Amide-Based Molecular Knots

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Abstract

More than a dozen new representatives of topologically chiral trefoil molecular knots based on amide bonds were synthesized via a supramolecular template route. The knotted scaffold was proven by X-ray analysis and by several resolutions of the racemates. The enantiomers could be baseline-separated chromatographically and their absolute configuration was determined by comparing the experimental with the theoretically calculated circular dichroism curves. Conclusions about the formation mechanism via hydrogen bonding templates are drawn.

Of the little-known class of knotted molecules [1] hitherto only some of the (historically first) phenanthroline type [1c], of the nucleic-acid type [1d] and of the crown/quat type [1e] have been synthesized. In 2000 we developed a simple template synthesis of new trefoil knots **1** in up to 20% yield [2], which proceeds under self-organisation of relatively simple starting compounds (an isophthalic acid dichloride, a diphenylmethane derived diamine and a pyridine-2,6-dicarboxylic acid dichloride (see below). These knots include twelve CONH groups in a 96-membered ring skeleton (for a stereoscopic view see Figure 2).

A baseline separation [3a] of the racemate [2] of the trefoil knot **1a** (see Figure 5) was achieved via HPL-chromatography on a non-commercial Chiralpak-AD column [4], in which the silica gel and the chiral stationary phase (CSP) are covalently bound, so that the material is not 'bleeding out', even if lipophilic eluents are used in cases where the knots are sparingly soluble in hydrophilic solvents.

Molecular knots, for which we proposed the general name 'knotanes' [3a,b] (in analogy with the coinings catenane, rotaxane, pretzelane), in the case of trefoil knots are topologically chiral, and in a few cases Sauvage *et al.* [1b] have been successful in the resolution of racemates.

Experimental CD spectra (mirror symmetrical curves (a), (b)) of the pure enantiomers of **1a** are shown in Figure 4 and compared with calculated ones (c).

The CD spectra were calculated prior to the actual experimental measurements via a semi-empirical π-electron method (time-dependent Pariser-Parr-Pople, TDPPP), accounting for all benzene and amide building blocks [3a]. The resulting theoretical spectrum (c) represents a remarkable close fit to the experimentally obtained curve. The absolute configuration was derived therefrom [5].
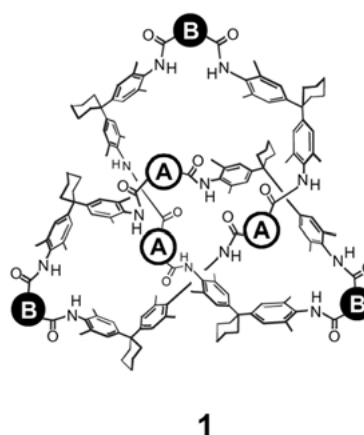

Figure 1. Amide-based knot type **1** (**A** = substituted *m*-phenylene; **B** = substituted 2,6-pyridine-diyl).
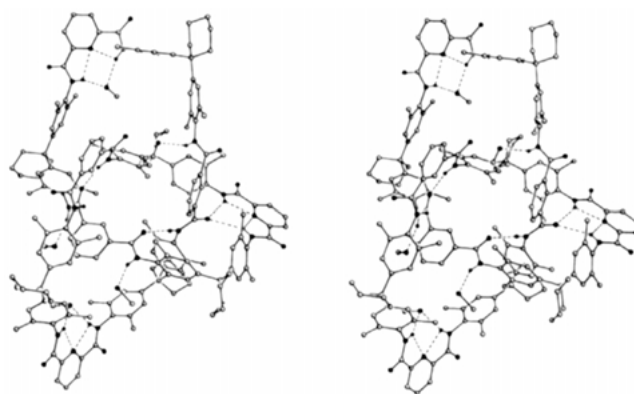

Figure 2. Stereoscopic view of amide knot **1a**. Dotted lines indicate hydrogen bonds.
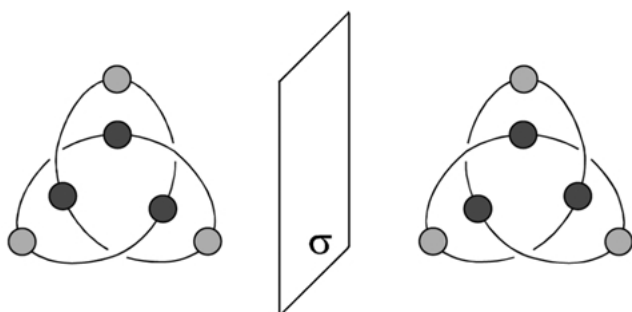
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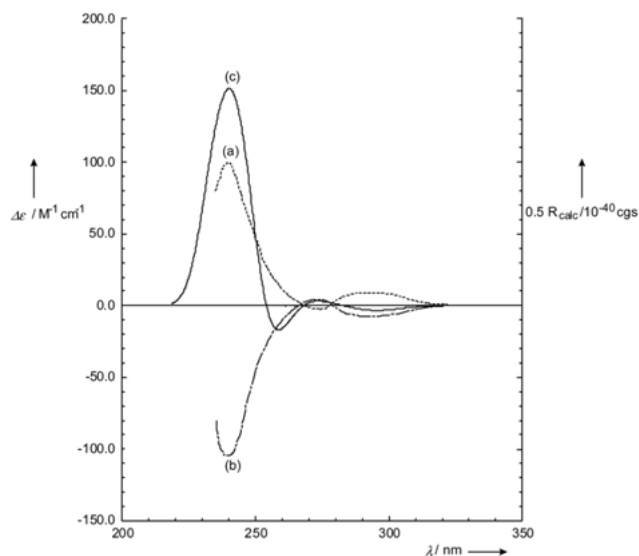Figure 3. Topological chirality (enantiomers) of trefoil knots.

