Diastereoisomeric Molecular Knots by Combination of Central and Topological Chiralities

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We report an unprecedented example of diastereoisomerism created by reaction of topologically chiral molecular knots (knotanes) bearing hydroxy groups with centrochiral (1*S*)-(+)-camphor-10-sulfonyl chloride. The diastereoisomers of knotanes bearing on their periphery one and three camphorsulfonyl units have been completely separated using commercial silica gel (Kromasil) and chiral (Chiralpak AD) HPLC columns respectively. The circular dichroisms of the separated samples have been measured and consequences of the chiral induction discussed.

Introduction

The type of molecular diastereoisomerism[1] arising due to the presence of more than one chiral element in the same molecule (so called σ-diastereoisomerism[2]) has been known since Pasteur's famous experiments with tartaric acid. Nowadays the formation of diastereoisomeric intermediates by means of chemical reaction or non-covalent association of enantiomerically pure chiral reagents (chiral auxiliaries) with enantiomeric mixtures is an important tool in NMR analysis[3] and separation science.[4]

Most of the diastereoisomeric species known so far, such as sugars and peptides, have multiple stereocenters.[1,2] Diastereoisomers involving the combination of different stereogenic units (e.g. central and axial stereogenic units) in one molecule, recently reviewed by Nicolaou and Siegel,[5] are scarce. The cyclodiastereoisomeric [3]rotaxane assembled in our group[6] is a rare example of diastereoisomerism due to the existence of different orientations of two unsymmetric monosulfonamide macrocycles encircling the axle. Topologically chiral diastereoisomeric molecular composite knots synthesized by the Sauvage group[7] exhibit another type of diastereoisomerism brought about by two topologically chiral units in one molecule, as do the molecular dumbbell[8] and the knotaxanes,[9] [composed of two covalently linked amide-type molecular knots (knotanes)] recently synthesized and chirally resolved by our group. Circular DNA[10] containing a multicatenated structure bears on its backbone numerous chiral centers in the deoxyribose units, and therefore represents a unique natural blend of topological and central chiralities. The combination of topological and central chiralities in an artificial molecular system was introduced in 1996 by Sauvage et al., who reported the first chiral resolution of an ionic molecular knot,[11] by the crystallization of a dicopper(I) complex of a racemic phenanthroline-based trefoil molecular knot with (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl phosphate.

Results and Discussion

We report the first example of diastereoisomeric species produced by a covalent linking of topologically chiral and centrochiral units. As the topologically chiral platform we have used monohydroxy- **1** and trihydroxyknotanes **2** which have been shown to be valuable building blocks for many syntheses.[8−12] Acylation of **1** and **2** with commercially available (1*S*)-(+)-camphor-10-sulfonyl chloride in THF in the presence of Et_3N gives rise to diastereoisomeric sulfonates **3** and **4** respectively. ^{1}H NMR and FAB MS confirmed the structure of **3** and **4**, and HPLC analysis showed their high purity. Analysis of the ^{1}H NMR spectra of the diastereoisomeric knotanes **3** and **4** reveals, however, no splitting of the knotane protons, reflecting the fact that the distance of the chiral centers in the camphorsulfonyl moieties is insufficient to produce diastereoisomerism in the ^{1}H NMR spectrum.

We successfully resolved the diastereoisomeric pairs of both **3** and **4** using HPLC. Figure 1 depicts chromatograms showing the resolution of both **3** and **4**. Interestingly, the complete separation of the diastereoisomers of **3** could be performed on an achiral silica gel column, whereas the resolution of the diastereoisomers of **4** could only be accomplished by using a commercial Chiralpak AD chiral

