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Novel Amide-Based Molecular Knots: Complete Enantiomeric Separation, Chiroptical Properties, and Absolute Configuration**

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Amir-Hossain Parham, Michael Knott,
Walter M. Müller, Ute Müller, Yoshio Okamoto,*
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and Stefan Grimme*

Recently we described the first knot-shaped molecule[1] containing amide bonds.[2] We now report the syntheses of new "knotanes",[3] the first complete separation of a racemic knotane mixture, and the experimental and theoretical characterization of the compounds; we also give hints about a possible formation mechanism.

The baseline separation of the racemic trefoil knot **3aα**[2] (see Scheme 1) was achieved by high-pressure liquid chromatography (HPLC)[4] on a Chiralpak-AD-type column that is not commercially available, in which the silica gel and the chiral stationary phase are covalently bound so that the material does not "bleed out", even if lipophilic eluents are used. While, previously, eluents like hexane/ethanol (85/15) without trichloromethane resulted only in incomplete resolution (peaks with "shoulders"),[2] we were now able to

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separate the enantiomers with an astonishingly large separation factor (α) of 2.14 (Figure 1, Table 1).

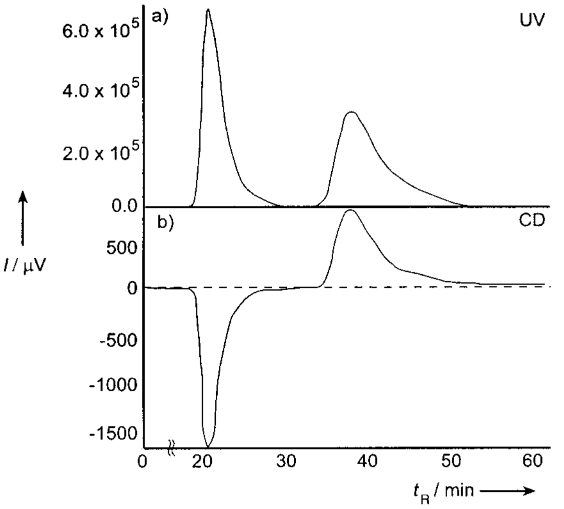


Figure 1. Separation of racemic knot **3aα** by HPLC: a) UV detection and b) circular dichroism detection of both enantiomers. Both graphs were measured at $\lambda = 280$ nm and show intensity I against retention time t_R.

The experimental circular dichroism (CD) spectra of the enantiomers of **3aα** are shown in Figure 2; the two curves a and b are mirror symmetrical and exhibit maxima at 240 nm ($\Delta\varepsilon = +100, -108\,\text{mol}^{-1}\text{L}\,\text{cm}^{-1}$), 272 nm ($\Delta\varepsilon = \pm 4\,\text{mol}^{-1}\text{L}\,\text{cm}^{-1}$), and 293 nm ($\Delta\varepsilon = \pm 8\,\text{mol}^{-1}\text{L}\,\text{cm}^{-1}$). Curves c and d in Figure 2 are theoretically calculated CD spectra of knotane **3aα** that were simulated prior to the actual experimental measurements. They were calculated with a semiempirical π-electron method (time-dependent Pariser–Parr–Pople, TDPPP),[6a] with all benzene and amide building blocks accounted for (altogether 156 π electrons, 144 atoms). The TDPPP calculation and the subsequent simulation of the CD spectrum[6b] were based once upon the crystal structure (Figure 2, curve c) and once upon a fully optimized AM1 geometry (Figure 2, curve d).[6c] Considering the simplicity of the calculation method and the complexity of the molecule, the resulting theoretical spectrum represents an astonishingly close fit to the experimentally obtained curve. The AM1-geometry method delivers a quite accurate prediction of the position and intensity of the strong band at 240 nm. The multitude of transitions of this band result mainly from the exciton-coupled $B_{a/b}$ states of the benzene/benzeneamide units. The slightly positive band at around 290 nm in the CD spectrum corresponds to the intensive shoulder in the UV spectrum ($\varepsilon = 40\,000\,\text{mol}^{-1}\text{L}\,\text{cm}^{-1}$), caused by the lowest transitions in the benzeneamide-units. The negative Cotton effect at 270 nm, also correctly predicted by the calculation, is due to the coupled L_b transitions. Since the sign of the two weak signals relies heavily on the applied geometry, they do not allow an assignment of the absolute configuration. In contrast, the strong band at 240 nm is stable in respect to variations in the calculations and allows the absolute configuration of the laevorotatory enantiomer at 365 nm (with a negative Cotton effect at 240 nm) to be clearly assigned as ppp.[7, 8] The strong blue shift of this band when the crystal structure is used as the basis for the TDPPP calculation is explained by a higher degree of intertwinement between the amide and the benzene units (decrease of conjugation) compared to the AM1 structure, which seems to reflect better

