such a chiral rotaxane with suitable bridges leads to cycloenantiomeric [1]rotaxanes as shown in Fig. 5. We recently described the first synthesis of [1]rotaxanes such as **17a–j** and the dependency of the chiroptical properties on the length of their aliphatic bridges [12]. Therefore, a cycloenantiomeric bis(sulfonamide) [2]rotaxane with a sulfonamide group in its axle and wheel, respectively, was intramolecularly dialkylated by homologous bifunctional oligomethylene reagents to form chiral [1]rotaxanes bearing bridges of different length between the axle and the wheel. The [1]rotaxanes **17a–j** were obtained in yields of 22–64% by using 1, ω -dibromoalkanes containing 1 to 10 methylene groups to bind the two sulfonamide nitrogens covalently. The racemates of the [1]rotaxanes **17a–d** showed a clear baseline separation by high-performance liquid chromatography (HPLC) on a Chiralcel OD column [13]. The separation factors α are higher with decreasing length of the bridges, and in every case the (–)-enantiomer was eluted first. The Cotton effects obtained for each of the enantiomers are mirror images over the whole region of the spectra. The molar CD spectra reach an extremum in the aromatic region at 197–212 nm. Remarkably, the circular

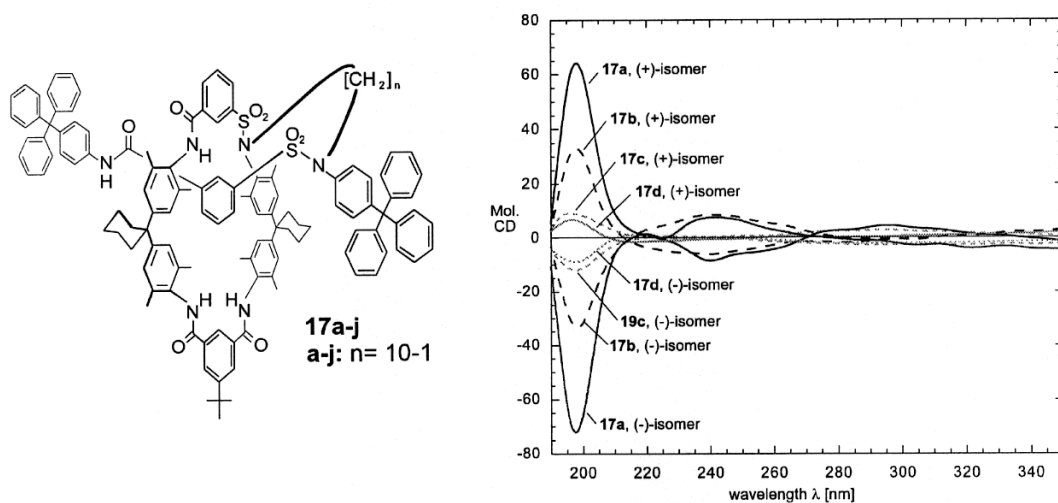


Fig. 5 Covalently bridged [1]rotaxanes **17** and CD-spectra of the separated cycloenantiomers of **17a–d**.

dichrograms showed Cotton effects with decreasing intensity in the same direction as the length of the aliphatic bridge is decreased. In comparison with the circular dichrogram of the nonbridged [2]rotaxane the Cotton effects are smaller as well. Clearly, the homologous bridges in **17** have an impact on the conformation of the [1]rotaxanes due to steric and electronic factors.

Recently, we succeeded in extending the term of cyclochirality on [3]rotaxanes [5]. Even by using two orientated achiral macrocycles threaded on an achiral and symmetrical axle compound a diastereomeric [3]rotaxane is formed (Fig. 6).

