Free-Radical Ring Contraction of Six-, Seven-, and Eight-Membered Lactones by a 1,2-Shift Mechanism. A Kinetic and ^{17}O NMR Spectroscopic Study

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Since 1967,[1,2] the mechanism of the β-(acyloxy)alkyl radical rearrangement and that of its more recent cousins the β-(phosphatoxy)alkyl,[3,4] the β-(nitroxy)alkyl,[5] and the β-(sulfonatoxy)alkyl[5] rearrangements has proven to be a fascinating puzzle that has challenged the ingenuity of physical organic chemists. On the basis of a large amount of kinetic and labeling data accrued by several groups worldwide, we have recently pieced together the comprehensive mechanistic picture illustrated in Scheme 1.[6,7]

In this continuum of mechanisms, the slower rearrangements take place through a moderately polarized five-membered cyclic transition state (2,3-shift), whereas the more rapid ones prefer the three-membered cyclic transition state (1,2-shift) with its greater separation of charge. Thus, the mechanism is a function of substrate. As the migrating group becomes more capable of supporting negative charge and/or the carbon framework of stabilizing positive charge, a greater proportion of the three-membered mechanism is to be expected. In the ultimate situation, when the system is capable of carrying fully separated charges, ion pair mechanisms and fragmentations may occur.[8,9] Unfortunately, while labeling studies have revealed a number of cases of pure 2,3-shifts,[10−12] no examples of pure 1,2-shifts have yet been forthcoming, even though they are expected to be favored by entropic factors. Labeling studies have brought to light several systems that proceed to a considerable extent, and some predominantly, through a 1,2-shift suggesting the operation of parallel 1,2- and 2,3-shift mechanisms, but the possibility of caged radical ion pair mechanisms could not be conclusively excluded.[11,13−15] Carboxylate esters typically prefer the *Z* conformation[16,17] from which a β-(acyloxy)alkyl radical could rearrange via the 1,2- or 2,3-manifold. On the other hand, an ester constrained to the higher energy *E* conformation can only access the transition state for the 1,2-shift, if it exists, failing which an ion-pair mechanism must be involved (Scheme 2). We reasoned that this problem might be addressed through the rearrangements of lactones and proceeded to demonstrate, in the first instance, that lactones are capable of undergoing rapid radical ring contractions and expansions.[18,19] Here, we describe the first examples of conformationally constrained β-(acyloxy)alkyl radicals undergoing rearrangement by a pure 1,2-shift mechanism together with its kinetic characterization.

Our first problem lay in the regiospecific ^{17}O-labeling of the lactones in either the sp^2 or sp^3 oxygen. Initial attempts to form labeled bromohydrins by reaction of $H_2{}^{17}O$ water[20] and NBS across the alkenoic acids, each prepared by Wittig olefination of benzaldehyde, resulted in distribution of the label between the bromohydrin and the acid as revealed by ^{17}O NMR spectroscopy of the subsequent lactones.[21] To circumvent this problem, various esters were assayed but most led to complications in the deprotection step. Ultimately, **3** was converted to the desyl ester[22] **10**, which reacted cleanly with *N*-bromosuccinimide and $H_2{}^{17}O$ in acetone to give bromohydrin **11**. Photolysis in aqueous acetonitrile[22] provided **6-$^{17}O_1$** in excellent yield, and this was converted without further purification, using the Yamaguchi protocol,[23] to the labeled lactone **16**.[24] ^{17}O NMR spectroscopy revealed a single resonance at δ 187.4 fully consistent with the indicated regiochemistry.[21] Unfortunately, application of the same approach to the lower homologues was foiled by the instability of the bromohydrin esters. To label the six-membered ring, the unlabeled lactone **7** was reduced by DIBAL to the corresponding lactol **12**, which was converted to the pentenyl ester **13**.[25] Hydrolysis with $H_2{}^{17}O$ and NBS then gave the labeled lactol, which was converted to the corresponding lactone **14** by oxidation with PCC. Again, ^{17}O NMR spectroscopy demonstrated

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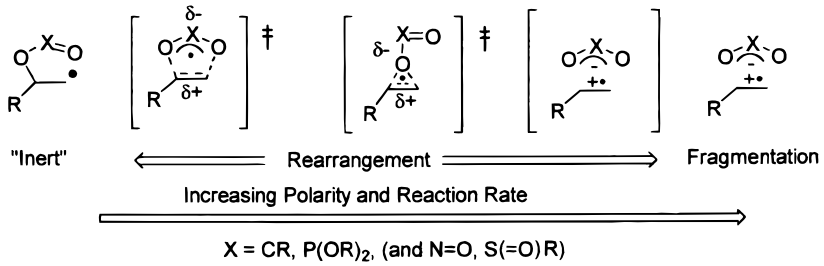
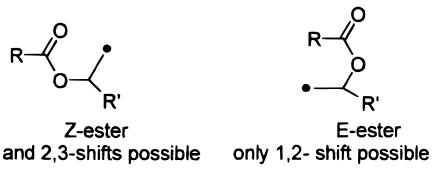
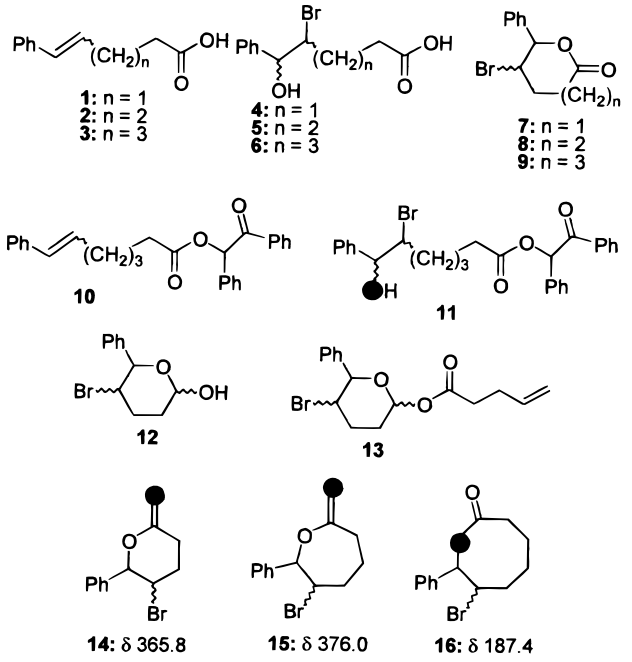
Scheme 1



