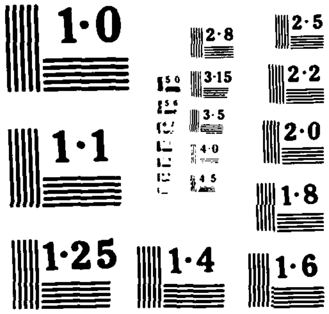
AD-A163 124 ANNUAL LETTER REPORT ON ONR (OFFICE OF NAVAL RESEARCH) 1/1
CONTRACT NUMBER N00014-85-K-0228(U) COLORADO UNIV AT
BOULDER 02 DEC 85 N00014-85-K-0228
UNCLASSIFIED F/G 7/4 NL

END
FILMED
4-
DTIC



NATIONAL BUREAU OF STANDARDS
MICROCOPY RESOLUTION TEST CHART

University of Colorado
Boulder, CO 80309

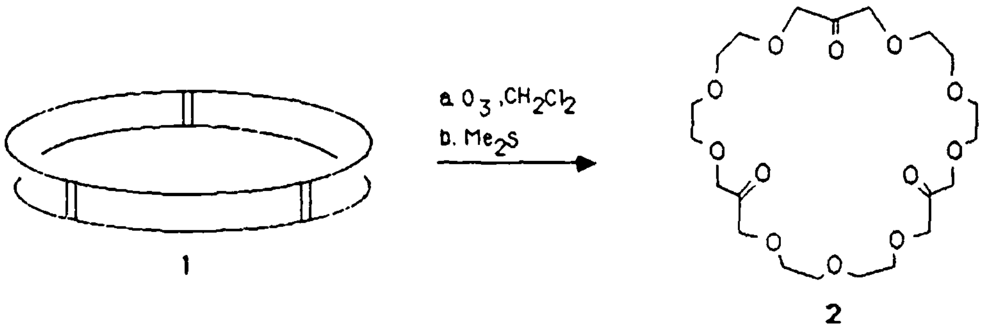
ONR Contract No. N00014-85-K-0228
Annual Letter Report
December 2, 1985

Introduction. During the past year, several exciting developments in topological stereochemistry have occurred, both theoretical and experimental. Concerning the theory of topological stereochemistry, the mathematics groups involved in the project have proven several of the conjectures presented in our Tetrahedron report, and exciting work on the topology front is in progress, as described in the report from the University of Iowa part of the consortium.

With regard to the synthetic topological stereochemistry under way on the Boulder campus of the University of Colorado, efforts are, of course, focusing on synthesis of a molecular knotted ring. Recent results in two projects directed towards this goal are discussed ~~below~~ in this report, one dealing with development of improved methods for breaking the rungs of the molecular Möbius ladders, and the other dealing with experiments on the four-rung THYME polyethers. A preprint of a paper accepted for publication in Tetrahedron describing this work in detail, is enclosed.

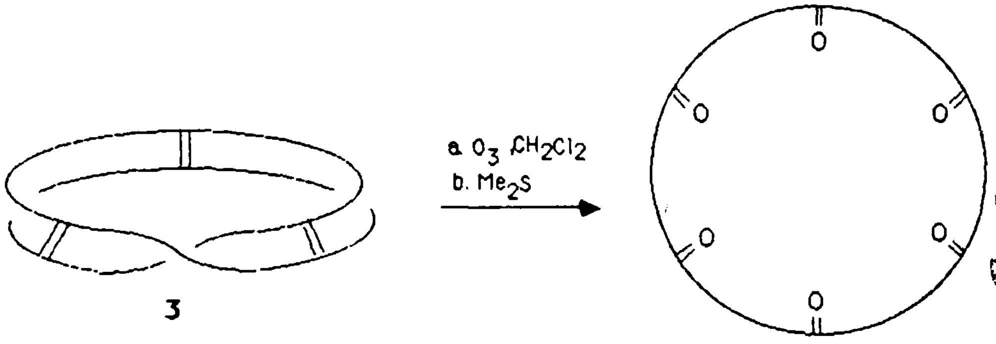
How to break the rungs of a Möbius ladder. Our approach to synthesis of a molecular knotted ring involves preparation of a Möbius ladder with three half-twists, then cleavage of the rungs of the ladder to give a trefoil knot. The rungs of the ladders prepared by the THYME polyether strategy are C-C bonds, and may be broken in a number of ways. Several years ago it was shown that cleavage of the 3-rung Prism **1**, and the 3-rung Möbius ladder **3** with ozone in dichloromethane at -78°C under carefully controlled conditions led to an excellent yield of the crown ethers **2** and **4**, respectively. Full characterization of these materials, however, has proven a difficult problem. Analytical gel permeation chromatography indicates that **4** is larger than **2**, as expected. In addition, the ^{13}C NMR spectrum of the two cycles are consistent with the structures shown. Obtaining clean ^{1}H NMR spectra at 250 MHz, however, has proven problematical. The integration of the ethyleneoxy peaks is always high relative to the methylene peak α to the carbonyl groupings. A major goal in the past year was obtaining mass spectra of these two materials.

