Molecular Knots

DOI: 10.1002/anie.200601938

Spontaneous Knotting—From Oligoamide Threads to Trefoil Knots**

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Dedicated to Professor Vincenzo Balzani on the occasion of his 70th birthday

Until now oligoamide-based molecular knots were accessible only by intermolecular one-pot condensation of three diamide molecules **1** and three acid chloride molecules **2** (Scheme 1, Route A).[1–3] To explain the process of knotting we suggested the intermediate formation of longer oligoamide threads **3a** or **4**.[2] From crystal structure analyses[2] of amide knots like **6**, as well as further experimental and theoretical data,[4] we assumed that folding of linear thread precursors like **3a** or **4** (Scheme 1, Routes B/C) to knotted thread parts might be preprogrammed on the basis of favorable hydrogen-bond patterns in noncompetitive solvents (for example, dichloromethane).[5] The intermediate formation of **3b** from **5** cannot be ruled out completely, although the reaction conditions (stoichiometry of the addition of **2a**: one equivalent in Route B, two equivalents in Route C) do not really support this assumption. Herein, we report the first synthesis, isolation, and characterization of threads **3a** and **4**, as well as their successful conversion into the corresponding knotanes **6** (Scheme 1).

The synthesis of the elongated threads **3a** and **4** as potential precursors for the formation of amide knots is depicted in Scheme 2. This synthesis opens up the possibility to distinguish between Routes B and C. Therefore the isolated threads **3a** and **4** were separately treated with **2** and with **1** and **2**, respectively, and it was then examined whether the molecular knot **6** was formed.

Route B: Thread **3a** folds by itself, then threads intramolecularly through the previously formed loop and thus spontaneously creates an open knot **3b** (Scheme 1, Route B).[6] To prove the existence of this intertwined structure, we treated the isolated decaamide with various 4-substituted pyridine dicarboxylic acid dichlorides **2a–d** (Scheme 3). In the case of the unknotted thread **3a**, this reaction should yield an achiral macromonocycle **7**, whereas the open knot **3b** should lead to an isomeric (closed) topologically chiral knot **6** with three pyridine units. This reaction also opens up a new class of monosubstituted knots **6a–d** if a substituted pyridine dicarboxylic acid dichloride **2** is used instead (Scheme 3).

On the one hand, this strategy gives more insight into the template mechanism of the knotting of neutral (uncharged) molecules (without cation assistance[3]), and on the other hand, it makes the synthesis of new trefoil knots with different subunits possible. Such a spontaneous self-knotting process **3a**→**3b** of low-molecular synthetic thread molecules on a preparative scale has, to the best of our knowledge, not been reported before.[7]

Indeed the reaction of the long thread **3b** with pyridine dicarboxylic acid dichloride (**2a**) yields the unsubstituted knot **6a** with three identical pyridine units, which we already synthesized previously by Route A, and this product is in accordance with our proposed mechanism for Route B. The reaction yielded 13 mg (11 %) of the pure knotane **6a**.

Chromatographic enantiomer separation of the new knotanes **6b–d** and the "Bonn-knot" **6a**, which was obtained by this route for the first time, was achieved by means of enantioselective HPLC employing chiral stationary phases (CSPs), namely the amylose-derived Chiralpak IA[8] and the diphenylethanediamine-based (*R,R*)-ULMO packings. Both CSPs exhibited promising levels of stereodiscrimination for the topologically chiral knotane enantiomers. However, under optimized chromatographic conditions, the ULMO-type CSP provided superior performance in terms of enantioselectivity, efficiency, and scope of applications. The HPLC and CD data are identical to those of samples previously synthesized[9] by Route A. Figure 1 shows the HPLC separation and CD spectra of the new knots **6b** and **6c** (for a detailed analysis of the HPLC chromatogram for the estimation of purity of compound **6b**, see the Supporting Information).

