in agreement with the assignments of Y112 (5.29 ppm), I113 (5.05 ppm), and I149 (5.39 ppm) in rabbit skeletal TnC.[12] The downfield shifts of these four resonances and the observation of characteristic crosspeaks in two-dimensional NOE experiments[14] suggest their involvement in a short three-residue antiparallel β-sheet between sites III (positions 112–114) and IV (positions 148–150) which has been observed in the X-ray structures of TnC.[15] An analogous β-sheet is also observed in the site III[3] and site IV[5] homodimers.

The ^{1}H NMR spectrum of Ca_2-SCIII/SCIV (Figure 2C) is nearly identical to that of Ca_2-TR_2C (Figure 2D) and quite distinct from those of the homodimers Ca_2-$SCIII_2$ (Figure 2A) and Ca_2-$SCIV_2$ (Figure 2B), indicating the preferential formation of a two-site SCIII/SCIV heterodimer similar in fold to the carboxyl terminal domain of TnC. These results show that, at least for calcium-binding proteins, synthetic peptides can be folded and assembled specifically into stable protein domains, similar to results obtained for coiled coils,[16] zinc fingers,[17] and fragments of BPTI.[18]

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Experimental Studies on the Hook and Ladder Approach to Molecular Knots: Synthesis of a Topologically Chiral Cyclized Hook and Ladder[1]

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The colored figure-of-eight knot illustrated Figure 1 is the simplest known topological rubber glove[2] and represents the only class in the topological hierarchy of molecular chirality not yet realized in an actual molecular structure.[1] This type of knot cannot result from the Möbius ladder approach to synthsis of knots and links,[3-5] suggesting exploration of a new topological approach, the "hook and ladder",[2c] with the ultimate goal being creation of a molecular topological rubber glove. Herein we report the first synthesis of a molecular hook and ladder and its bismacrocyclization to afford the topologically novel $^1/_4$-twist cyclized hook and ladder.

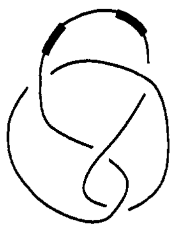
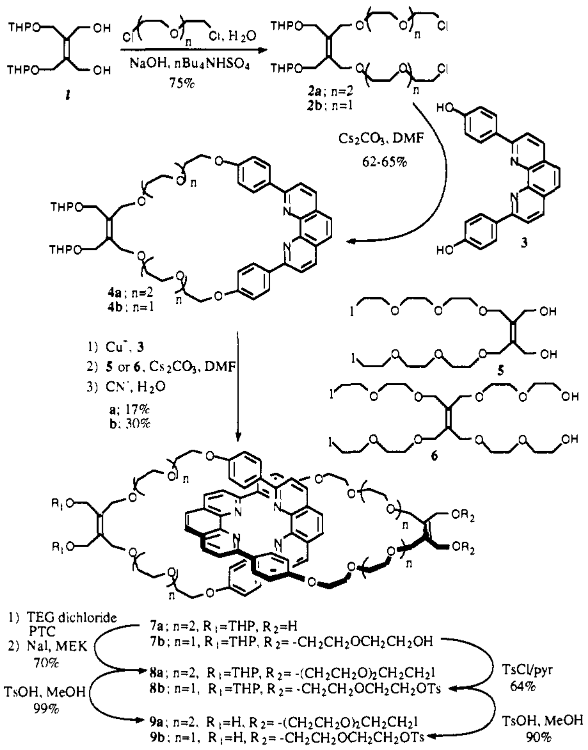
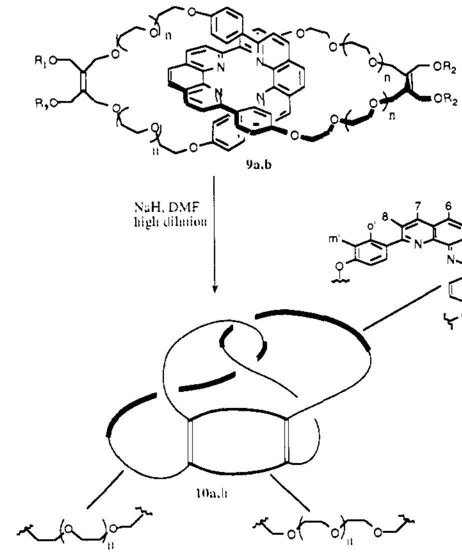


Figure 1. Topological rubber glove.

Scheme I. Synthesis of Hook and Ladders **9a** and **9b**



Scheme II. Synthesis and Proposed Conformation of the Cyclized Hook and Ladder Compounds **10a** and **10b**



The key hook and ladder intermediate is actually a catenane (the hook) functionalized with rungs and uprights on each ring (the ladder). Furthermore, the ends of the uprights are func-

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[1] This paper is part 8 in a series on topological stereochemistry. Previous papers in the series: Walba, D. M. A Topological Hierarchy of Molecular Chirality and other Tidbits in Topological Stereochemistry. In *New Developments in Molecular Chirality*; Mezey, P. G., Ed.; Kluwer Academic Publishers: Boston, 1991; pp 119–129 and references therein.

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tionalized such that they may be connected chemically. For molecular realization of this structure, we felt that Sauvage catenanes[6] and tetrakis(hydroxymethyl)ethylene (THYME) polyether rungs and uprights[4] would prove nicely complementary.