Frustratingly, a nice molecular ion was observed for the small cycle **2** by chemical ionization mass spectrometry, while under identical conditions no peaks at all were observed for the large cycle **4**. Recently, utilizing equipment and expertise kindly provided by scientists at the NIH Clinical Mass Spectrometry Research Resource, University of Colorado Health Sciences Center, FAB mass spectrometry on compounds **2** and **4** has been successfully achieved. As expected, the small cycle **2** gives a rather small protonated molecular ion (with no other peaks observed), while cycle **4** gives a very nice, large protonated molecular ion. For us, observation of this ion in the mass spectrometer constitutes a breakthrough in this part of the project. The Department of Chemistry in Boulder has recently taken delivery of its own high mass, high resolution mass spectrometer possessing FAB capability, and such measurements should be routine on campus in the very near future.



1

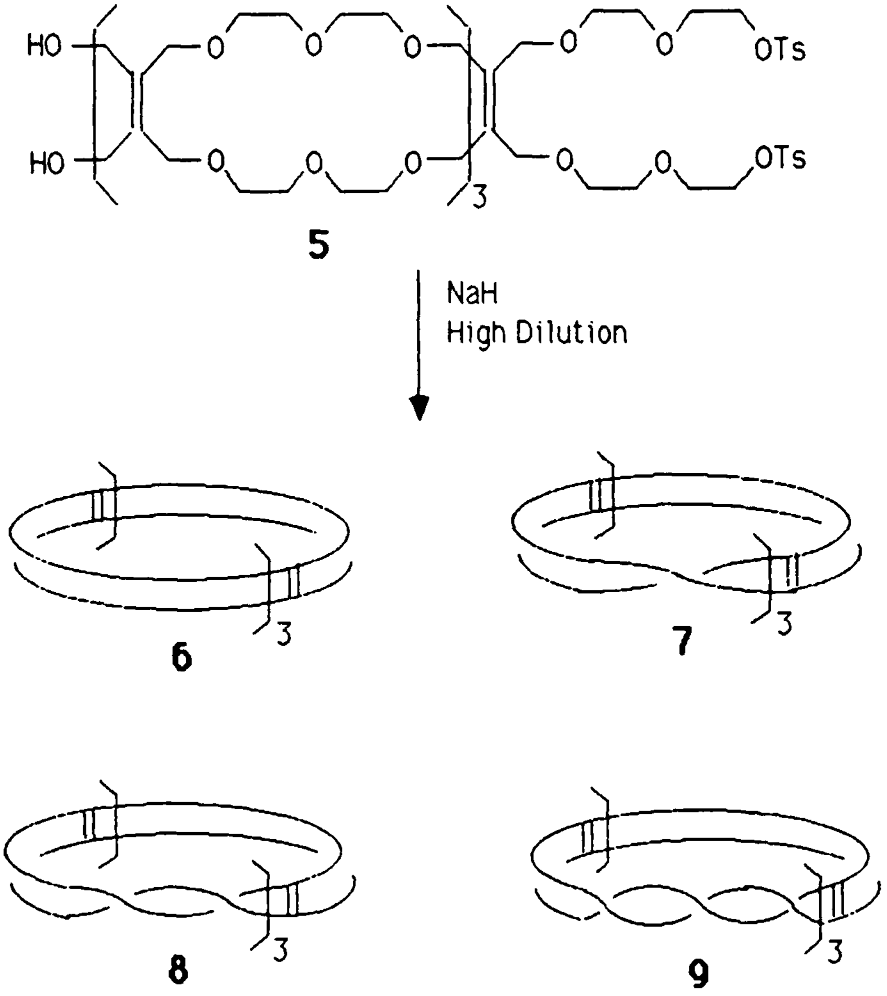
2



3

4

Given the carbon NMR and Mass spec evidence, the problems with attaining a clean proton NMR spectrum for compounds **2** and **4** were at first confusing. However, we have now shown that, in fact, the cycles **2** and **4** are quite unstable. Thus, simply upon standing at room temperature, cycle **2** is quantitatively converted to a new product, quite distinct by TLC, which shows a very complex carbon and proton spectrum. This material is tentatively identified as the product, or mixture of products, deriving from intramolecular aldol condensation of the carbonyl units. This result, in fact, is not at all surprising. Efforts to block the carbonyl reactivity of the products of ozonolysis by reduction, Wittig olefination, and thioketalization, are currently under way. Stabilization of these polyketones with respect to aldolization is particularly important for future work, since it is



expected that a knotted polyketone will be especially prone to intramolecular trans-annular reactions.

The four-rung THYME polyethers. Based upon examination of CPK molecular models, we had predicted that cyclization of the four-rung diol-ditosylate **5** would afford four products, with 0, 1, 2, and 3 half twists (**6**, **7**, **8**, and **9**, respectivley). In the event, very slow addition of a DMF solution of compound **5** to a suspension of NaH in DMF, followed by removal of solvent in vac. and flash chromatography of the crude product on silica gel, gave a 65% yield of a mixture of polyether cycles. Analytical and preparative chromatography on C-18 reverse phase HPLC resolved four products. However, two of these products were produced in a combined yield of <1%! It has not proven possible to isolate enough of either of the minor products in pure form to characterize them. The major products, however, were easily purified and characterized. One of these materials shows a singlet in the ^{1}H NMR spectrum for the allylic methylene, implying that it was the untwisted isomer **6**, which in this system is "turning inside out" rapidly on the NMR time scale. Subsequent single crystal X-ray analysis of this nicely crystalline materials confirms the structure as **6**.

