Selective Homolytic Cleavage of Primary over Secondary Carbon-Oxygen Bonds in Cyclic Thionocarbonates: The Effect of Bond Angle Strain Energy

Frederick E. Ziegler* and Zhong-li Zheng

Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06511-8118

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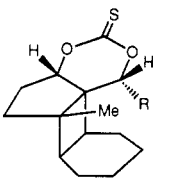
Summary: Several cases of the selective homolytic, tri-*n*-butylstannyl radical promoted fragmentation of primary over secondary carbon-oxygen bonds in 6-membered cyclic thionocarbonates have been uncovered. Molecular mechanics calculations (MM2) simulate the transition states for these reactions and have revealed that bond angle distortion is a prime contributor to the abnormal course of these reactions.

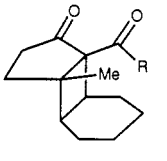
The homolytic fragmentation of thiocarbonyl derivatives of secondary alcohols in the presence of tri-*n*-butylstannyl radical (Barton-McCombie reaction)[1] occurs more readily than with the derivatives of primary alcohols.[2] When the opportunity for competition been primary and secondary (or tertiary) fragmentation arises in 5- and 6-membered cyclic thionocarbonates, fragmentation toward the secondary (or tertiary) site prevails.[3]

In a prelude to a projected synthesis involving homolytic fragmentation, we have investigated the deoxygenation of thionocarbonate **1a**, itself prepared from photoadduct **2a**[4] followed by sequential reduction with $LiAlH_4$[5] and derivatization with thiophosgene. Realizing that 2-halobicyclo[3.2.0]heptanes undergo tri-*n*-butylstannane-induced reductive fragmentation to 3-ethyl-1-pentene,[6] the expectation was that C-O bond cleavage would occur at the secondary site of **1a** to give cyclobutane ring cleavage leading to allylic alcohol **3**. Surprisingly, allylic alcohols **4a** were formed exclusively as a 1:1 mixture, the products of primary C-O bond cleavage and fragmentation of the more substituted cyclobutane bond.

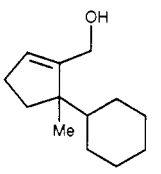
Molecular modeling reveals substantial overlap between both C-O bonds and the cyclobutane C-C bond that suffers fragmentation. To test whether or not a concerted fragmentation was playing a part in the process, the specifically deuterium-labeled substrate **1b** was prepared. The β-keto ester **2a** was reduced with $LiAlD_4$ and the resultant d_3-diol was oxidized under Swern conditions[7] to give the d_1-β-keto aldehyde **2b**. Treatment of the **2b** with $ZnCl_2$ in ether followed by reduction with L-Selectride (Aldrich) followed by DIBAL afforded **1b** (~95% stereoselective) after treatment with thiophosgene. The chemical shifts



1a, R = H
b, R = D



2a, R = OEt
b, R = D



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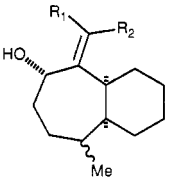
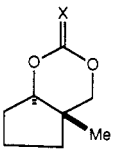
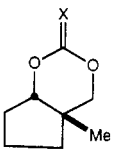


4a, $R_1 = R_2 = H$
b, $R_1 = H$, $R_2 = D$
c, $R_1 = D$, $R_2 = H$

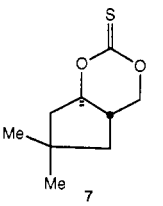
of the protons adjacent to oxygen in **1a** were assigned by coupling constants and NOE studies; the stereochemistry of **1b** followed accordingly. Subjection of **1b** to the fragmentation conditions gave a 1:1 mixture of d_1-allylic alcohols **4b** and **4c**.[8] The vinyl region of the ^1H NMR spectrum integrated for half the vinyl region of **4a** relative to the methine proton adjacent to oxygen. A control experiment conducted with **1b** and 25 mol % of Bu_3SnH afforded recovered, unscrambled starting material thereby ruling out a reversible radical cage mechanism for the scrambling. At this juncture we chose to examine the reduction of several substrates that were devoid of the cyclobutane ring, had the methyl group replaced by hydrogen, and tested the effect of the stereochemistry of the heterocyclic ring.



5a, X = S
b, X = O



6a, X = S
b, X = O



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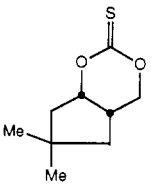

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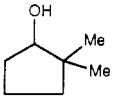

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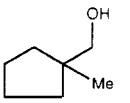

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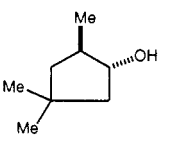

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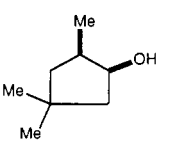

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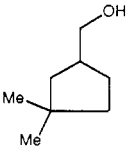

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(1) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. For recent reviews, see: (b) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609. (c) Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem.* **1981**, *53*, 15.