In analogy to the covalently linked tartaric acid, we obtained a cyclodiastereomeric compound. If there is only one oriented wheel on a symmetrical axle, a [2]rotaxane with no stereoisomerism results. Rotaxanes like **16a** bearing two wheels, the atomic sequences of which can be arranged clockwise or anti-clockwise, should occur in a *meso* form (*m-16a*) and a pair of enantiomers (*R/S-16a*). The orientation of the enantiomers is caused by a different sequence of the three amide groups and the *N*-methylsulfonamide group. The two wheels can have the same or the opposite direction. In the case of the same direction the *meso* compound *m-16a* is obtained, and the opposite direction of the wheels leads to *R-16a* and *S-16a*. Enantioseparation was successfully carried out using HPLC on a chiral solid phase column (Chiralpak AD) [13]. The (+)-enantiomer was eluted first under base line separation. The reten-

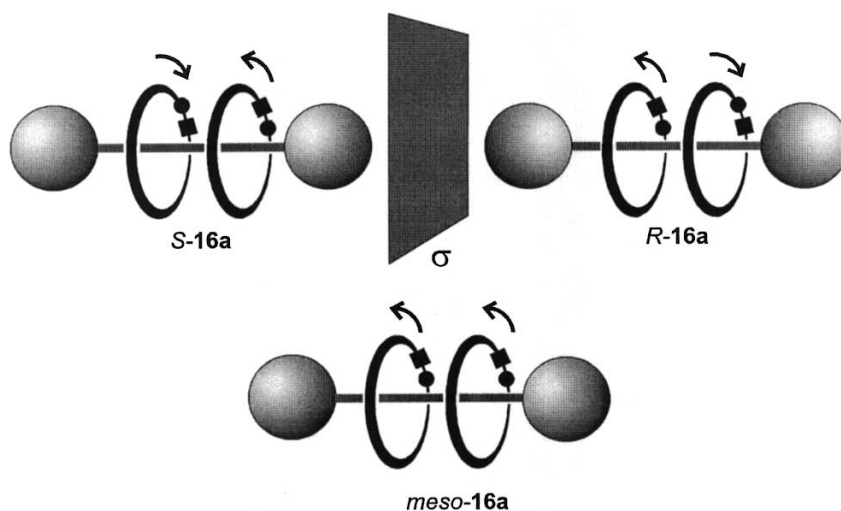


Fig. 6 Cyclodiastereomeric [3]rotaxane.

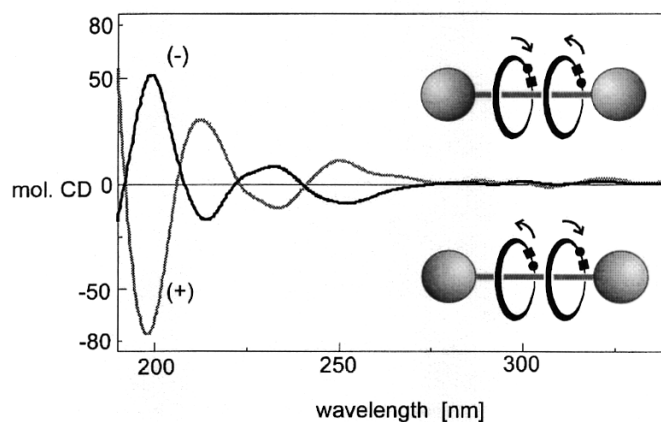


Fig. 7 Circular dichroism of the cycloenantiomers of **16a**.

tion time of the latter, however, differed only slightly from that of the *meso* form **16a**. Nevertheless, we were able to separate **16a** and the (–)-enantiomer. Both enantiomers show significant circular dichroisms with four marked Cotton effects as well as optical rotation at different wavelengths, (Fig. 7) whereas the *meso* form is not optical active. The remarkable property of these [3]rotaxanes is the mechanical bonding of their achiral components, axles, and wheels, which leads to cyclodiastereomeric species. The stereoisomers are formed in statistical ratios (*meso*-**16a**: (+)-**16a**: (–)-**16a** = 2:1:1).