Table 1. Experimental data of enantiomer separation.

Compd	HPLC resin	Eluent n-hexane/ Cl_3CH/iPrOH	Flow rate [mL min^{-1}]	Selectivity factor $\alpha = k'_2/k'_1$
3aα	Chiralpak-AD-type[5]	30/20/1	0.5	2.14
3aβ	Chiralpak-AD-type[5]	30/20/1	0.5	2.14
3bα	Chiralpak-AD-type[5]	15/10/1	0.5	11.32
3cα	Chiralcel-OD-type[9]	65/30/5[a]	0.8[b]	1.34
3aα	Chiralpak-AD-type[9]	75/21/4	0.7[a]	1.60
3aγ	Chiralpak-AD-type[5]	60/40/1	0.5	1.92
3aδ	Chiralpak-AD-type[5]	60/40/2	0.5	1.78

[a] With ethanol instead of isopropylalcohol. [b] Column dimensions: 250 × 4 mm.

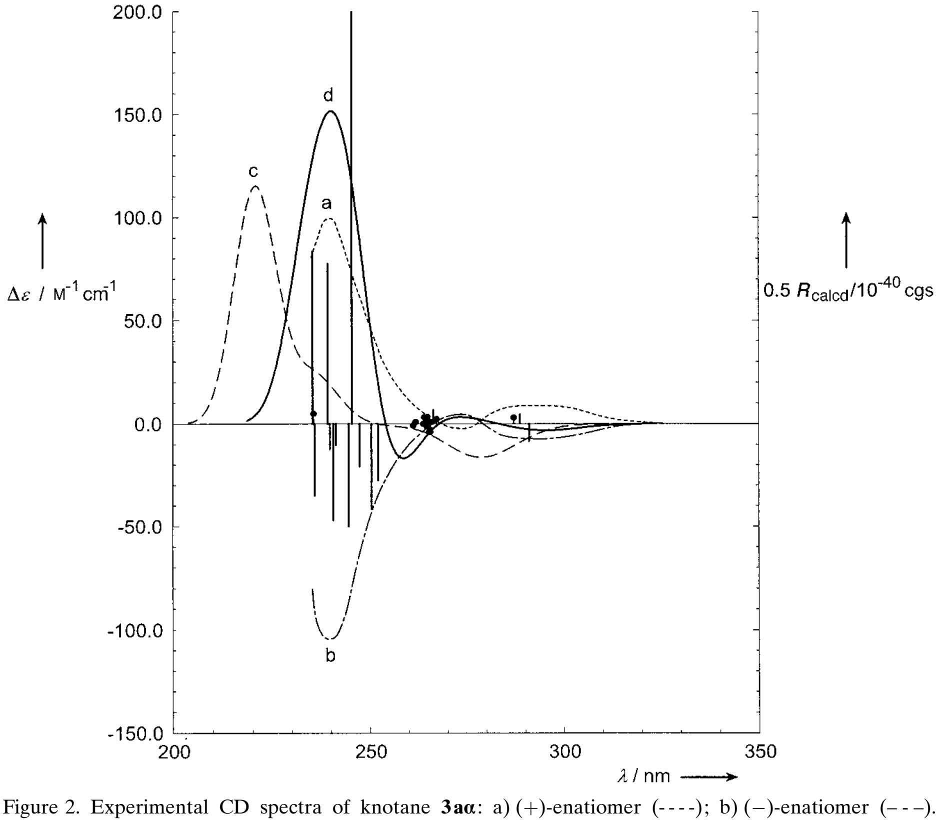
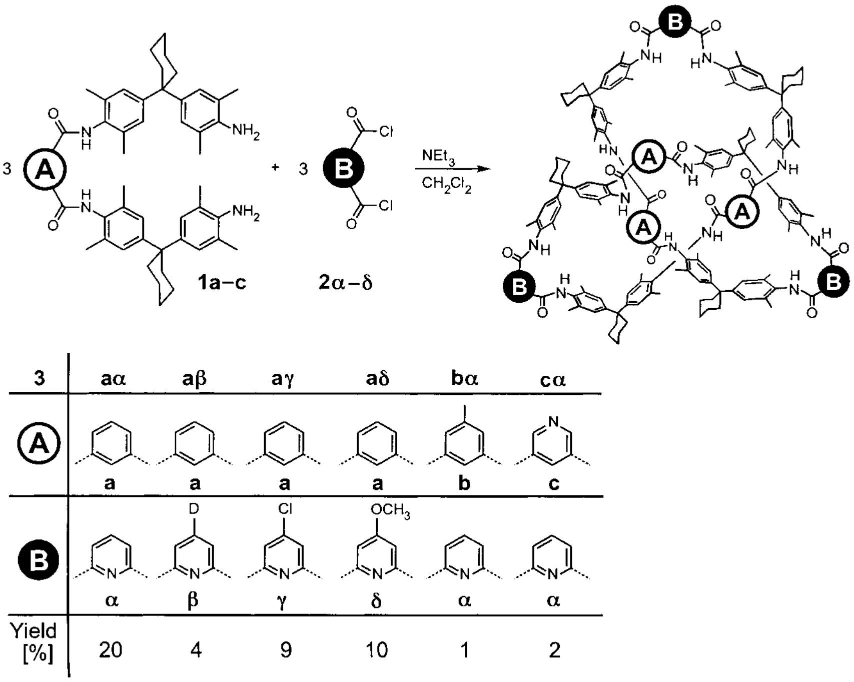


Figure 2. Experimental CD spectra of knotane **3aα**: a) (+)-enatiomer (----); b) (−)-enatiomer (- - -). Theoretical CD spectra of knotane **3aα**: c) Based on the X-ray crystal structure analysis (– – –); d) based upon the knot structure calculated with AM1 (——).

the situation in solution. We know from molecular dynamic simulations (5 ps at 300 K)[6d] that the knot structure is relatively fixed by hydrogen bonds and sterically demanding substituents. This allows us to conclude that no significant differences in the theoretical simulation are to be expected due to the flexibility of the molecular knot.

The limits and possibilities of knotane formation were explored (Scheme 1). Initial attempts to synthesise the knot **3aα** from the "inverted building block" (that is, by treatment of the extended diamide with acid chloride **2α** to form building block "**1α**" (not shown) and then trimerization and cyclization with isophthalic acid dichloride failed to deliver any isolable amounts of knotane. The previously published synthesis of **3aα** proved to be quite solvent dependent: The use of dimethylformamide as the solvent instead of dichloromethane did not lead to the formation of knotane in noticeable amounts. In order to make the ^{1}H NMR signal assignment of the **3aα** knotane easier, the diamide **1a** was treated with 5-deutero-2,6-pyridine dicarboxylic acid dichloride **2β**. The enantiomers of the new knotane **3aβ** were separated under conditions similar to those for **3aα**, in order to verify the previous results. The steric bulk of a methyl group in the 5-position seems to be sufficiently small to allow a new molecular knot **3bα** to be formed from 5-methyl-isophthalic acid diamide **1b**. The racemate separation on the Chiralpak-AD column is mentioned earlier (Table 1).



Scheme 1. New amide molecular knots **3**.