Figure 4. Experimental (a), (b) and theoretical (c) circular dichrograms.

2 a: Y = CH

b: Y = CCH$_3$

c: Y = N

3 a: X = CH

b: X = CD

c: X = CCl

d: X = CCOCH$_3$

1 a: X = CH, Y = CH

b: X = CH, Y = N

c: X = CH, Y = CCH$_3$

d: X = CD, Y = CH

e: X = CCl, Y = N
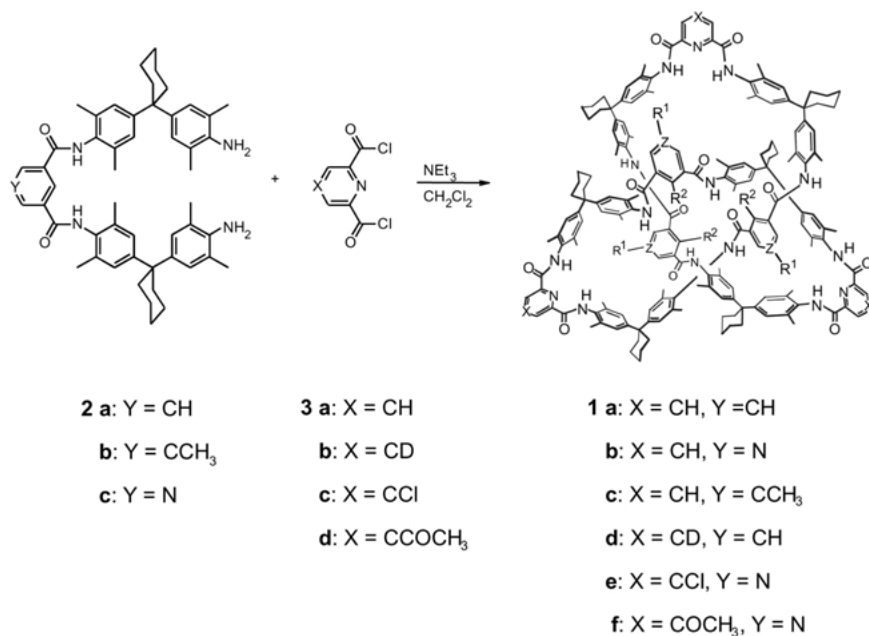
f: X = COCH$_3$, Y = N

Figure 5. New synthesized knots.

This knotane synthesis is variable with respect to substituents at the isophthalic acid rings (A), the pyridino rings (B) (see Figure 1) and the amide nitrogens, so that an extended 'chemistry of molecular knots' is possible via derivatisation and subsequent reactions.

From the more than a dozen new knots of this type characterized so far it emerges that whereas big substituents in the 5-position of the isophthalic acid units hamper the knot yields, such substituents in the 4-position of the three pyridine units are well tolerated.

The preferred formation of knot **1** over formation of a topologically isomeric catenane (of the same mass) or the topologically isomeric macromonocycle (with 12 CONH groups each) is attributed to templating hydrogen bond patterns between amide groups [6], as in comparable template syntheses of catenanes and rotaxanes [7–9].

Summing up the results of these knotane syntheses so far, we draw the following conclusions regarding the nature of the template formation mechanism. Whilst no additional templating agent (external template) is used, all six educt molecules are reacting in an 'internal templating reaction' that yields the molecular knot. A helical host loop, suggested by the X-ray crystal structure of the knot **1a** [2], could wind itself around the isophthaloyl amide guest **2** [3]. The host/guest bonding is achieved via hydrogen bonding between amide groups of host and guest parts [7]. The two

remaining acid chloride functions **3a** react with the terminal amide groups of the loop, thus forming the molecular knot in the course of a hitherto unknown pre-organisation pattern.

In spite of the complex formation mechanism, knotane syntheses can be carried out using modified building blocks as well as the introduction of many functional groups (e.g., methoxy or carbethoxy groups). The cleavage of such groups that are also useful for solubility steering, allows for the first time to use molecular knots as precursors for further reactions (e.g., chiral nano scaffolds) [10].

We therefore have strong evidence to believe that in the future the up-to-now rather rare topologically chiral molecular knots will increase significantly in number, functionality and dimension, as has been realized during the past few years in the field of catenanes, rotaxanes and more complex topologically chiral bridged representatives ([1]rotaxanes, pretzelanes, 'supramolecular eight' [11]).

Acknowledgements

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