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INTRAMOLECULAR PERICYCLIC REACTIONS OF ACETYLENIC COMPOUNDS[a,b]

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CONTENTS

In this report we will consider reactions of acetylenic substrates which require the triple bond to become part of an intramolecular pericyclic transition state. Only those processes will be considered in which a contiguous array of atoms is involved. Not within the scope of this report are reactions, such as the internal Diels–Alder, where two interacting bonding systems within the same molecule are separated by a number of other atoms, since such reactions energetically resemble normal bimolecular processes which merely have the advantage that both reacting components are located within the same molecular framework.

A large number of organic reactions proceed via cyclic, intramolecular transition states, which are most commonly six-membered. In such reactions the presence of olefinic bonds, by virtue of their sp^2 bond angles of 120°, aids in the conformational alignment needed to attain that transition state. Acetylenic bonds on the other hand, with sp bond angles of 180° which require a ground state colinearity of three contiguous bonds, should hinder the attainment of the requisite transition state geometry. For example, in the acetylenic Cope rearrangement of **2** the ground state internuclear distance between the

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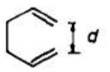
[a] Paper No. 9 in the series "Intramolecular Pericyclic Reactions of Acetylenes".
[b] Based in part upon the Ph.D. Dissertations of John J. Collins and Nicholas Filipp.
[c] Polaroid Fellow, 1977.



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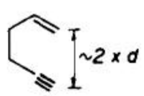

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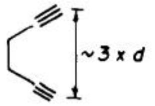

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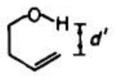

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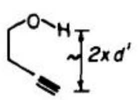

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two carbons engaged in the bond-forming process is about twice that in its olefinic analog **1**. In **3**, where two acetylenic bonds are involved, the situation appears still more unfavorable since the intranuclear distance is now about three times that in **1**. Similar considerations apply to the retro-ene reactions of acetylenic substrates such as **5**, wherein the internuclear distance between the migrating proton and the receptor site is about twice that in the corresponding olefinic substrate **4**. It is not surprising, therefore, that acetylenic compounds were long believed incapable of participating in such reactions.

In recent times it has been found that most bonds may be deformed considerably from their preferred ground state geometry and, in the case of acetylenes, the preparation of cyclooctyne, and the transitory formation of smaller cycloalkynes down to cyclopentyne,[1] suggest that deviation from linearity is not improbable. The fact that propyne has a low energy bending mode[2] at 333 cm^{-1} suggests that higher levels of this vibration could easily be populated at a small energetic cost. Indeed, Creighton[3] has calculated the populations for various vibrational levels of the $C–C\equiv C$ bending mode, at 625°K, to be: $v_0 = 30\%$, $v_1 = 27\%$, $v_2 = 18.5\%$ and $v_3 = 11.4\%$, and the amplitude of the v_3 vibration to be about 25°. Similarly, the initial products expected from pericyclic reactions of acetylenes contain an allenic bond, and such bond systems are also capable of considerable deformation,[5] as evidenced by the preparation of 1,2-cyclohexadiene.[6] One might anticipate, therefore, that intramolecular reactions of acetylenes should be attainable, but with higher activation energies and slower rates than corresponding reactions of their olefinic analogs. It is the purpose of this report to show that such simple assumptions do not lead to a correct prediction of reactivity, that acetylenes can readily participate in such reactions, that they will frequently do so at rates exceeding those of their olefinic analogs, but that the requirements of their transition states may differ substantially from those of their olefinic counterparts.

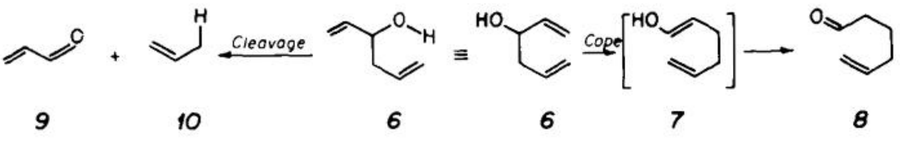
Reactions which proceed via cyclic, intramolecular transition states are usually concerted, in that the bond-forming process provides energetic assistance to the bond-breaking process.[7] The nature of such processes can be probed by several experimentally verifiable criteria: the energy of activation should be lower than that required to break any individual bond within the molecule; the entropy of activation should be negative since the cyclic transition state represents a loss of rotational, and sometimes vibrational, degrees of freedom relative to the ground state; and, where pertinent, stereochemical integrity should be preserved, which requires asymmetric induction by a chiral site in the reactant to a newly created site in the product. To establish the kinetic criteria, it is necessary for the reaction to be unimolecular, first order and homogeneous. Such characteristics are more readily determined for gas phase than for solution phase reactions, since in the latter case it is often more difficult to distinguish the primary reaction pathway from pre-equilibria and secondary reactions of the initial product. A large number of olefinic reactions have rigorously met the above criteria and have thereby been shown to proceed via intramolecular, pericyclic pathways. The criteria for concert have been less firmly established in the case of acetylenic reactions, and most frequently the case for concert rests on the analogy to the known reaction pathway for the corresponding olefin.