The X-ray crystal structure analysis of knotane **3aα**[2] showed the existence of intramolecular hydrogen bonds between the amide protons and the pyridine nitrogen atom. This could allow a preference of conformation in an intermediate structure during the synthesis, thus allowing the knotted structure to be formed. The aim of the following reaction was to investigate whether the knot synthesis failed when the specific conformation of the intermediate structure was not allowed to form. The 3,5-pyridine building block **1c** was reacted with acid chloride **2α** to yield the knotane **3cα**. This was separated into its enantiomers on a chiral stationary phase (CSP) of the OD type,[9] in which the stationary phase forms a branched, polymeric coating on the silica and makes it, therefore, solvent resistant (Table 1). The separated peak volumes were collected from several experiments on this column and an external CD spectrometer was used to record the two mirror-symmetrical CD spectra. Similar chromatographic separation results were obtained for **3cα** with a two dimensionally branched CSP of the AD type; under the same separation conditions as above an *α* value of 1.6 was obtained (Table 1).

Furthermore the 2,6-pyridinedicarboxylic acid dichlorides **2γ** and **2δ**, substituted in the 4-position, were reacted with the building block **1a**. The successful syntheses yielded the knotanes **3aγ** and **3aδ**, which could be quantitatively baseline separated into their respective enatiomers (Table 1).

Summing up the results of the knotane syntheses so far, we are able to draw the following conclusions regarding the nature of the templating formation mechanism:[2, 10] No additional templating agent (external template) is used, rather all six educt molecules are reacting in an "internal templating reaction" that yields the molecular knot. A helical host loop, suggested by the crystal structure[2] of the knot **3aα** could wind itself around the guest **1a** (Figure 3). The host/guest bonding is then achieved through hydrogen bonding. The two remaining acid chlorides **2a** react with the terminal amide groups of the loop, thus forming the molecular knot **3aα**: A novel preorganization pattern.[11]

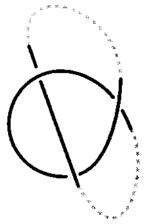


Figure 3. Postulated supramolecular template to allow formation of the molecular knot (host loop and amide host are fixed by hydrogen bonds between the CONH hydrogen atoms and the carbonyl oxygen atoms.

In spite of the complex formation mechanism, knotane synthesis can be carried out with other arene building blocks, such as thiophene rings,[12a] as well as with the introduction of other functional groups (for example, methoxy groups in **3aδ**). The cleavage of ether groups[12b] allows, for the first time, the use of molecular knots as precursors for further reactions (for example, nano particles[13]). We therefore have strong evidence to believe that topologically chiral molecular knots,[1–3] which up until now have been rather rare, will increase significantly in number in the future.

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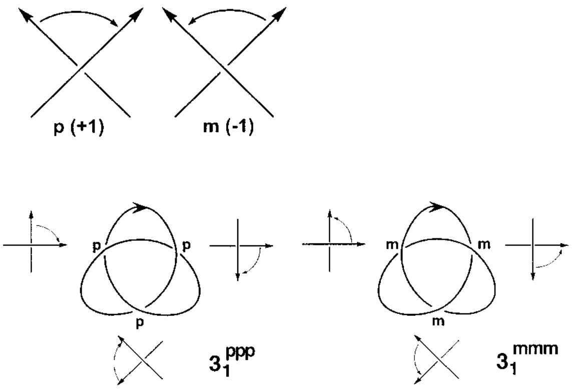

Figure 4. Determination of the chirality of knotted molecules.

Synthesis of the First 1,3,4-Triphosphole Complex[**]

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Dedicated to Professor Manfred Regitz on the occasion of his 65th birthday

The development of phosphorus-containing 6π-arenes such as phosphinines (phosphabenzenes) is currently attracting attention because of the considerable interest from industry in novel directing ligands for catalytic processes,[1, 2] yet it still suffers from a lack of rational and efficient synthetic methods. Interesting candidates as novel ligands with 6π-electron systems besides phosphinines are phosphorus-rich hetero-

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