X-STRUCTURAL ANALYSIS OF HYDROGEN-BONDING PATTERNS

[1]- and [2]rotaxanes

For the first time, X-ray crystal structures of [1]rotaxanes were obtained and also of the cyloenantiomeric [2]rotaxane **18** from which they were derived [14]. Unlike the three other cases, different conformations were found for the two enantiomers of **19** in the racemic crystals. Those two structures differ mostly in the orientation of the *m*-xylylene bridge with respect to the wheel (“endo” for *R*-**19** and “exo” for *S*-**19**). In all five structures, the carbonyl oxygen of the sulfobenzoyl group of the wheel is pointing toward the center of the macrocycle (Fig. 8). This cisoid conformation enables the formation of a hydrogen bond with the amide proton of the axles. In the [2]rotaxane **18** the carbonyl oxygen of the axle is hydrogen-bonded in a bifurcated manner with the two amide hydrogens of the isophthalamide moiety. This pattern is reminiscent of that of [2]catenanes and [2]rotaxanes of the same type [15]. The cisoid structure of the sulfobenzoyl group is also found in the axles, causing a curved shape. An exception is **17g** where it is transoid and rather linear. In the [1]rotaxanes the two sulfonamide groups are pulled together by the bridges, which leads to a different position of the axles relative to the wheels, as compared to the [2]rotaxane **18**. The bifurcated hydrogen bonds of **17h** and *R*-**19** are longer (i.e., weaker) than those of **18**. In the structure of *S*-**19** one of both is entirely missing. For **17g** the pattern of the H-bonds in the crystal differs from that of the other molecules: A methanol hydroxyl group is inserted between one of the isophthalamide hydrogens of the wheel and the carbonyl oxygen of the axle under formation of two short hydrogen bonds. Here also, the wheel is nearly planar. In the other structures, the hydrogen bonds induce a distortion of the wheel. This is especially pronounced for the [2]rotaxane

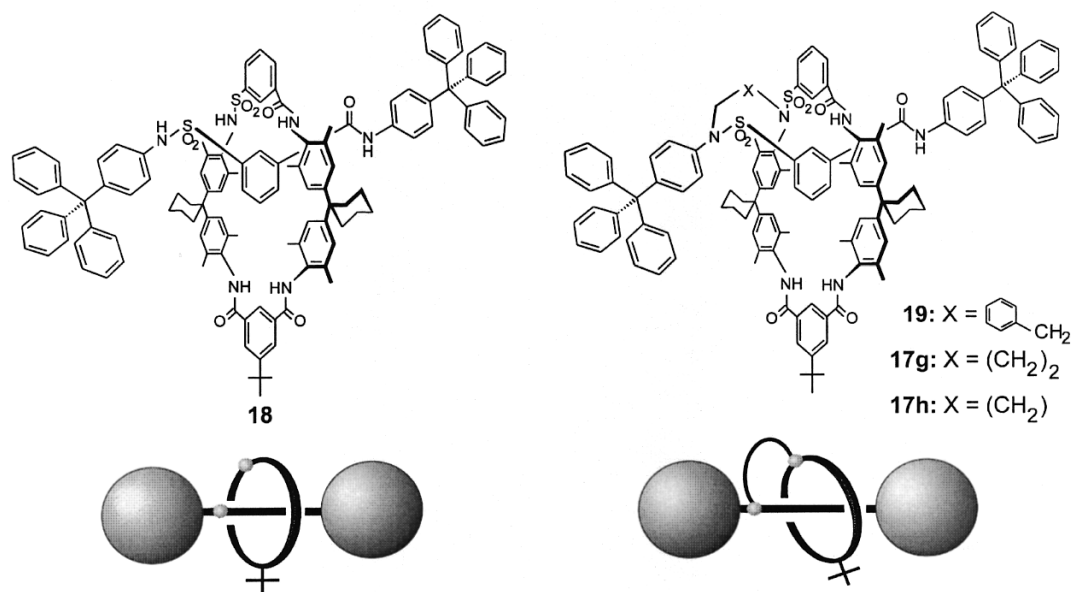


Fig. 8 Sulfonamide based [2]rotaxane **18** and [1]rotaxanes **17g–h**, **19**.

18 which, on the other hand, has the three shortest wheel-to-axle hydrogen bonds. This pattern of three intercomponent hydrogen bonds furthermore supports the selectivity of binding for secondary amides in solution found for macrocyclic lactams like the wheel used here [16].