In this report we will first consider the results of studies in our laboratory, over the past decade, of some pericyclic reactions of acetylenic compounds and will develop possible rationales for the observed behavior. The second part of this report consists of a survey of selected reactions of acetylenic substrates which are likely to fall into this category and which illustrate the broad synthetic utility of these reactions.

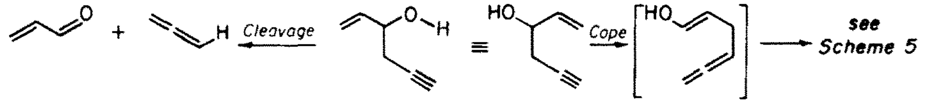
THE NATURE OF INTRAMOLECULAR, PERICYCLIC TRANSITION STATES FOR ACETYLENIC COMPOUNDS

Acetylenic oxy-Cope reactions

Our interest in intramolecular pericyclic acetylenic reactions stems from some surprising results observed during studies of oxy-Cope systems. The oxy-Cope reaction of **6** encompasses a competition

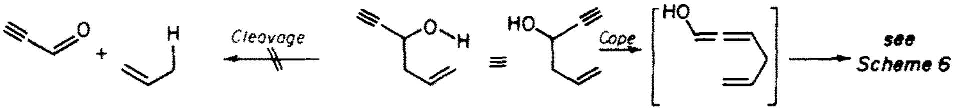


between two well-established, concerted, pericyclic processes of olefins: the Cope rearrangement and the β-hydroxyolefin retro-ene cleavage.[8] Although both reactions can occur readily in either gas or liquid phase, the ketonization of the initial Cope product, enol **7**, can occur only in the condensed phase, to provide **8**, due to the orbital symmetry-forbidden nature of [1,3] hydrogen shifts. The ratio of the two sets of final products obtained, **8**/(**9** + **10**), is highly dependent upon substitution in **6** and therefore represents a sensitive probe into the energetics of the two competing processes.[8] We decided to utilize this probe to investigate the consequences of substituting an acetylenic bond for either of the olefinic bonds in **6**.



11 *11*

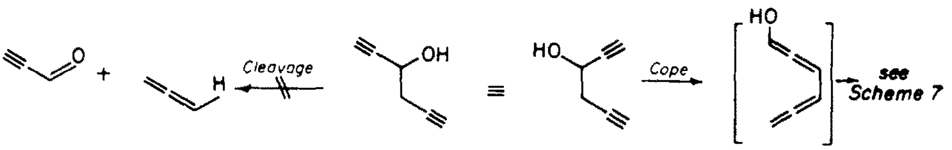
Although it could reasonably be expected that both Cope and cleavage processes of **11** would at best proceed with difficulty due to the additional energy increment required to distort the acetylenic bond angle, compound **11** thermolyzed readily in the vapor phase to yield products from both pathways.[9] Furthermore, the ratio of Cope/cleavage products was the same as for olefinic analog **6**. Surprisingly however, thermolysis of **11** proceeded to completion under conditions where a substantial fraction of **6** remained unreacted. Even more surprising was the case of **12**, where it was anticipated that the acetylenic Cope process might at best compete only poorly with the olefinic retro-ene. Instead, the observed products were totally those to be ascribed to the Cope process and no retro-ene fragmentation could be detected.[10] Table 1 summarizes results of a study of relative rates in these reaction systems,[11] based on the combined disappearance rate of **6** as 1.00. The rates of the acetylenic Cope and cleavage processes in **11** are about 2.5 times those of their olefinic analogs in **6**, and in the case of **12**, where no cleavage occurs, the rate of the acetylenic Cope process is about 5 times that in **6**.



