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A Study of the Effect of *Z*- and *E*-Olefinic Geometry on the Rates of Ring Closure of 13-Membered Dienes

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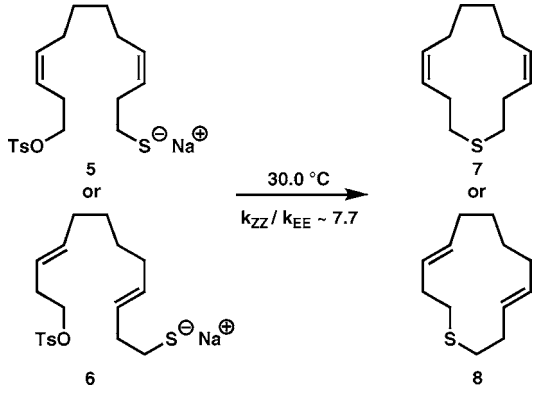
ABSTRACT



An analysis is presented to explain the faster rate of ring formation 5 → 7 as compared to 6 → 8.

Intramolecular cyclizations to form large rings (e.g., of ring size 12−30 members) have received little attention in recent years, even though they are poorly understood. Since 5- and 6-membered carbocyclic structures can be formed by cyclization reactions more rapidly and efficiently than larger rings, the activation entropies for the latter are generally thought to be more negative, and this factor is invoked to explain lower rates of ring closure. As early as 1935,[1] Ruzicka proposed that the probability of cyclizations should decrease as the distance between the reacting centers on the open chain increases. A series of kinetic studies by Illuminati, Mandolini, and their colleagues[2] confirmed the numerous qualitative chemical studies that indicated slow rates of cyclization for rings in the range from 8 to 11 members.[3] In addition, their work showed only small differences in the rates of cyclization (for lactone formation) for 12- to 23-membered rings.[4] Studies in this laboratory revealed that rates for the lactonization of ω-hydroxy-alkanoic esters varied moderately and irregularly with ring size as follows (ring size/relative rate): 12/0.20, 13/0.36, 14/1.0 (standard), 15/1.0, 16/2.5, 17/1.9, 18/1.35, 19/0.55, 20/1.55, 21/0.60. It is clear that the simple notion that the distance between the two reacting subunits at the ends of a chain in its *maximally* extended form determines rates of ring closure is oversimplified. There are several reasons why this should be so. As the number of atoms in the chain increases, the total number of non-extended, that is partially folded, conformations increases. Also the number of conformations of the cyclized structure increases. These two factors would tend to increase the rate of ring closure.

(1) Ruzicka, L. *Chem. Ind. (London)* **1935**, *54*, 2.
(2) For a review of this work, see: Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.
(3) (a) Galli, C.; Illuminati, G.; Mandolini, L.; Jamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591−2597. (b) Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051−1056.
(4) Corey, E. J.; Brunelle, D. J.; Stork, P. J. *Tetrahedron Lett.* **1976**, *17*, 3405−3408.

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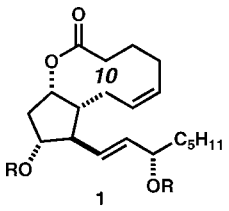

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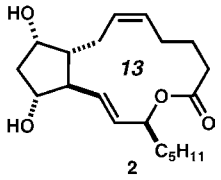

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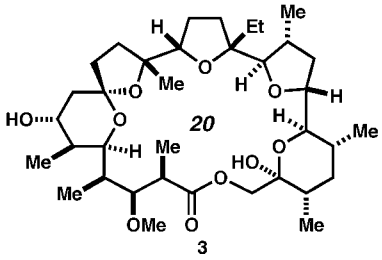

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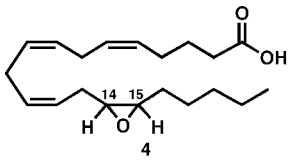
Still another factor that should be consequential is the number of bond rotations required to access the cyclic transition state from any particular conformation of the starting compound. That number decreases with an increasing number of non-rotatable (e.g., endocyclic, double, or triple) bonds in the path of atoms that separates the reactive terminii. Thus, it is easy to understand why the macrolactones **1**−**3** (10-, 13-, and 20-membered rings, respectively) can be produced rapidly and in high yield by lactonization of the corresponding hydroxy acids.[5] There are numerous other cases of the facilitation of cyclization reactions by decreasing the flexibility of the chain undergoing ring closure.[6]