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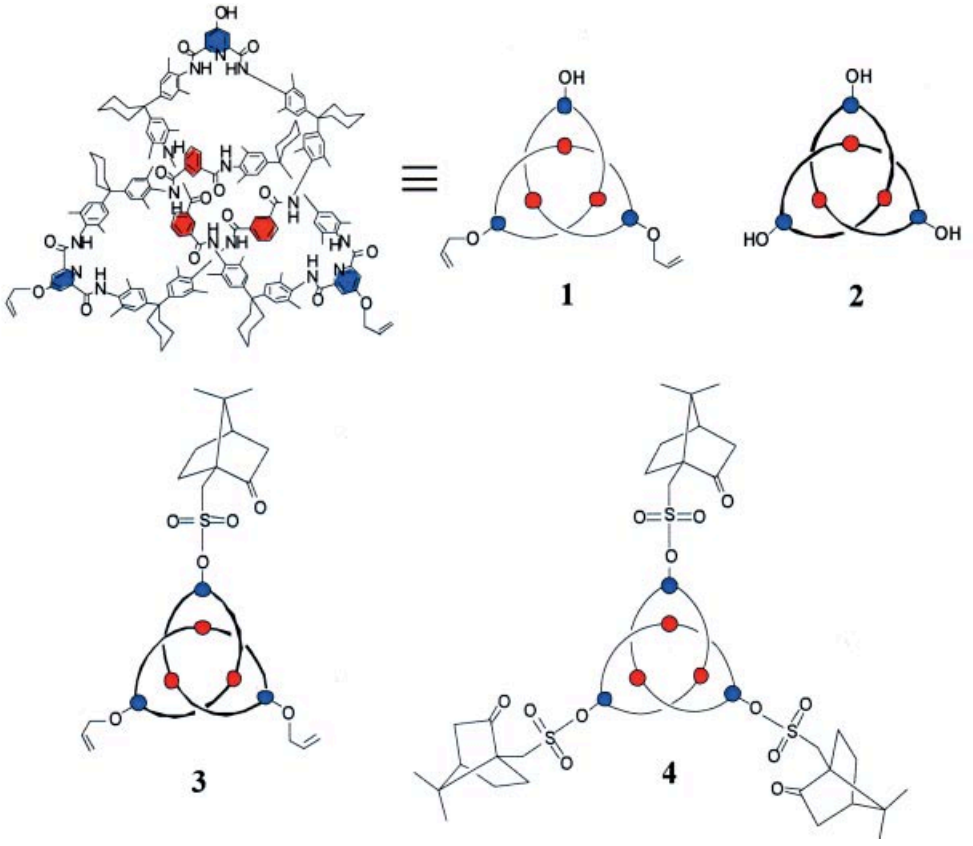

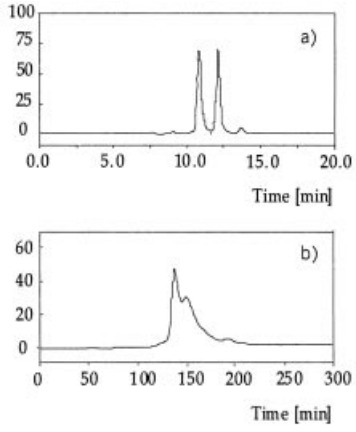

Figure 1. a) Separation of the diastereoisomers of **3** (column: Kromasil, material: silica gel, particle size 5 micron, hexane/ethanol, 60:40); b) Separation of the diastereoisomers of **4** (column: Chiralpack AD, material: noncovalent cellulose carbamate, hexane/2-propanol, 60:40)

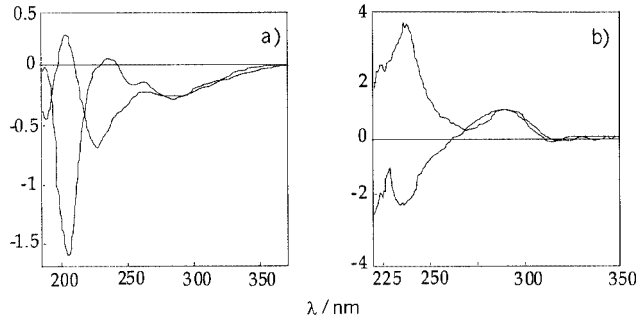

Figure 2. Circular dichrograms of diastereoisomers of a) **3**; b) **4** (recorded in 2,2,2-trifluoroethanol)

HPLC column. We can explain this difficulty by the tight homochiral periphery of **4**; the three camphorsulfonyl moieties interact with the stationary phase and shield the racemic knotane core. The chiral induction of the (1*S*)-(+)-camphor-10-sulfonyloxy moieties on the knotane centers in the diastereoisomers of both **3** and **4** breaks down the mirror-image symmetry of circular dichrograms (Figure 2) that is present in the enantiomers of knotanes.[8,9,12]

Conclusion

To sum up, the covalent linking of topologically chiral knotanes with centrochiral camphor units gives rise to an unprecedented type of diastereoisomerism. The fact that the mono-sulfonate **3** can be easily resolved by silica gel column chromatography suggests that this process could be utilized for the preparative diastereoisomer-mediated chiral resolution of racemic knotanes. The circular dichrograms of the resolved diastereoisomers of **3** and **4** demonstrate the vivid influence of the peripheral camphor units on the topologically chiral nano-sized knotane cores.