12 *12*

Table 1. Relative thermolysis rates at 350°

	k_{Combined}	k_{Cope}	k_{cleavage}
Hexa-1,5-dien-3-ol, <u>6</u>	1.00	0.60±0.02	0.40±0.02
Hex-1-en-5-yn-3-ol, <u>11</u>	2.56±0.25	1.53±0.15	1.03±0.010
Hex-5-en-1-yn-3-ol, <u>12</u>		3.24±0.22	---



13 *13*

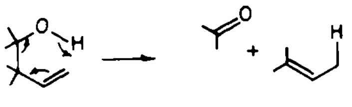
With diacetylenic compound **13**, where great difficulties might be anticipated for the Cope process, there again were no detectable traces of cleavage products.[12] From the data in Table 1 it can be estimated that this Cope process must proceed at a rate at least 8 times faster than the acetylenic cleavage in **11** in order for that competing retro-ene process to remain undetected, since the acetylenic process for **12** was about 8 times faster than its undetected competing olefinic cleavage in **6**. This would make the rate of the bis-acetylenic Cope process at least 12 times faster than the olefinic one in **6**.

In the absence of a competing retro-ene cleavage, the kinetics of the acetylenic oxy-Cope reaction of **12** could be determined, and some evidence for the concerted nature of that process was obtained: the reaction followed the first-order rate equation with $E_a = 30 \pm 2$ kcal/mol and $\Delta S^{\neq} = -14 \pm 2$ eu.[10] In **11**[9] and **13**[12] only circumstantial evidence for concert could be established.

In summation, the results obtained from acetylenic oxy-Cope systems suggested that the presence of acetylenic bonds accelerated the rates of reaction paths which involved those bonds: although Cope and cleavage processes in **11** both require acetylenic participation, the overall rate was faster and the product ratio was unchanged from that of olefinic **6**; the olefinic cleavage process in **12** could not compete with the acetylenic Cope component; and the acetylenic cleavage in **13** could not compete with a Cope process which involved two acetylenic bonds. Although involvement of cyclic transition states could only be inferred, any energetic requirement for acetylenic bond distortion was obviously no deterrent in these reactions. We therefore decided to launch a more detailed investigation of such reactions of acetylenic substrates.

The retro-ene cleavage of β-hydroxyacetylenes

As an initial subject for study of the participation of acetylenes in six-membered intramolecular transition states, the thermal cleavage of β-hydroxyacetylenes, **5**, seemed well suited. Although no simple examples of this reaction had been reported, it constitutes one of the competing processes in the acetylenic oxy-Cope reactions described above. Furthermore, the corresponding retro-ene cleavage of β-hydroxyolefins, **4**, had been studied in great detail and had been rigorously established as a unimolecular, first-order, homogeneous, concerted process, and thus ample literature data on olefinic substrates were available[13] for comparison with the behavior of analogous acetylenic compounds.



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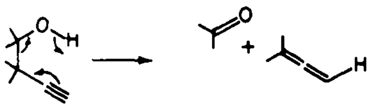

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Thermolyses of eight variously substituted butynols proceeded cleanly to give only the carbonyl compounds and allenes expected from a retro-ene cleavage in a homogeneous, first-order reaction.[14] Results of these thermolyses are summarized in Table 2, together with available data for analogous

Table 2. Kinetic parameters for the vapor phase thermolyses of 3-butyn-1-ols and some analogous 3-buten-1-ols at 350°[a,b]

	Acetylenic			Olefinic			
	E_a (kcal/mol)	$\Delta S^\ddagger$ (eu)	Relative Rate	E_a (kcal/mol)	$\Delta S^\ddagger$ (eu)	Relative Rate	$k_{acet/olef}$
Parent β-hydroxy compound	39.4	-11.1	1.0	40.7	-11.4	1.0	2.8
1-Methyl	39.5	-9.4	2.0	40.2	-10.5	2.9	1.9
1-Ethyl	40.2	-8.0	2.6				
1,1-Dimethyl	39.8	-8.5	2.5	40.5	-8.6	5.5	1.3
1,1,2,2-Tetramethyl	39.9	-6.5	7.2				
4-Ethyl	41.6	-10.3	0.25				
4-Butyl	41.3	-10.9	0.21				
4-Phenyl	41.4	-9.1	0.5	42.8	-9.1	0.2	6.9
1-Phenyl[c]	36.2	-10.4	19	36.0	-11.6	33	1.4
1-Vinyl[d]			20			22	2.5

[a] Calculated from the data in ref. 14.

[b] For purpose of emphasis, these compounds are named as derivatives of the parent alcohols.

[c] Extrapolated from data obtained from dilute solution at lower temperatures.