Since the isolated yields of the trefoil knot **6a** starting from **3b** do not exceed those obtained by condensation of shorter threads, we assume that, depending on the choice of conditions, a certain ratio (or a dynamic equilibrium) between the knotted decaamide **3b** and its unknotted isomer **3a** exists. Both species can react with pyridine dicarboxylic acid

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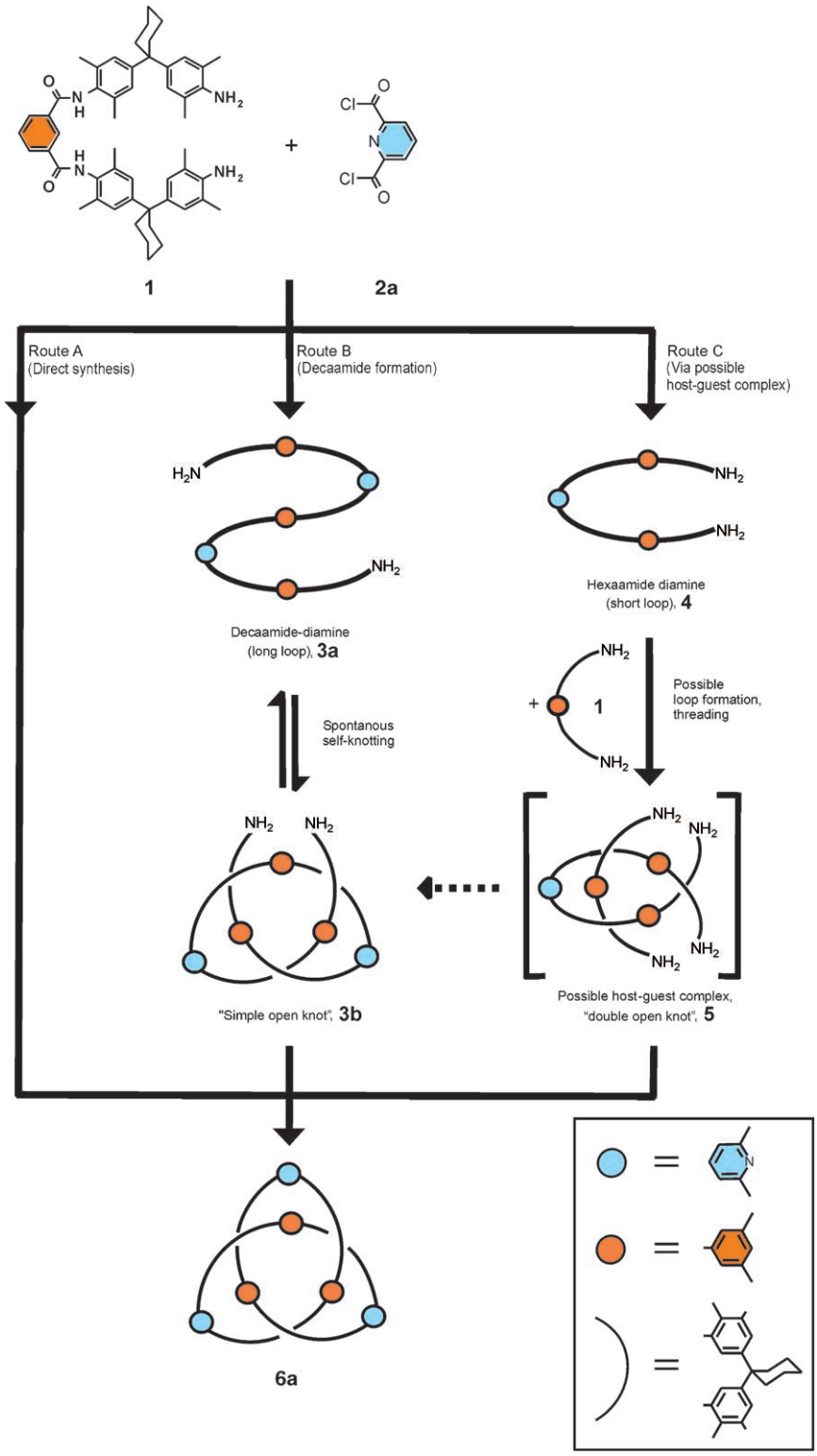
[**] We are grateful to the Sonderforschungsbereich "Template" (SFB 624) of the Deutsche Forschungsgemeinschaft for valuable support. We would also like to express our special thanks to Dr. Barbara Kirchner for preliminary theoretical calculations of closed and open knots.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Synthetic pathways and mechanistic alternatives for the formation of amide knots from **1** and **2a** or from the elongated thread molecules **3a** and **4**. Route A: one-pot synthesis from building blocks **1** and **2a**. Route B: intramolecular self-knotting of thread **3a**. Route C: possible intermolecular host–guest interaction ("bimolecular template" **5**) between two thread molecules (**4** and **1**).

dichloride **2a** to yield either the knot or the unknotted monomacrocycle **7** as well as polycondensation products, thus resulting in a decrease of the yield of the trefoil knot.