(2) Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743.

(3) (a) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718. (b) Liang, D.; Pauls, H. W.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1123. (c) Ziegler, F. E.; Zheng, Z. *Tetrahedron Lett.* **1987**, *28*, 5973. (d) De Bernardo, S.; Tengi, J. P.; Sasso, G.; Weigele, M. *Ibid.* **1988**, *29*, 4077.

(4) The photoaddition of 2-carbethoxy-3-methyl-2-cyclopentenone [Smith, A. B. III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855] was conducted in neat cyclohexene (N_2) using a 450-W medium-pressure lamp with a Pyrex filter. For an intramolecular photoaddition using this chromophore, see: Crimmins, M. T.; DeLoach, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 800.

(5) The structures of the diols were confirmed by single-crystal X-ray analysis.

(6) (a) Hill, E. A.; Theissen, R. J.; Cannon, C. E.; Miller, R.; Guthrie, R. B.; Chen, A. T. *J. Org. Chem.* **1976**, *41*, 1191. (b) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1083.

(7) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(8) The cis stereochemistry of thionocarbonate **6a** (and **8**) was assigned on the basis of NOE enhancements between ring juncture substituents. No NOE was observed for the trans isomer **5a** (and **7**).

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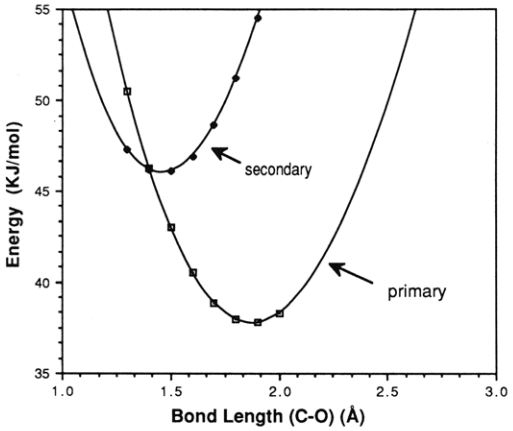

Figure 1. Energy vs bond length for trans carbonate **5b**.

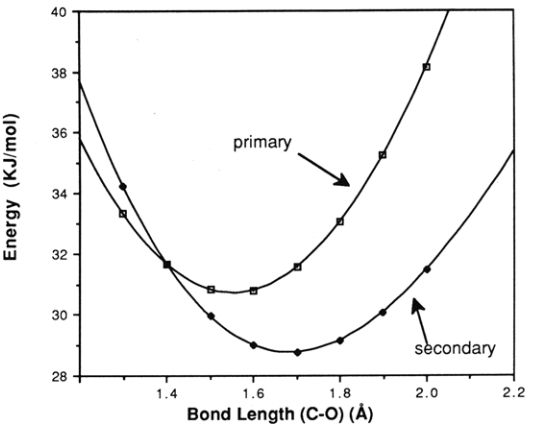

Figure 2. Energy vs bond length for cis carbonate **6b**.

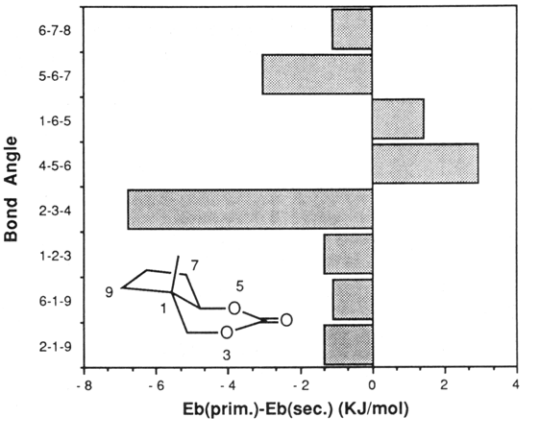

Figure 3. Difference in angle bending energy (>0.5 kJ/mol) for primary vs secondary C–O bond of trans carbonate **5b** at 1.7 Å.