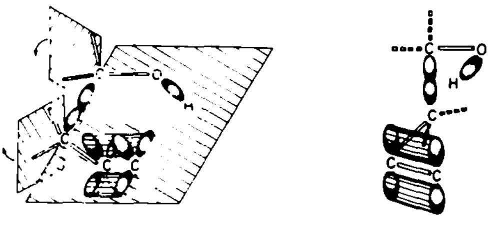
[d] Vinyl substituents correspond to oxy-Cope systems 11 and 6, and are included for purpose of comparison.

butenols. The low E_a and negative $\Delta S^{\neq}$ parameters are in accord with a cyclic transition state, but due to the large error limits usually associated with such values, little insight can be gained from comparisons within the series. Most E_a values are within experimental error of each other (±1.5 kcal/mol), and indeed there is little to distinguish between olefinic and acetylenic parameters. The same holds true for $\Delta S^{\neq}$ values, where the estimated uncertainties are ±2 eu. Some trends within a series, however, may be meaningful. For a concerted reaction with a cyclic transition state, increased substitution may lower the activation energy, since substituents weaken bonds which must be broken in the reaction process, and will usually render the entropy of activation less negative, since substituents restrict ground state rotational freedom so that there is less of an entropy loss in going to the cyclic transition state.[15] Although entropy trends are in this direction (for example, compare the parent compound with the 1-methyl, the 1,1-dimethyl, and the 1,1,2,2-tetramethyl derivatives) those of E_a are not, but the latter may be hidden by experimental uncertainties.

Better insights into the reaction process may be gleaned from comparisons of reaction rates, since these are considerably more reliable than derived activation parameters. In all comparable cases, the acetylenic compound thermolyzed at a faster rate than did the corresponding olefin, i.e. the ratio of k_{acet}/k_{olef} is always greater than unity.[14] In general, substitution in the 4 position leads to decreased relative rates in both series, at least partly for steric reasons as previously reported[8] for olefins. In the case of the 4-phenyl substituent, the transition state for the olefin is resonance destabilized since the double bond moves out of conjugation during the reaction process; this is not the case for the acetylene wherein conjugation can be maintained by the non-reacting component of the acetylenic Π-system, and as a result, the ratio of k_{acet}/k_{olef} is the largest of any reported in this study.[14]

Substituents at C_1 and C_2 provided an interesting clue to the nature of the reaction process.[14] A 1-methyl substituent has a larger accelerating effect in the olefin series than it does in the acetylenes. The effect of two methyl substituents at C_1 is additive in the olefin series but not in the acetylenes. In the latter series, the relative rate of the 1,1,2,2-tetramethyl derivative is also nowhere near what is to be expected on the basis of the effect of a single methyl group. To account for these differences in rate effects, and also for the unexpectedly enhanced reactivity of acetylenes vis-a-vis their olefinic analogs, the transition states illustrated in Fig. 1 were proposed. With the cylindrically symmetric acetylenic system, a Π lobe can become available in any direction for bond formation with the migrating hydrogen atom. A planar structure then becomes possible which requires the least deformation of the linear acetylenic system and which permits a maximum overlap of participating orbitals, centered in the plane of the transition state. However, such a planar transition state requires eclipsing of the non-participating σ bonds at C_1 and C_2. The rotary motion normally associated with developing sp^2 carbons in pericyclic reactions is replaced by a 60° swinging motion of each of the two planes defined by these σ bonds at C_1 and C_2, respectively, toward one another while the C_1–C_2 bond is breaking. By contrast, the transition state for the analogous olefinic cleavage cannot be planar. Not only would the *cis* terminal vinylic proton interfere with the approaching migrating hydrogen, but the available Π lobes are centered in a plane orthogonal to such a potential transition plane. Consequently, the migrating hydrogen must approach C_4 from a direction orthogonal to the plane of the olefinic system and the most likely transition state, in accord with numerous experimental reports for similar reaction,[17] is chair-like with the non-participating σ bonds at C_1 and C_2 in a staggered conformation. This geometry is in accord with the suprafacial process required for orbital symmetry conservation in a 1,5-sigmatropic hydrogen shift.[18]

The difference between the transition state geometries of olefinic and acetylenic substrates accounts for the fact that in all cases of C_1 or C_2 substitution, where comparable data are available, there is a smaller rate enhancement for the acetylenic compound than for its olefinic analog. Although substitution



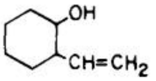
ACETYLENIC SYSTEM OLEFINIC SYSTEM

Fig. 1. Schematic illustration of the transition state geometry for β-hydroxy-acetylenes and -olefins.