The disubstituted long thread **3c** was obtained by reaction of **1** with the methoxy-substituted pyridine dicarboxylic acid dichloride **2b** (see the Supporting Information). Subsequent cyclization with acid chloride **2a** afforded the disubstituted knotane **6e** (Scheme 4), also in accordance with our conclusions above. HPLC separation and the corresponding CD spectra are similar to those shown in Figure 1.

Furthermore we achieved the synthesis of knotane **6d** by cyclization of the long thread **3b** with the methoxy-substituted isophthalic acid dichloride **2d**. This knotane, owing to the ring-closure reaction with the methoxyisophthalic unit, consists of four isophthalic units and just two pyridine units, whereas all other previously synthesized amide knots contained three isophthalic units and three pyridine units (Scheme 3). Thus a new class of trefoil knots[11] that was previously not accessible is opened up (for HPLC separation and CD spectrum, see the Supporting Information).

Route C: The proposed mechanism for Route B above (perhaps also via the monoacylic derivative of **3b**) is not the only possible synthetic pathway. Knotanes are also obtained by reaction of the shorter thread **4** with diamine **1**, possibly by formation of the supramolecular complex **5** and sequential cyclization with two pyridine dicarboxylic acid dichloride molecules **2** (Scheme 1). Here we assume that the hexaamide diamine **4** arranges itself into a cisoid conformation as a result of hydrogen bonding between the pyridine nitrogen atoms and the amide hydrogen atoms and subsequently forms a helical loop. This loop should be additionally stabilized at the points of intersection of the molecule by further hydrogen bonding. The loop could then act as a host (template) for diamine **1**, so that the organic complex **5** could be formed after the threading process, and **5** could then act as a "bimolecular template". Cyclization with successively added pyridine dicarboxylic acid dichloride **2a** affords the knotane **6a** (4% yield; Scheme 5). Hence the final cyclization step might even proceed via the open knot **3b** as well.

The racemate of **6a** was separated into enantiomers, and HPLC and CD data proved to be identical to earlier samples. Route C therefore proved to be an alternative reaction mechanism, and the knotanes **6e** (5%