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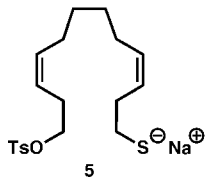

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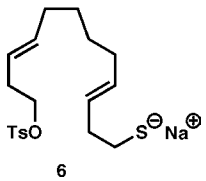

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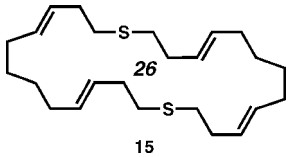
One starting point for the present study was the finding that *cis*-14,15-epoxide of arachidonic acid (**4**) could be formed selectively and easily by intramolecular oxygen-transfer reaction of peroxyarachidonic acid.[7] A second stimulus was the discovery that selective intramolecular oxygen-transfer reactions of polyunsaturated peroxyacids containing *E*-olefinic linkages is considerably less favorable than the case of the all-*Z* tetraenoic acid arachidonic acid (B. Liau, unpublished work). We decided to study this effect quantitatively by measuring the rates of cyclization by S_N2 displacement of the *Z*,*Z*-substrate **5** and the *E*,*E*-substrate **6** under identical conditions.

The pathway of the synthesis of the acetates **13** and **14**, which served as precursors of the products of cyclization, *Z*,*Z*-sulfide **7** and *E*,*E*-sulfide **8**, is outlined in Scheme 1. 1,7-Octadiyne (**9**) was transformed in 28% yield to diol **10** by deprotonation and reaction with ethylene oxide. Diol **10** was divergently advanced to both *Z*,*Z*-diene **11** and *E*,*E*-diene **12** in good yield by Lindlar reduction and reduction with $LiAlH_4$, respectively. The Lindlar reduction of **10** formed a 9:1 mixture of desired *Z*,*Z*-diene **11** and overreduced products. Fortunately, purification of the *Z*,*Z*-product could be effected by chromatography with $AgNO_3$ impregnated silica gel after monotosylation[8] of **11**.

The 13-membered ring-containing products **7** and **8** were prepared by treatment of the acetoxy tosylates **13** and **14** with NaOMe in 1:1 THF−MeOH. The stereochemistry of the olefinic linkages in the *Z*,*Z*- and *E*,*E*-series was confirmed by ^{1}H NMR spectroscopy. The yields of **7** and **8** were concentration dependent (especially for the *E*,*E*-case) because of the formation of dimeric bis-sulfide byproduct (**15**) at higher concentrations.



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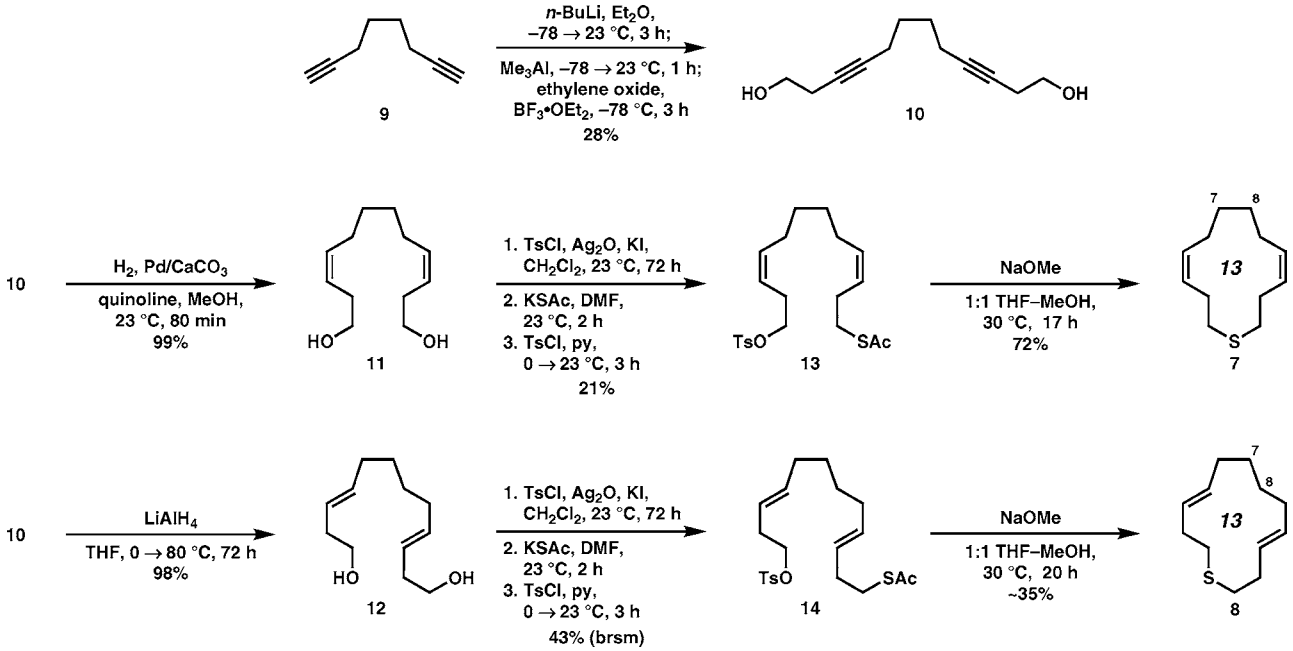
The rates of cyclization of the *Z*,*Z*- and *E*,*E*-sodium thiolates **5** and **6** were determined at low concentration by ^{1}H NMR. Specifically, the acetates were treated with $NaOCD_3$ in 1:1 THF-d_8−CD_3OD under Ar, which caused rapid cleavage of the *S*-acetyl bond to form the sodium thiolate **5** or **6**, a reaction that is very fast even at −30 °C (from ^{1}H NMR studies), and then the rates of cyclization were followed by observing the development of peaks characteristic of product (**7** or **8**) at 30.0 °C, specifically the methylene protons at C(7) and C(8) of **7** and **8** (Scheme 1).