The trans and cis diols corresponding to thionocarbonates **5a** and **6a** were prepared by $LiAlH_4$ reduction of methyl 1-methyl-2-oxocyclopentanecarboxylate.[9] The cis diol formed thionocarbonate **6a** with thiocarbonyldiimidazole in refluxing THF while the trans diol required the more reactive thiophosgene in pyridine catalyzed by DMAP to form **5a**. Similarly, trans and cis thionocarbonates **7** and **8** were prepared from methyl 2-oxo-4,4-dimethylcyclopentanecarboxylate (from irradiation of 2-diazodimedone).[10] Under the radical reaction conditions, the trans thionocarbonate **5a** gave alcohols **9** and **10** in a 47:1 ratio (50% yield); primary bond cleavage predominated. This result demonstrated that the cyclobutane ring of **1** was not responsible for the observed course of bond cleavage. By comparison, the cis thionocarbonate **6a** gave rise to alcohols **9** and **10** in a 1:32 ratio (61% yield) following the course of secondary C–O bond cleavage. These two results suggest some aspect of ring strain as the causative agent. Rüchardt[11] has championed steric compression as a driving force for many radical reactions. Accordingly, the methyl group was removed and replaced with a hydrogen in the trans and cis thionocarbonates **7** and **8**. The previously observed selectivity prevailed: trans thionocarbonate **7** gave secondary alcohol **11** and **13** (21:1; 55%) and cis thionocarbonate **8** gave alcohols **12** and **13** (1:19; 63%). These results exclude local steric considerations and mandate an analysis of the transition states for C–O bond fragmentation.

The approach to the transition-state analysis employing MacroModel is to compare the total energy for each structure as the primary or the secondary bond is lengthened.[12] Ideally, this computation should be conducted on the initial radical derived from addition of the tri-*n*-butylstannyl radical to the C–S double bond. The lack of suitable parameters for the radicals and for the C–S double bond required the use of the cyclic carbonates **5b** and **6b**. The constraint mode of MacroModel permits the assignment of new equilibrium bond lengths. The assignment of a large force constant to the bond in question assures that the selected bond retains its length during the minimization process. Moreover, the contribution of the lengthened bond to the total energy is minimal, thereby allowing an assessment of the strain increase or decrease in the rest of the molecule. The minimized, nonconstrained structure of trans cyclic carbonate **5b** has a primary C–O bond length of 1.409 Å while the secondary bond is 1.399 Å. The cis isomer **6b** has two C–O bond lengths of 1.402 Å. In an acyclic compound bearing a carbon–heteroatom bond, the C–Het bond length increases as the carbon is substituted with alkyl substituents. Therefore, it does not appear that bond length itself controls the selectivity.

When the primary C–O bond of trans cyclic carbonate **5b** is allowed to lengthen, the total energy of the structure begins to drop (Figure 1). On the contrary, when the secondary bond is lengthened, the energy rises abruptly.[13] When the analysis is applied to the cis isomer **6b**, lengthening of the secondary C–O bond is more favorable than lengthening of the primary bond although the difference is not as dramatic as in the previous case (Figure 2). These calculations qualitatively mirror the experimental results.

An analysis of the individual contributing terms to the total energy reveals that the bond angle bending strain (E_b) plays a major role in the regioselectivity of the reactions. In trans lactone **5b** (see inset of Figure 3), the ∠2,3,4 of the nonconstrained structure is 120°, while this angle should be 110° in an acyclic system. This angle is reduced, and accordingly the energy, upon lengthening of the primary C–O bond. At the same time, the related ∠4,5,6 is increased but with less of an energy increase. These angle contributions are displayed in Figure 3 where the histogram plots the difference in angle bending energy (>0.5 kJ/mol) for the primary less the secondary bond of **5b** at an arbitrary

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(10) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728.
(11) (a) Rüchardt, C. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 830. (b) Rüchardt, C. In *Topics in Current Chemistry*; Springer Verlag, New York, 1980; Vol. 88, p 1.
(12) MacroModel 2.0, W. C. Still, Columbia University.
(13) Neither the minima nor the positive slope sides of these parabolas have physical meaning. In addition, the curves do not locate the transition state.

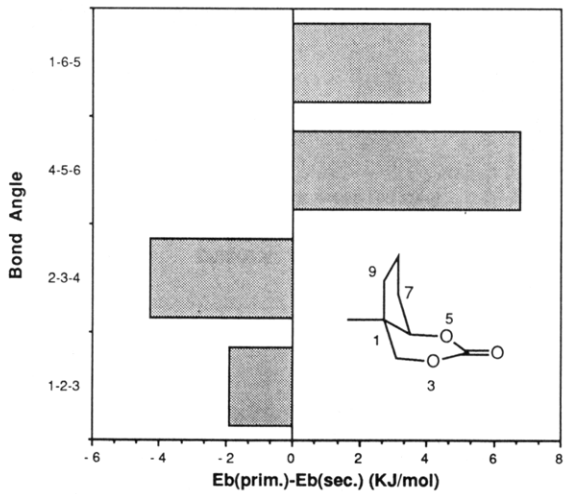

Figure 4. Difference in angle bending energy (>0.5 kJ/mol) for primary vs secondary C–O bond of cis carbonate **6b** at 1.7 Å.