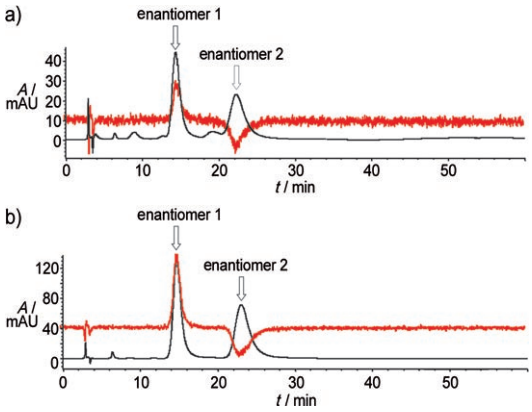
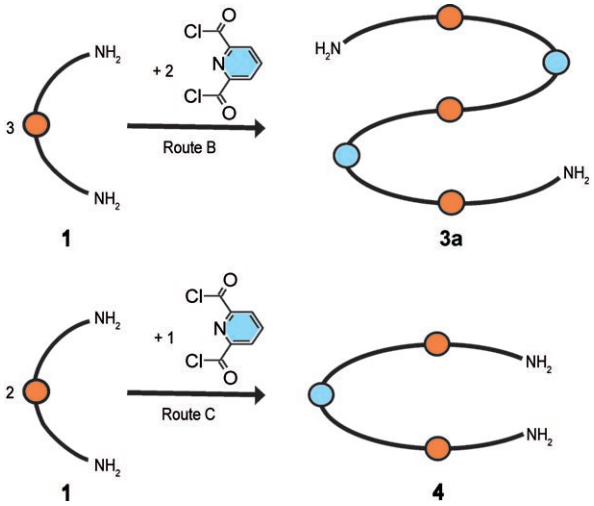
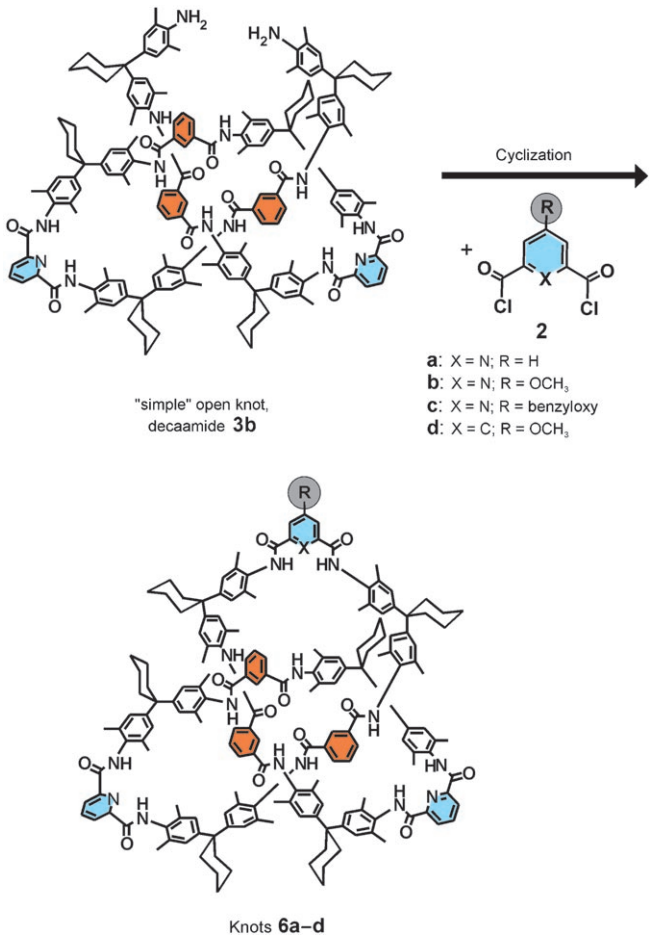


Figure 1. HPLC separation (*tert*-butyl alcohol/*n*-heptane 50:50; flow rate 0.5 mL min^{-1}; $T = 65\,^{\circ}C$; black curve) and CD-spectra (red curve) of **6b** (a) and **6c** (b), synthesized through Route B using *(R,R)*-ULMO material as the chiral stationary phase (developed by W. Lindner et al.[10]).



Scheme 2. Synthesis of the isolated threads **3a** and **4**.

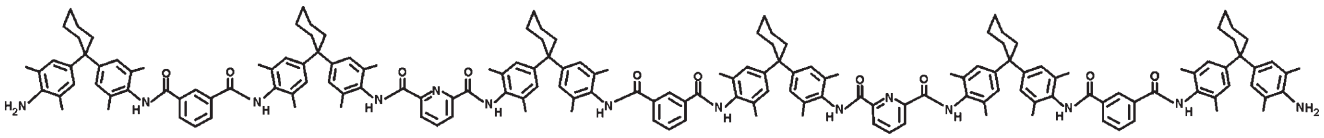
yield) and **6f** (2% yield) were also synthesized by this route, through reaction with acid chlorides **2b** and **2c**, respectively (Scheme 5). Therefore Route B as well as Route C both open up new perspectives for the synthesis of new trefoil knots with



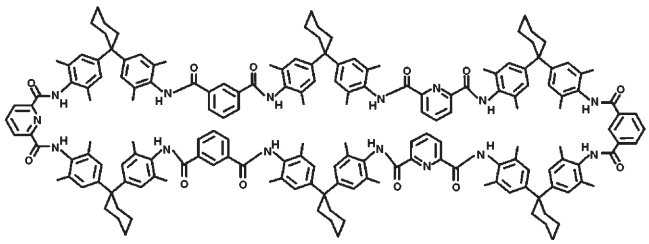
Scheme 3. Reaction of the isolated decaamide **3b** with **2a–d** and formation of the unsubstituted "Bonn-knot" **6a** and the new monosubstituted knots **6b–d** (Route B).

substitution patterns that are not accessible by Route A. However, even the use of linear precursors does not necessarily result in high yields because of the dynamic nature of the process.