At concentrations below 0.01 M, the cyclization reactions were kinetically first order to a good approximation, and the following values of the first-order rate constant, k_1 (30.0 °C), were extracted from the data: $0.0291 \pm 1 \times 10^{-4}$ min^{-1} for the *Z*,*Z*-substrate **5**, and $0.0038 \pm 1 \times 10^{-4}$ min^{-1} for the *E*,*E*-substrate **6** at 0.005 M substrate concentration. From this result, a ratio of relative rates of cyclization of the *Z*,*Z*-sodium thiolate **5** and the *E*,*E*-sodium thiolate **6** of approximately 7.7 follows. Consistent with this difference in rates of ring closure is the markedly greater tendency for concentration-dependent formation of the dimeric product all-*E*, bis-sulfide **15** which possesses a 26-membered ring.

We believe that the faster rate of 13-membered ring formation for the *Z*,*Z*-sodium thiolate **5** as compared with the *E*,*E*-sodium thiolate **6** is the resultant of at least three identifiable factors. First, assuming a linear transition state for displacement, that is, $\angle$ S$^-$−C−OTs = 180 °, and an S−C distance of ca. 2 Å the minimum number of bond rotations required for generating the cyclic transition state

(5) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 653−654.
(6) For a review see Rousseau, G. *Tetrahedron*. **1955**, *51*, 2777−2849.
(7) Corey, E. J.; Niwa, H.; Falck, J. *J. Am. Chem. Soc.* **1979**, *101*, 1586−1587.
(8) Bouzide, A.; Sauvé, G. *Org. Lett.* **2002**, *4*, 2329−2332.

Scheme 1



is estimated to be six for the *E*,*E*-sodium thiolate **6** and only three for the *Z*,*Z*-sodium thiolate **5**. This factor would favor a faster cyclization of **5** relative to **6**, as observed. Second, there are more conformations within 2 kcal/mol of the global maximum for cyclization of the *Z*,*Z*-substrate **5** (11) than for the *E*,*E*-substrate **6** (7), as determined from MM3 calculations. This factor also is expected to lead to faster cyclization of **5** relative to **6**, since there are more reaction pathways available for forming the *Z*,*Z*-product **7**. Finally, the distance between S^- and C−OTs, the reacting termini, is greater in the most extended conformation for **6** as compared with **5**. We believe that this last factor can play a modest role in determining the relative rates of closure but that it is probably not dominant.

In conclusion, the results reported herein strongly point to the general proposition that the presence of *Z*-olefinic linkages on an atom path between two reactive groups favors ring closure relative to *E*-olefinic bonds or saturation. The same is also likely to be true for *cis*-1,2-disubstituted 3- to 5-membered rings or 1,2-disubstituted aromatic rings.

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Supporting Information Available: Experimental procedures and spectral data for reaction products **7**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org

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