The second major product of cyclization of compound **5** shows an AB pattern for the allylic methylene protons—consistent with any of the twisted isomers **7** - **9**. We suggest that this material is, in fact, the four rung Mobius ladder **7**, based upon arguments presented below. Interestingly, compounds **6** and **7** are well resolved by gel permeation chromatography! That is, even though they have identical molecular weights, the twisted product **7** behaves as if it were larger in solution than the untwisted product **6**. This seems highly reminiscent of the behavior of circular DNAs, where the topology of the helix controls the conformation of the circle in solution, and suggests the intriguing possibility that very large topologically stereoisomeric THYME cylinders and Möbius ladders might be separable by size exclusion chromatography. If this proves true, it opens the door for synthesis of such novel topological constructions as the double-looped catenane and the molecular Star of David.

Why are not all four products formed in equal amounts? In examination of CPK models, it seemed that the twisted products were no more strained than the untwisted one. However, it has now become quite clear that in large cyclic molecules such as these, space filling models are not a reliable method for estimation of strain energy. Our conjecture is that the twisted isomers, including **7**, are strained relative to the untwisted products, and this is the reason why compounds **8** and **9** are formed in only very small amounts. Note that the initial cyclization of the diol-ditosylate locks the molecule into either the 0,2 half-twist manifold, or the 1,3 half-twist manifold. The partitioning between 0 and 2, or 1 and 3 half-twists is then suggested to be determined by thermodynamics, i.e. the least strained products predominate. We know from X-ray crystallography that in the 0,2 half-twist manifold 0 half-twists is formed exclusively. It seems very unlikely, given the "twisting strain" hypothesis, that in the 1,3 half-twist manifold, 3 half-twists would be formed exclusively. Thus, we postulate that the twisted product of cyclization of **5** must be the one half-twist isomer **7**.

Our approach to solving the problem of synthesis of the desired three-half twist isomer is the obvious intuitive one: if three half-twists is too strained, use a longer strip. Thus, we are currently working on synthesis of the 5-rung diol ditosylate homologue of compound **5**, in the hope that this material will give a useful yield of three half-twist isomer. In addition, several possible approaches to inducing twist in polyether ladders of this type are under consideration.

END

FILMED

2-86

DTIC