at C_1 or C_2 weakens the C_1–C_2 bond and thereby decreases the activation energy required for either acetylenic or olefinic cleavage, eclipsing of the non-participating σ bonds in the acetylenic case partially counteracts this effect. Consequently, as shown in Table 2, the ratio k_{acet}/k_{olef} decreases with substitution at C_1, relative to the parent compounds, in an amount paralleling the degree of repulsion between eclipsed substituents.[14]

Substitution of phenyl or vinyl groups at C_1 leads to substantial rate increases in both series since both groups aid Π-bond formation at the site of the incipient carbonyl. Although the phenyl group has a larger effect, by 2.5 kcal, on weakening the C_1–C_2 bond than does the vinyl substituent,[19] it also has a larger mass which requires a larger energy increment for its rotatory or swinging motion as C_1 rehybridizes from sp^3 to sp^2. Here again, bond eclipsing with the large phenyl group partially offsets the effect of bond-weakening in the acetylenic case and results in a smaller relative rate increase for the acetylene than for the olefin. On the other hand, the vinyl group represents the smallest steric requirement, based on its rotational barrier,[16] of any substituent utilized in this study and thus the ratio of k_{acet}/k_{olef} with the vinyl substituent is closest to that of the parent system.[14]

The difference in transition state geometries also accounts for an earlier observation of Arnold and Smolinsky,[20] who found that although **14** underwent a retro-ene cleavage cleanly, **15** was quite unreactive. Since the mode of preparation involved addition of appropriate organometallic reagents to cyclohexene oxide, **14** and **15** undoubtedly had trans configurations with which **14** can readily accommodate a chair-like transition state. Since planarity of the participating six atoms in *trans*-**15** is not feasible, the compound does not undergo the retro-ene cleavage.



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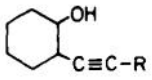

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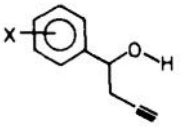

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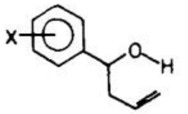

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Phenyl substitution at C_1 increased the rate by a factor of 19 in the acetylenic series and by 33 in the olefinic one. If the above argument is correct, then this difference in rate acceleration is due solely to steric inhibition in the acetylenic case. Further substitution in the meta and para positions can not introduce any additional steric effects, and such substituents should therefore provide a probe for the electronic reaction demands at C_1 in each series. For this purpose eight 1-aryl-3-butyn-1-ols, **16**, were thermolyzed in dilute solutions in an inert solvent.[21] These rate studies could not be accomplished in the gas phase since the reaction proceeded too rapidly, at temperatures necessary to vaporize these compounds, to be monitored by glpc and these reactants were only partially vaporized at temperatures sufficiently low to permit accurate analyses. Again, all eight derivatives thermolyzed cleanly to give only the expected retro-ene products from a strictly first-order reaction. Although a gas phase Hammett study of the olefinic series had already been reported,[22] the conditions utilized were sufficiently different to negate comparisons between the two studies. Consequently, the same eight derivatives in the olefin

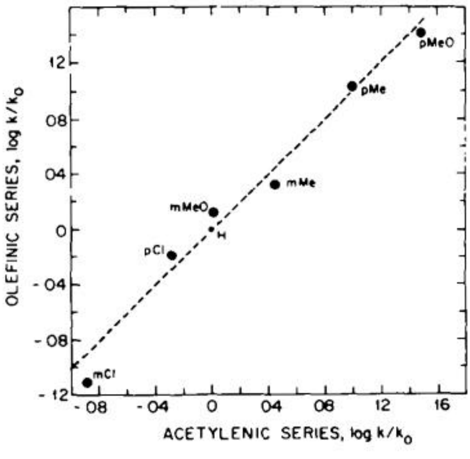
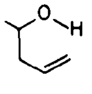


Fig. 2. Linear free energy relationship for thermolyses of 1-aryl-3-buten-1-ols and 1-aryl-3-butyn-1-ols at 260°.

series, **17**, were also thermolyzed under conditions identical to those used for the acetylenes. The data from these thermolyses, without that from X = p-Me_2N which failed to thermolyze cleanly in the olefin series, is shown in Fig. 2 as a linear free energy plot. The slope of this plot is 1.03 and differs by only 3% from the theoretical value for perfect matching of aromatic substituent effects. It was concluded that such identical effects, observed in the absence of steric factors, indicate that the differences in rate accelerations by alkyl substituents must indeed reflect steric factors alone.[21]

