INTRAMOLECULAR ENE REACTIONS OF 1,7-OCTENYNES: THE INVOLVEMENT OF 1,2-CYCLOOCTADIENE INTERMEDIATES

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Summary: 1,2-Cyclooctadienes are proposed as intermediates in the intramolecular ene cyclization of acyclic 1,7-octenyne derivatives.

Although it may not be generally appreciated, a number of pericyclic reactions can be utilized for the synthesis of strained molecules. The feasibility of such approaches are evaluated in a straightforward manner from consideration of the thermodynamics of the reaction. Recent examples include the Diels-Alder cycloaddition and [3,3] signatropic rearrangements for the synthesis of bridgehead alkenes¹ and dienes.^{2,3} We report in the present communication that the ene reaction may also involve "strained" organic molecules and reaction intermediates.⁴

An investigation of the thermolysis of dienyne ether 1 revealed that in addition to the expected Diels-Alder cycloadduct 2,² an unanticipated product, aldehyde 3 was also produced (eq. 1).



At 402°C in the gas phase at atmospheric pressure (contact time 10 sec), dienyne ether 1 yields approximately 12% of enyne aldehyde 3. At 420°C, the aldehyde 3 accounts for over 20% of the reaction products.⁵ Analysis of the temperature-product distribution profile suggests that aldehyde 3 is not a secondary product of the Diels-Alder reaction manifold. To account for its formation, a two-step sequence, shown in scheme 1, is proposed.

The first step in the rearrangement is initiated by an intramolecular ene cyclization^{6,7} with transfer of the propargylic hydrogen at C-7 and formation of the unusual oxocycloocta-2,3-diene 4.⁸ The subsequent step requires a retro ene fragmentation involving a hydrogen α to oxygen to give product aldehyde 3. Consistent with this proposal is the result of a deuterium labeling experiment employing isotopically labeled dienyne ether 1b (>98% ²H at C-5 by ¹H NMR and mass spectroscopy). The aldehyde product isolated from this reaction (3b) was dis-

tinguished by the absence of the triplet at 9.72 ppm and the appearance of a single proton multiplet at 2.16 ppm. The oxacycloallene 4 apparently does not accumulate under the reaction conditions since an effort to detect this compound in the crude thermolysis mixture was not successful.



The first step in the rearrangement involves generation of a relatively strained 1,2-cyclooctadiene ring. This carbocycle has a calculated strain energy of approximately 14 kcal/mol.⁹ The feasibility of cyclization may be evaluated by consideration of the energetics of the parent ene reaction (eq. 3), estimated using group eqivalents¹⁰ to be exothermic by 23 kcal/mol. The net enthalpy change for the first step in equation 2, therefore, may be roughly estimated to be exothermic by 9 kcal/mol.²¹



The second step in the rearrangement, a retro-hetero ene fragmentation¹² of a cycloallene, is well precedented. Earlier work by Crandall¹³ and more recent work by Johnson¹⁴ report that the FVT of 1,2-cyclononadiene yields, among other products, 1,8-nonenyne, a product directly analogous to aldehyde 3.

The failure to detect cycloallene as a thermolysis product suggests a facile fragmentation reaction.¹¹ 1,2-cyclooctadienes are calculated to have several low energy conformations.⁹ From consideration of the stereoelectronic requirements for the concerted ene cyclization, the most plausable transition state leads to <u>twist-boat</u> conformation (4c) of cyclic oxallene 4. In this conformation the <u>syn</u>-hydrogen at C-8 is suitably disposed for delivery to the allenic carbon at C-4. Other conformations of the cycloallene (i.e., twist chair 4d), which are estimated to be separated by a barrier in excess of 8 kcal/mol,⁹ do not permit hydrogen transfer from C-8.

Johnson has recently shown that nine and ten membered cyclic allenes have several fragmentation manifolds available that could, in the case of cyclooxallene 4, result in the formation of isomeric oxadiene fragmentation products. Although we cannot at this point rigorously rule out some contribution from this pathway, these regioisomeric fragmentations must be relatively unimportant. The high regiospecificity for fragmentation of cyclic oxallenes 4 may result from the activating influence of the oxygen heteroatom, and the aforementioned conformational bias.

In an effort to develop an understanding of the structural requirements for the rearrangement, enyne ether 5 was subjected to the thermolysis conditions. At temperatures in excess of 480°C, aldehyde 7 was found to be a product of the thermolysis mixture. The yield of aldehyde 7 was only 3-5% based upon enyne ether 5. The dominant reaction manifold at these temperatures involves a characteristic ene fragmentation to produce 1,2-propadiene and 4-pentyn-1-al.¹² The harsher conditions required for the reaction of 5 compared with 1 implies the vinyl substituent at C-3 activates the molecule towards ene reactions.¹⁵ The results of deuterium labeling



studies employing substrate (5b) were consistent with the proposed two-step reaction involving transient formation of the cyclic oxallene intermediate 6.