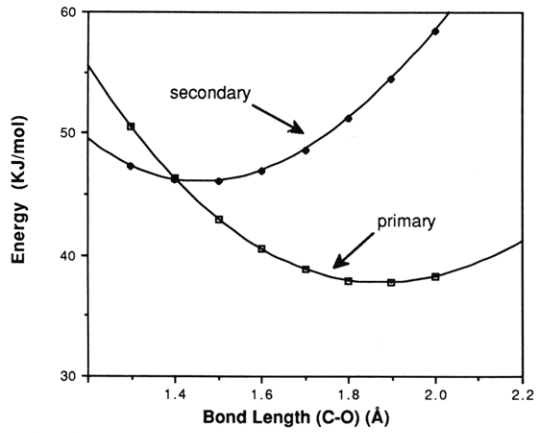

Figure 5. Energy vs bond length for trans carbonate **1a**.

length of 1.70 Å. The negative bars indicate favorable primary bond cleavage (inhibition of secondary cleavage) while the positive bars show favorable secondary bond cleavage. The relief of bond angle strain is principally in ∠2,3,4 and ∠5,6,7 with smaller, near equal contributions from ∠1,2,3, ∠6,7,8, ∠2,1,9, and ∠6,1,9. Only the increase in ∠4,5,6 and ∠1,6,5 inhibits primary fragmentation. Figure 4 illustrates the same principle applied to the cis cyclic carbonate **6b**. Bond angle strain is now relieved by reduction of ∠4,5,6 and ∠1,6,5 when the secondary bond is lengthened. These two effects outweigh the energy increase associated with the increase in ∠1,2,3 and ∠2,3,4.

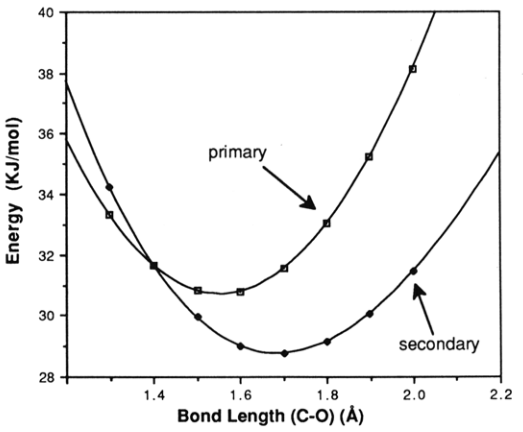

Figure 6. Energy vs bond length for cis stereoisomer of trans carbonate **1a**.

Figures 3 and 4 illustrate another interesting feature of the relief of bond angle strain. While the relief of bond angle strain of the cis isomer **6b** is highly localized in two complementary pairs of internal bond angles of the heterocyclic ring, the relief of bond angle strain in trans isomer **5b** is more global in nature. Not only are the internal angles of the heterocyclic ring that play a role in the cis isomer **6b** involved, but also external bond angles to both rings (∠2,1,9 and ∠5,6,7) and internal angles of the cyclopentane ring (∠6,1,9 and ∠6,7,8).

When the primary/secondary bond stretching computation was applied to the trans cyclic carbonate **1a**, the cleavage of the primary bond was favored (Figure 5). Because our synthetic objective requires fragmentation of a secondary C–O bond, the calculation on the cis cyclic carbonate stereoisomer of **1a** suggests that this goal can be realized (Figure 6). The computational method also confirmed the mode of fragmentation of thionocarbonates **7** and **8**.

This study illustrates the power of computational methods for the illucidation of a reaction mechanism that is not obvious based upon steric arguments derived from inspection of molecular models.

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A Highly Stereoselective Glycosylation of 2-(Phenylselenenyl)-2,3-dideoxyribose Derivative with Thymine: Synthesis of 3′-Deoxy-2′,3′-didehydrothymidine and 3′-Deoxythymidine

Chung K. Chu,* J. Ramesh Babu, J. Warren Beach, Soon K. Ahn, Haoqiang Huang, Lak S. Jeong, and Sang J. Lee

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Georgia, Athens, Georgia 30602

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Summary: A highly stereoselective synthesis of 3′-deoxy-2′,3′-didehydrothymidine (D4T) and 3′-deoxythymidine (D2T) was achieved from the condensation of 2-(phenylselenenyl)-2,3-dideoxyribose derivative and silylated thymine in the presence of trimethylsilyl triflate.

Since the discovery of the anti-human immunodeficiency viral (HIV) activity of 3′-azido-3′-deoxythymidine (AZT, Retrovir) by Mitsuya et al.,[1] a number of nucleosides have been found to possess potent anti-HIV activity in vitro. At the time of this writing, 3′-azido-2',3′-dideoxyuridine (AZddU, AZDU or CS-87),[2,3] 2′,3′-dideoxycytidine

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