However, Huisgen suggested that virtually equal ρ values for the olefinic and acetylenic series must not be taken as an indication of equal polarity of the respective transition states.[23] The difference between rate accelerations brought on by phenyl substitution at C_1 in butenol and butynol was ascribed to lack of coplanarity of the phenyl Π system with the developing carbonyl Π system in the acetylenic compound. Steric interference between the phenyl substituent at C_1 and its neighboring hydrogen at C_2, in a planar acetylenic transition state, inhibits resonance interaction with the developing Π system. Since no such inhibition occurs in the olefinic transition state, there is a larger phenyl resonance contribution to transition state stabilization in that series, and a greater rate acceleration results. Consequently, the effects of additional substituents on the phenyl group in **17** can be fully transmitted to the transition state. However, in **16** these effects will be felt only to the extent permitted by partial overlap of the non-coplanar Π-systems. Therefore, despite the fortuitous near-identity of ρ values, a greater transition state polarity is indicated for acetylenes than for olefins.[23]



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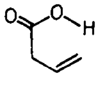

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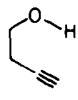

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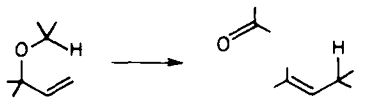
The concept of differing transition state geometries for retro-ene reactions of acetylenes and olefins was not in accord with a report by Kwart and Lattimore.[24] The retro-ene cleavages of 4-penten-2-ol, **18**, 3-butenoic acid, **19**, and 3-butyn-1-ol, **5**, proceeded with virtually identical reaction rates and activation parameters and there were no noticeable substituent effects. Furthermore, no medium dielectric effects were observed and equal rates were reported in both gas and liquid phases. Moreover, all three substrates gave maximum kinetic isotope effects when the transferring hydrogen was replaced by deuterium. The authors claimed these data to be in accord only with a fully symmetrical transition state in which there can be no significant charge development on any of the atoms involved in the transition state.

Subsequently, Kwart *et al.*[25] reported a more extensive study of the retro-ene cleavage of several allylic ethers and of benzyl propargyl ether, **20**, which provided similar results. Here the authors concluded that, despite differences in unsaturation, the transition state geometries were identical, with a completely symmetrical structure for the hydrogen transfer. The evidence cited for the complete absence of any charge development included a Hammett ρ value of zero based upon the retro-ene reactions of four benzylic allyl ethers.

In order to explore the issues raised by Prof. Huisgen's comments and to resolve the contradiction between our findings and those of Kwart *et al.*, a systematic study of the retro-ene cleavage of propargylic ethers was undertaken.[26]

The retro-ene reaction of propargylic ethers

The retro-ene reaction of allylic ethers, **21**, has been known since 1962,[28,29] but only in a few instances have absolute kinetic data been reported.[13,25,30] Existing evidence points to a homogeneous, first-order, unimolecular process which involves a [1,5] sigmatropic hydrogen shift. By contrast, evidence for the occurrence of the analogous reaction of propargylic ethers, **22**, consisted solely of the



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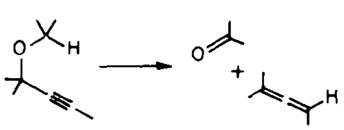

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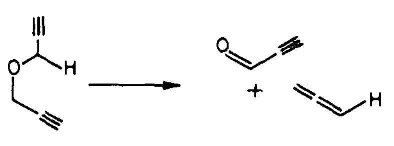
reported pyrolysis of dipropargyl ether, **23**, to produce propargylaldehyde and allene,[28] and the



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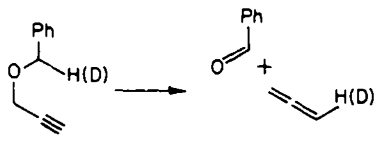

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above-mentioned[25] thermolysis of benzyl propargyl ether, **20**. As substrates for the study of retro-ene reactions, the ethers offer two advantages over the previously discussed β-hydroxy-olefin and -acetylene derivatives: the elimination of steric interactions of eclipsed substituents on adjacent carbon atoms and the possibility for probing charge development via a Hammett study at the site of the migrating hydrogen atom.

To first establish the generality of this reaction, twelve propargylic ethers with varying alkyl substituents as well as the benzylic propargyl ethers indicated in Fig. 3 were thermolyzed.[26] In each case, the only products formed from the homogeneous, first-order reaction were the carbonyl compound and the allene to be expected from a retro-ene cleavage. The kinetic results from the alkyl derivatives are summarized in Table 3.