Scheme 2



14 to be regiospecifically labeled as indicated (δ 365.8). This protocol could not be applied to the seven- and eight-membered congeners owing to the instability of the derivatized lactols. Finally, for the seven-membered series we had recourse to a more classical method in which bromohydrin **5** was equilibrated in THF/$H_2{}^{17}O$ leading to incorporation of the label into the carboxylate moiety, before lactonization by the Yamaguchi method. Fortuitously, exchange of the benzylic alcohol did not occur as ^{17}O NMR spectroscopy of the subsequent lactone **15** showed it to be cleanly regiochemically monolabeled as indicated (δ 376.0).



Each of the lactones **14**−**16** was reduced by tributyltin hydride, in the presence of 10^{-3} M benzeneselenol, in benzene at reflux with AIBN initiation leading, as demonstrated by ^1H NMR spectroscopy, to inseparable mixtures of the respective rearranged **17**−**19** and reduced **20**−**22** products. When these mixtures were examined by ^{17}O NMR spectroscopy, each rearrangement was found to have taken place with retention of the labeling regiochemistry. In no case was any indication found for scrambling of the label or inversion of the carboxylate group. Thus, the contraction of the six-, seven-, and eight-membered lactones occurs cleanly by the 1,2-shift mechanism. While this was expected for the six- and seven-membered series, it was less so for the eight-membered series, when a significant proportion of the *Z* conformation should be present.[26−29] Molecular mechanics calculations (MM2) conducted on the *E*- and *Z*-lactone radicals **23** and **24**, respectively, indeed found the *Z*-isomer to be some 1.7 kcal·mol^{-1} lower in energy in qualitative agreement with various computational studies[29−31] on heptanolactone itself. However, the same calculations revealed the C−O−C(=O)−C dihedral angle in **24** to be around 136°, which places the carbonyl oxygen significantly further away from the radical than in the fully planar system. Again, this observation is qualitatively in line with earlier calculations on heptanolactone itself.[30] When the C−O−C(=O)−C dihedral angle in **24** was constrained to 180° the energy of the system rose significantly (by approximately 3.7 kcal·mol^{-1}), which suggests that the barrier to the 2,3-rearrangement from the *Z* conformation will be very high. Taking all things into consideration, it appears that the initial conformational mix of radicals **23** and **24** will reflect that of the starting lactone, i.e., with a slight preponderance of the *Z* form (**24**). Then, owing to the unusually high barrier for the 2,3-shift, this *Z* radical rearranges by the 1,2-mechanism either directly itself or via rapid inversion to the appreciably populated *E* conformation (**23**). A final conclusion derived from the ^{17}O NMR experiments was that no scrambling of the label had occurred in the reduced products.

Table 1. Rate Constants for Ring Contraction at 80 °C

substrate	k (80 °C, s^{-1})[35]
7	$(9.9 \pm 1.8) \times 10^5$
8	$(1.7 \pm 0.1) \times 10^6$
9	$(1.1 \pm 0.1) \times 10^6$

Working in the unlabeled series, the rates of ring contraction (Table 1) were determined in benzene at reflux using our catalytic adaptation[32] of Newcomb's benzeneselenol clock reaction.[33] These rate constants are consistent with those of other radical ester rearrangements that proceed largely, but not exclusively, by the formal 1,2-shift.[11,13,34] Finally, using the same radical

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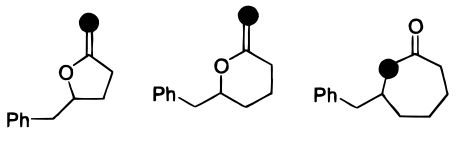
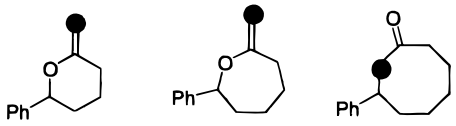
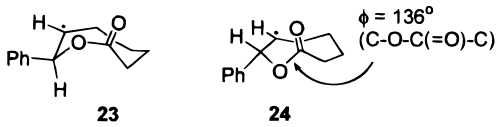


17: δ 333.9 **18:** δ 356.7 **19:** δ 196



20: δ 359.2 **21:** δ not resolved **22:** δ 181.9



23 **24**

clock method, the rate constants for the contraction of one example, the seven-membered lactone **8**, were determined over an 80° range of temperature leading to the Arrhenius equation (eq 1). It, too, is fully consistent with the kinetic parameters of other known radical ester rearrangements.[6]

$$\log(k, s^{-1}) = (11.8 \pm 0.5) - (9.0 \pm 0.8)/2.3RT \quad (1)^{35}$$

In conclusion, we have prepared three regiochemically mono-^{17}O-labeled bromolactones and have determined that each undergoes radical ring contraction by a 1,2-shift mechanism. Additionally, the kinetic parameters have been determined.

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Supporting Information Available: Details of preparation and characterization of all compounds and details and tables of data for the kinetics. This material is available free of charge via the Internet at http://pubs.acs.org.

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(35) Errors are at the 95% confidence interval (2.3σ).