Open knots: The "interception" of extended knotted threads would be interesting, not only with regard to the formation of cyclic knotanes, but also regarding the synthesis of open, stoppered amide knots that do not consist of metal



3a



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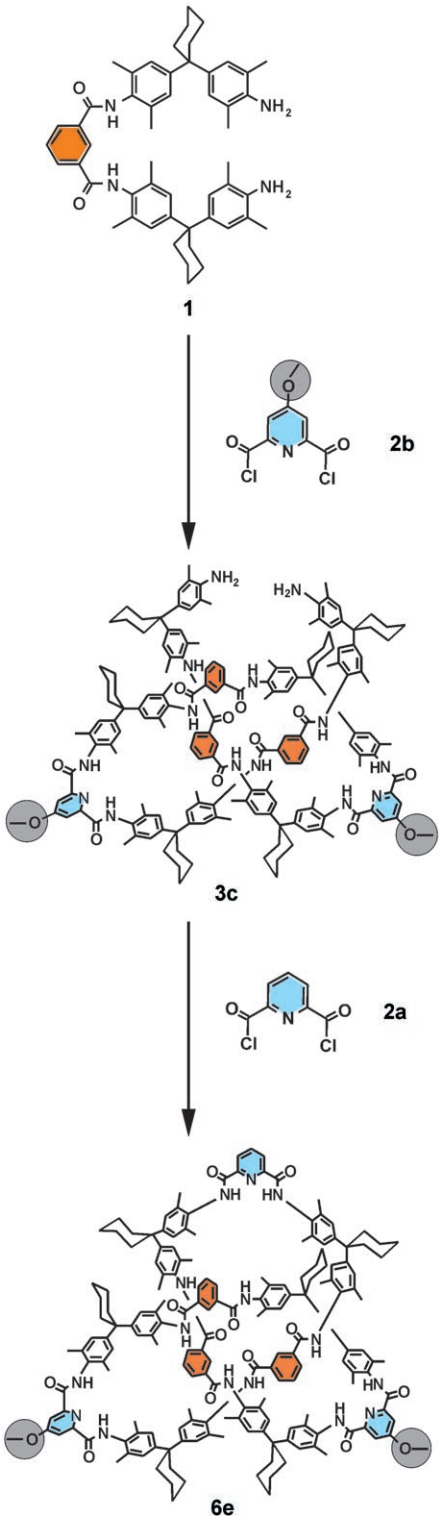
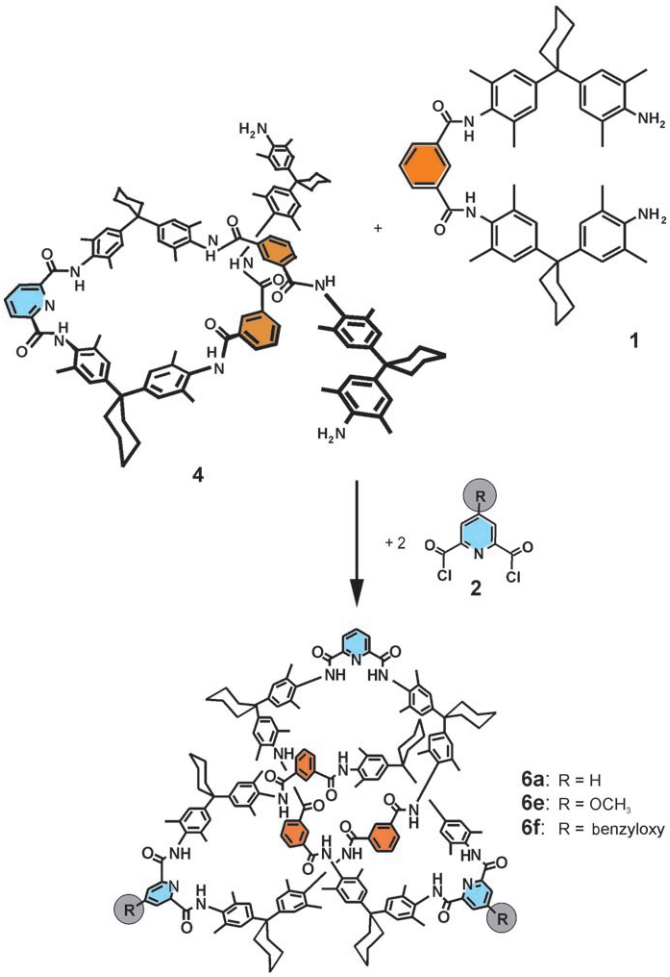