Table 3. Summary of kinetic parameters for gas phase thermolyses of alkyl substituted ethers and amines

	Propargylic Ethers	Allylic Ethers	Propargylic Amines
No. of examples	12	12	8
Temperature	300°C	300°C	270°C
E_a range (kcal/mol)	39.5 to 43.3	39.2 to 43.5	35.5 to 42.3
$\Delta S^{\ddagger}$ (eu)[a]	-6.3 to -12.8	-8.4 to -12.7	-7.2 to -16.3
$10^5 k$ range (sec^{-1})[a]	0.311 to 73.7	0.146 to 46.3	0.0528 to 7.85
k_{rel}[a,b]	0.24 to 57	0.6 to 190	1.0 to 150

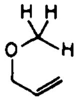
[a] Corrected for path degeneracy

[b] Based on parent compound

A review of the literature indicated that although an excellent relative rate study of the retro-ene reaction of 20 allylic ethers had been reported,[29] there was a paucity of absolute rate data. Consequently, twelve allylic ethers with varying alkyl substituents as well as the benzylic allyl ethers indicated in Fig. 3 were thermolyzed, and the kinetic results from these alkyl derivatives are also summarized in Table 3.

The thermolyses of propargylic ethers closely paralleled those of the β-hydroxyacetylenes. The low activation energies suggest that bond formation provides energetic assistance in the bond breaking process and the negative $\Delta S^{\neq}$ values are in accord with cyclic transition states. The ranges of observed E_a and $\Delta S^{\neq}$ values are not large and are again quite similar to those of their olefinic analogs. The trends in E_a and $\Delta S^{\neq}$ values in both ether series are consistent with the predictable effects of substituents on cyclic transition states and thus provide further evidence for the concerted nature of these reactions.[26] The E_a values for acetylenes were consistently slightly lower than those of analogous olefins, despite the additional energy increment necessitated by bond angle distortion, and the acetylenic derivatives always reacted faster by factors ranging from 1.3 to 5.5 at 300°.

As indicated in Table 3, within each series relative rates can vary by factors exceeding 200. Since rate differences usually diminish with increasing temperatures, relative rates of such magnitudes at 300° do indicate substantial alkyl substituent effects. These results are not in agreement with those reported by Kwart *et al.*,[25] discussed above, which were obtained with less systematic variations of substituents. One source of this discrepancy lies in the failure of Kwart *et al.* to correct observed reaction rates for path degeneracy. Thus, for the retro-ene reaction of methyl allyl ether, **21**, any one of three different



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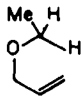

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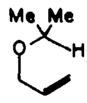

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hydrogens may participate in the cyclic transition state, whereas only two hydrogens are available in **24** and only one may participate in **25**. This factor is most readily accommodated by comparing rates on a "per hydrogen" basis. Although failure to consider these path degeneracies will not affect the calculation of E_a, it will affect the $\Delta S^{\neq}$ term and will also obscure interpretations of substituent effects based upon relative rate values. These consequences are exemplified in Table 4 by the data[26] for **21**, **24** and **25**. Thus in the case of **25**, the "raw" relative rate of 4 corresponds to a corrected value of 12. It should also be noted that the apparently random uncorrected $\Delta S^{\neq}$ values show the expected trend when the correction is applied. The discrepancies between our results and those of Kwart *et al.* are exacerbated by the high reaction temperatures, up to 600°, utilized by Kwart, which further diminish observable rate differences.

Table 4. Effect of path degeneracy (300°)[a]

	Disappearance Rate				Corrected Rate per Hydrogen			
	10^5k	k_{rel}	E_a	$\Delta S^{\ddagger}$	10^5k	k_{rel}	E_a	$\Delta S^{\ddagger}$
$CH_2{=}CH{-}CH_2{-}O{-}\underline{CH_3}$, **21**	0.732	1.0	43.1	-10.1	0.244	1.0	43.1	-12.2
$CH_2{=}CH{-}CH_2{-}O{-}\underline{CH_2}{-}CH_3$, **24**	2.10	2.9	43.5	- 7.3	1.05	4.3	43.5	-8.7
$CH_2{=}CH{-}CH_2{-}O{-}\underline{CH}(CH_3)_2$, **25**	3.04	4.1	42.4	- 8.4	3.04	12.5	42.4	-8.4

[a] Units are: k, sec^{-1}; E_a, kcal/mol; $\Delta S^{\ddagger}$ eu.