Molecular knot

Recently, we reported on probably the simplest synthesis of a new molecular trefoil knot in 20% yield, which proceeds under self-organization without any added auxiliary component (“self-templating”) [17]. In the course of the synthesis of larger macrocyclic compounds as concave (ditopic) templates (hosts) we treated the substrates 2,6-pyridinedicarboxylic acid dichloride **20** and diamine **21** under high dilution conditions (Fig. 9). This reaction gave, besides **23** (15% yield) and **22** (23% yield), a colorless product **24** in 20% yield which had a molecular weight of a 3:3 cyclization reaction product.

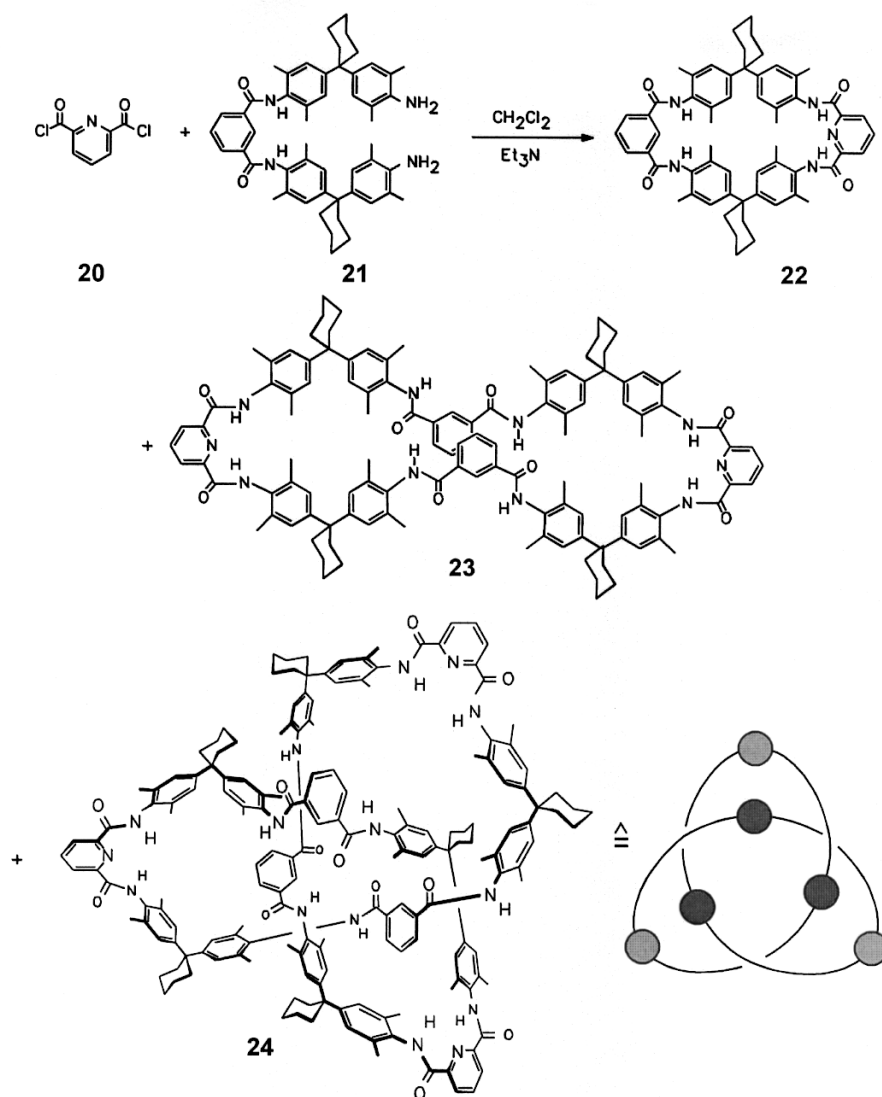


Fig. 9 Synthesis of the first amide-based trefoil knot **24**.

After crystallization, we were able to obtain an X-ray crystal structure analysis of **24** which revealed the structure of a topologically chiral trefoil knot. Besides a 96-membered araliphatic skeleton this knot includes twelve CONH groups. Only four of the twelve NH hydrogen atoms in the knot molecule participate in intramolecular hydrogen bonds. The hydrogen-bond pattern resembles that found in the [2]rotaxane **18**.

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