A deuterium labeling study has revealed that the parent hydrocarbon, 1,7-octenyne (8), also undergoes a similar reaction. Upon exposure of enyne 8b at atmospheric pressure to temperatures of 490°C (contact time 10 sec), 50% scrambling of deuterium between positions C-8 and C-6 was observed (eq. 5). It is important to note that $1-{}^{2}H-1$ -decyne does not exhibit scrambling under these same reaction conditions. Although 1,2-cyclooctadiene (9) has not been isolated from this reaction, its generation by an intramolecular ene cyclization is strongly implied.



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- For reviews of strained molecules see Liebman, J.F.; Greenburg, A. <u>Strained Organic</u> <u>Molecules</u>, Academic Press Inc., New York, 1978.
- 5. Aldehyde 3 IR(CCl₄) 3310, 3080, 2915, 2810, 2705, 2110, 1730, 1645,920, 635 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 9.72 (t, J=2.2 Hz, 1H, -CHO), 5.62 (d,d,d J=17.3, 10.3, 8.4 Hz, 1H, -CH=CH₂), 5.12 (d J=17.3 Hz, 1H, -CH=CH₂), 5.11 (d J=10.3 Hz, 1H, -CH=CH₂), 2.8 (m, 1H, -C-H), 2.45 (m, 2H, -CH₂-CHO), 2.24 (m, 2H, -CH₂-CH), 1.97 (t J=2.7 Hz, 1H, -E-H), 1.65 (m, 2H, -CH₂-C); ¹³C NMR (62.9 MHz, CDCl₃) δ 202(d), 140(d), 117(t), 84(s), 69(d), 48(t), 38(d), 33(t), 16(t); C_aH₂O requires 136.0889. Found: 136.0874.
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 (b) Deming, R.L.; Wulff, C.A., "The Chemistry of Ketenes, Allenes, and Related Compounds," Part 1, S. Patai, Ed., J. Wiley and Sons, New York, 1980, 155.
- 11. (a) Group equivalents for calculating °S are not available. By comparison with related cyclizations to form eight-membered rings,^{11b} the entropy of the ene cyclization may be estimated to be approximately -20 eu. This would imply that at the high temperatures necessary for these cyclizations, the equilibrium concentration of oxallene 4 would be quite low. (b) Shea, K.J.; Burke, L.D.; England, W.P. J. Am. Chem. Soc. 1988, 110, 0000.
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- 13. Crandall, J.K.; Watkins, R.J. Tetrahedron Lett. 1970, 1251.
- 14. Price, J.D.; Johnson, R.P. Tetrahedron Lett. 1985, 26, 2499.
- 15. Aldehyde 7a ¹H NMR (250 MHz, CDCl₃) δ 9.77 (t, J=1.6 Hz, 1H), 2.47 (t,d J=7.1, 1.7 Hz, 2H), 2.22 (t,d J=6.9, 2.6 Hz, 2H), 1.96 (t J=2.6 Hz, 1H), 1.76 (m, 2H), 1.56 (m, 2H). ¹³C NMR (62.9 MHz, CDCl₃) δ 202.2, 83.9, 68.9, 43.4, 28.0, 21.3, 18.3. Mass spectrum m/e (70 eV, isobutane, rel %) 113(3), 112(8), 111(100), 110(5), 109(15), 95(11), 93(86), 83(90). Aldehyde 7b ¹H NMR (250 MHz, C₆D₆) δ 9.29 (s, 1H), 1.85 (m, 2H), 1.74 (t J=6.7 Hz, 2H), 1.4 (m, 2H), 1.2 (m, 2H). Mass spectrum m/e (CI, isobutane- GCMS, rel %) 113(10), 112(100), 111(9), 110(16), 109(3), 98(9), 94(33), 93(19), 84(83), 83(27).
- 16. For a related finding see Snider, B. Acc. Chem. Res. 1980, 13, 426.
- 17. Figures 4c and 4d were generated using known coordinants for the twist boat and twist chair conformations of 1,2-cycloocadiene.⁹ Hydrogens were added using standard crystallography programs with bond distances of 0.95 Å. Distances between H(8_{yyn}) and C(4) for twist boat 4c and twist chair 4d are 2.64 and 4.58 Å, respectively.

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