Synthesis of the hook and ladder (actually two homologues, **9a** and **9b**) is shown in Scheme I.[7] One notable aspect of the synthesis is obviation of the need for orthogonal hydroxyl protecting groups by taking advantage of the differing reactivities of the phenolic and THYME hydroxyl groupings. Use of orthogonal protecting groups was a key feature of the Möbius ladder syntheses.[4] In addition, while the Sauvage catenane formation occurred more rapidly in the reaction forming a 38-membered ring (**4a** → **7a**), the yield of linked product was better in the 32-membered ring system (**4b** → **7b**) due to improved inhibition of unwanted decomplexation of diphenol **3** from the catenate precursor of **7b**.

Intramolecular cyclization of the hook and ladder molecules affords only one possible product from the initial cyclization. The second cyclization step may afford a number of possible topological diastereomers—the simplest being the racemic $^{1}/_{4}$-twist diastereomers **10a,b**, as illustrated in Scheme II. Examination of CPK models indicates that more highly twisted isomers of **10** are more strained and/or less flexible. This, in combination with our prior experience with the THYME polyethers suggesting that twisting in the THYME ladders is disfavored,[4b] led to the expectation that the major product of the cyclization would be the minimally twisted cyclized hook and ladder **10** as shown.

Cyclization of compounds **9a** and **9b** proceeded in a similar fashion, affording a single major product along with minor products as evidenced by TLC of the crude reaction mixture. In the latter case, two preparative runs each gave about a 60% yield of the major product after flash chromatographic purification on silica gel, allowing isolation of over 50 mg of the material.

In both cases, the ^{1}H NMR spectrum of the major product is nicely consistent with the expected $^{1}/_{4}$-twist structure **10**,[7] though the data do not rigorously rule out the possibility of knotted structures. Thus, the representation of structures **10** shown in Scheme II is a careful schematic illustration of the proposed preferred conformation (actually a large set of similar conformations) of compound **10b** as indicated by CPK models. This structure is consistent with the clear 2-fold symmetry observed in the room-temperature ^{1}H spectrum of compound **10b**. Thus, there are two sets of diphenylphenanthroline resonances (separate doublets for H_m and $H_{m'}$, H_o and $H_{o'}$, H_3 and H_8, H_4 and H_7, and an AB quartet for protons H_5 and H_6), consistent with the diastereotopic nature of these protons in conformation **10**.[8] While the spectrum of **10a** is not as well resolved, it is clearly consistent with this argument.

When heated in DMF-d_7 solution, the spectrum for each cyclized hook and ladder collapses in the high-temperature limit to one showing a single diphenylphenanthroline system.[8] The coalescence temperatures for the various pairs of protons all indicate an effective free energy of activation $\Delta G^{\ddagger}$ of about 20 kcal/mol for both compounds **10a** and **10b** for the process leading to exchange on the NMR time scale. This observation seems consistent with CPK modeling, where conformational changes can indeed exchange the protons which are diastereotopic in the conformation shown.

In conclusion, synthesis of the simplest cyclized hook and ladder graph has been achieved. The structure represents a new form of topologically chiral molecule possessing none of the classical elements of topological dissymmetry (an oriented link, a chiral link with more than two crossings, a knot, or a nonplanar graph).[9,10] Additional studies on the structure and properties of compounds **10** and other members of this unique class of topological stereoisomers will be reported in due course.

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Supplementary Material Available: Full experimental details for the preparation of all new compounds in the sequence leading to **10b** and analogue ^{1}H NMR spectra for compound **10b** taken at 25, 100, and 145 °C (15 pages). Ordering information is given on any current masthead page.

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[7] All new compounds in the sequence leading to **10a** were tentatively identified by ^{1}H NMR spectroscopy. Compounds **4a**, the copper complex of **4a** with **3**, **7a**, the copper complex of **7a**, the dichloride precursor of **8a**, and **9a** were characterized by FAB mass spectrometry. All new compounds in the sequence leading to **10b** gave consistent ^{1}H and ^{13}C NMR, IR, and FAB mass spectra, and compound **10b** was also characterized by electrospray mass spectrometry. Compounds **1**, **2b**, **4b**, and **6** gave satisfactory combustion analyses. The catenanes in the sequence consistently gave combustion analyses low in carbon, presumably due to inclusion of small amounts of solvent in the glassy products. Experiments aimed at producing high-resolution FAB mass spectra for the new compounds are in progress.

[8] The difference in chemical shift for the diastereotopic pairs of protons for **10b** is as follows: $\Delta\nu$ $H_{o,o'}$ = 48.9 Hz, $H_{m,m'}$ = 31.5 Hz, $H_{3,8}$ = 42 Hz, $H_{4,7}$ = 32 Hz, and $H_{5,6}$ = 8 Hz. At 145 °C, H_5 and H_6 give rise to a sharp singlet and H_m and $H_{m'}$ collapse to a single doublet. The pairs of protons with a large $\Delta\nu$ ($H_{3,8}$ and $H_{o,o'}$) coalesce, but remain very broad at 145 °C. The signal for protons H_4 and H_7, presumably a doublet, is hidden within the broad peak associated with the $H_{o,o'}$ protons.

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[10] The uncolored $^{1}/_{4}$-twist hook and ladder is topologically achiral. Structure **10**, however, *is* topologically chiral due to the coloring introduced by the phenanthroline units and the double bonds. We thank Professor Jonathan Simon of the University of Iowa Department of Mathematics for providing a proof of the topological chirality of this graph prior to publication.

Preparation, Characterization, and Crystal Structures of Octasilacubanes and Octagermacubanes[1]

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The chemistry of group 14 polyhedranes is receiving current intense interest.[2] In 1989, we reported the preparation and crystal structure of hexagermaprismane.[3] Sita and Kinoshita reported octastannacubane with its crystal structure.[4] Matsumoto et al. also reported octasilacubane[5] in 1988, but no crystal structure has been given so far.[6] We report here the first successful syntheses

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