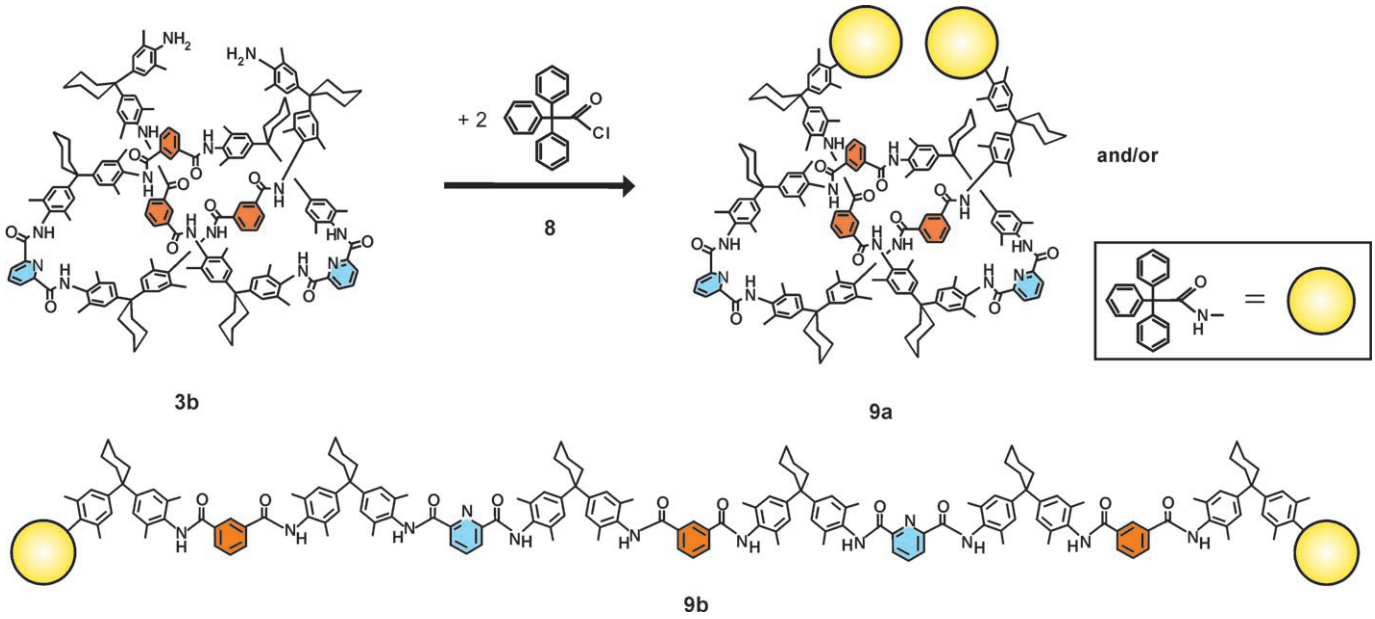
Scheme 4. Synthesis of the dimethoxy-substituted long thread **3c** and subsequent cyclization with **2a** to yield knotane **6e** (Route B).



Scheme 5. Alternative synthesis of knotanes **6a**, **6e**, and **6f** by reaction of the short thread **4** with diamine **1** and acid chlorides **2a–c**, possibly via the supramolecular complex **5** (Route C).

complexes.[3] Interception of the decaamide diamine **3b** with a monoacid chloride with significant steric demand seemed feasible because of the expandable molecular scaffold. After purification of the decaamide diamine **3a** (or **3b**) and a subsequent separate reaction with stopper **8** (Scheme 6), we obtained a pure compound with a mass corresponding to either the stoppered open knot **9a** or the stoppered thread **9b** (29% yield; for MALDI-TOF spectrum, see the Supporting Information). This synthetic pathway corresponds to Route B (Scheme 1).