Experimental Section

General Remarks: Melting points were determined with a Reichert Thermovar microscope and are uncorrected. NMR spectra were recorded using 300 and 400 MHz Bruker instruments; the solvent signals were used for internal calibration. Only well resolved signals in ^{1}H NMR spectra are referenced below. For the detailed dis-

cussion on the NMR spectra of knotanes see ref. 12b. Mass spectra were recorded using a Concept 1H spectrometer from Kratos Analytical Ltd., Manchester, GB (FAB).

(1*S*)-(+)-Bis(allyloxy)-camphor-10-(sulfonyloxy)knotane (3): A solution of (1*S*)-(+)-camphor-10-sulfonyl chloride (10 mg, 0.042 mmol) in dry THF (2 mL) was added to a stirred solution of bis(allyloxy)monohydroxyknotane (**1**) (60 mg, 0.021 mmol) and triethylamine (0.1 mL, 0.7 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 24 h and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel with CH_2Cl_2/ethyl acetate (5:1) as eluent. R_f = 0.80; yield 42 mg (64%); m.p. >300 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, ppm): δ = {0.06, 0.86, 0.96, 1.07, 1.24, 1.37, 1.49, 1.57, 1.59, 1.82 (br), 1.97, 1.99, 2.02, 2.11, 2.20, 2.25, 2,.26, 2.28, 2.29, 2.32, 2.36, 2.42, 3.89, 3.90}} (CH_2 and CH_3), 4.90 (m, 4 H, O*CH*$_2$), 4.98 (br., 1 H, ArH), 5.32−5.48 (m, 4 H, *CH*$_2$=CH), 5.84 (d, J_3 = 7 Hz, 1 H, ArH), 6.08 (m, 2 H, *CH*=CH_2), {6.42, 6.45, 6.52, 6.64, 6.65, 6.81 (br.), 6.83, 6.91, 6.96, 6.99, 7.16, 7.34, 7.35, 7.38, 7.41, 7.44, 7.50, 7.52, 7.54, 7.57, 7.76−7.82, 7.87−7.92, 8.20−8.26, 8.31, 8.32} (39 H, ArH), {8.27, 8.58, 8.61, 9.07, 9.14, 9.34, 9.36, 9.54, 9.57, 9.79, 10.21, 10.25, 10.49, 10.52, 10.58, 10.62, 10.99, 11.00, 11.09, 11.12} (12 H, NH) ppm. FAB MS: 3061.7 [M$^+$]. $C_{193}H_{211}N_{15}O_{18}S$ requires M^+ = 3061.0.

Tris[(1*S*)-(+)-camphor-10-(sulfonyloxy)]knotane (4): A solution of (1*S*)-(+)-camphor-10-sulfonyl chloride (25 mg, 0.1 mmol) in dry THF (2 mL) was added to a stirred solution of trihydroxyknotane (**2**) (80 mg, 0.029 mmol) and triethylamine (0.1 mL, 0.7 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 24 h and the solvent was then evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel with CH_2Cl_2/ethyl acetate (5:1) as eluent. R_f = 0.65; yield 31 mg (31%); m.p. > 300 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, ppm): δ = {0.06, 0.87, 0.96, 1.07, 1.24, 1.39, 1.49, 1.58, 1.82 (br.), 1.97, 1.99, 2.02, 2.11, 2.21, 2.26, 2.29, 2.32, 2.36, 2.42, 3.89, 3.90} (CH_2 and CH_3), 4.98 (t, J_3 = 7 Hz, 1 H, ArH), 5.33 (s, 1 H, ArH), 5.84 (d, J_3 = 7 Hz, 1 H, ArH), {6.44, 6.46, 6.52, 6.63, 6.65, 6.81 (br), 6.83, 6.91, 6.96, 7.00, 7.17, 7.21, 7.34, 7.37, 7.40, 7.46, 7.51, 7.52, 7.54, 7.57, 7.78, 7.81, 7.89, 7.91, 7.92, 8.20−8.26, 8.31, 8.32} (39 H, ArH), {8.27, 8.61, 9.08, 9.15, 9.34, 9.54, 9.79, 10.25, 10.58, 10.62, 11.09, 11.12} (12 H, NH) ppm. FAB MS: 3408.6 [M$^+$]. $C_{207}H_{231}N_{15}O_{24}S_3$ requires M^+ = 3409.4.

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