A compound of the mass corresponding to **9a**/**9b** is not only available by Route B. We also obtained this substance from a one-pot synthesis similar to Route A (Scheme 1) with yields of around 0.5%. In this case, the stopper component **8** was added slowly after a reaction time of one hour, so that it could intercept (that is, terminate) the intermediate threads **3b** and **3a**. Since **9a** is chiral, whereas **9b** is achiral, this was the starting point for further investigations. However, attempts to resolve the enantiomers of this compound on the (*R,R*)-ULMO CSP[10], employing the chromatographic conditions optimized for cyclic knots, failed (for the HPLC chromatogram, see the Supporting Information). This implies that there might be an equilibrium at room temperature between stoppered thread **9b** and the open knot **9a** as a result of the insufficient steric demand of the stopper (as deduced from newer theoretical calculations and modelling[12]). The barrier of this equilibrium should be less than 30 kcal mol^{-1} at



Scheme 6. Synthesis of the open stoppered amide knot **9a**, or the stoppered thread **9b**, by reaction of the decaamide diamine **3b** with two stopper molecules **8** in a manner analogous to Route B.

room temperature.[13] For further clarification of this aspect, the synthesis of even bulkier stopper components is necessary, but such components are not yet known.

The spontaneous reversible self-knotting of oligoamide threads, which is demonstrated here for the first time, opens up new perspectives. New knotane architectures may be obtained by, for example, changing the spacer between amide groups and by further extension of the thread, thus converting the molecules into cyclic and open knots with extended loops (expanded knotanes) as well as open-chain knots with longer threads. By further extension of the thread part, it might be possible for knots to be successively tied together like a string of pearls. Polymers of this kind should be very elastic, since open knots can be tightened and loosened like shoelaces. Finally, our results regarding self-threading, self-knotting, and self-templating can be expected to stimulate the development of new intertwined topologies. Just as the information needed for the knotting is already contained in the constitution and the amide sequence of **3a**, other cyclic and open entanglements and knottings might be achievable by the skillful design of starting materials.

Experimental Section

Synthesis of the short (**4**) and the long (**3b**/**3c**) threads: Compound **1** (3.00 g, 3.87 mmol) was partially dissolved in chloroform (5 mL), and dichloromethane (95 mL) was added. After addition of triethylamine (2 mL), a solution of **2a** (0.14 g, 0.69 mmol) or **2b** (0.16 g, 0.70 mmol) in dichloromethane (75 mL) was added slowly over a period of 2 h at room temperature. The reaction mixture was stirred overnight, the solvent was removed under reduced pressure, and the residue was purified two times by column chromatography (dichloromethane/ethyl acetate 3:1 und 2:1) to afford **4** (518 mg, 0.31 mmol, 16%) or the methoxy-substituted analogue **4**-OCH_3 (375 mg, 0.22 mmol, 17%) as well as **3b** (151 mg, 0.06 mmol, 5%) or **3c** (130 mg, 0.05 mmol, 4%). All melting points are greater than 220°C.

For the spectroscopic data of **3b**, **3c**, and **4**, see the Supporting Information.

Knotanes **6a**–**e** by Route B: Decaamide **3b** or **3c** was dissolved in dichloromethane (30 mL), and triethylamine (0.5 mL) was added. A solution of the appropriate acid chloride **2a**–**d** in dichloromethane (10 mL) was slowly added over a period of 1 h. The reaction mixture was stirred at room temperature for 48 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (dichloromethane/ethyl acetate 4:1). All melting points are greater than 220°C.

Knotanes **6a**, **6e**, and **6f** by Route C: Hexaamide **4** and diamine **1** were dissolved in dichloromethane (100 mL) and stirred at room temperature for 48 h. After the addition of triethylamine (0.5 mL), a solution of the appropriate acid chloride **2a**–**c** in dichloromethane (30 mL) was added slowly over 2 h. The reaction mixture was stirred for an additional 12 h at room temperature, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (dichloromethane/ethyl acetate 4:1). All melting points are greater than 220°C.

For further experimental details, spectroscopic data of **6a**, **6e**, and **6f**, as well as the synthesis of **9a**/**9b**, please refer to the Supporting Information.

Received: May 16, 2006
Published online: October 10, 2006

Keywords: enantiomer separation · molecular knots · nanostructures · supramolecular chemistry · template synthesis

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[12] We thank Dr. B. Kirchner, Dr. W. Reckien, and M. Eggers of the Institut für Physikalische und Theoretische Chemie der Rheinischen Friedrich-Wilhelms-Universität Bonn for preliminary classical and Car–Parrinello simulations.

[13] Variable-temperature ^{1}H NMR experiments between −50 and 55 °C showed no substantial changes.