Since alkyl substituents exerted effects on these reactions which were in excess of what could reasonably be expected on the basis of steric factors, it seemed desirable to compare developing polarities in the transition states of the two ether series. The results of Hammett studies on both systems are summarized in Fig. 3. The acetylenic series exhibits a ρ value greater than that of the olefins, albeit both are still small. Again, it must be realized that the elevated temperatures necessary for these determinations have a leveling influence on rate differences. These positive ρ values are in accord with small increases in negative charge density, at the carbon bearing the migrating hydrogen, in the transition states of both series. These results are in conflict with the ρ value of zero previously reported by Kwart *et al.* for the allyl ethers.[25] We believe this earlier value to be in error and suggest that it results from the use of only three substituents, all with low σ constants, and again, the use of a much higher reaction temperature. In conjunction with the alkyl substituent effects noted above, these results favor a concerted but non-synchronous process with some charge development in the transition states of both series, but with the development of greater polarity within the acetylenic substrates. This conclusion is in total agreement with Huisgen's interpretation of the results from the Hammett studies of the β-hydroxy-olefins and -acetylenes.

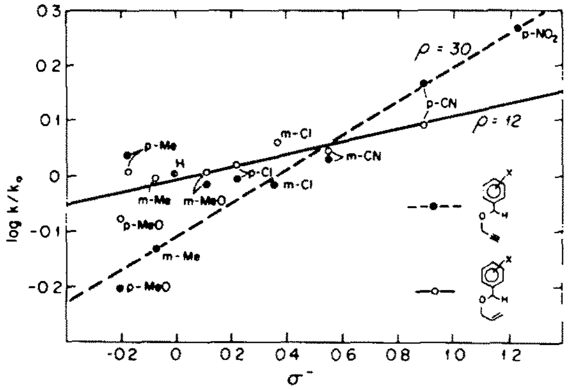
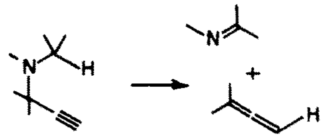


Fig. 3. Hammett plots for thermolyses of benzylic propargyl ethers and benzylic allyl ethers at 270°.

Admittedly, differing substituent effects in reactions of olefinic and acetylenic substrates may imply any of several reaction characteristics: the transition state polarities may differ; the sensitivity of the reaction to charge development may differ; or the timing of the transition state along the reaction coordinate may differ so that varying amounts of the effect of a particular substituent are reflected in the transition states. The above conclusions are based on our conviction that polarity differences best accommodate the total evidence which is summarized in this report. Additional aspects of the retro-ene cleavage of propargylic ethers will be discussed in the sections dealing with concertedness and with planarity of the acetylenic transition state.

The retro-ene reaction of propargylic amines

Egger and Vitins have reported that the presence of a hetero-atom within a retro-ene transition state lowers the activation energy of the process, relative to an all-carbon system, and suggest that this effect indicates a pronounced polar character for that transition state.[31] We therefore investigated[32] the thermolyses of propargylic amines, **26**, in which the oxygen atom of the propargylic ethers is replaced by a nitrogen atom, in order to ascertain the effects of the more basic nitrogen upon the acetylenic retro-ene reaction. There is less data available on comparable olefinic analogs, **28**, than in the ether series since kinetic data on the retro-ene reactions of only five allylic amines have been reported.[33] One example of such an acetylenic retro-ene reaction had been observed.[34] although the authors did not designate it as such: thermolysis of amines **29** produced allenes **30** in poor yield.



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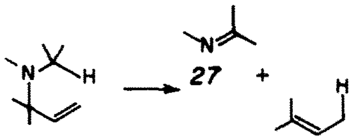

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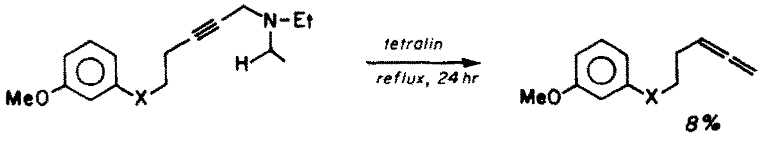
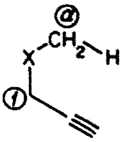


29 $X = O, CH_2$ **30**

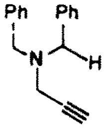
Fifteen amines with phenyl and/or various alkyl substituents were initially thermolyzed in a flow system, over the temperature range of 350–460°, to delineate the scope of the reaction.[32] In fourteen of these compounds the retro-ene cleavage constituted the major reaction path, as was previously observed with β-hydroxyacetylenes and propargylic ethers. Since the N-alkyl imines, **27**, formed from reactions of tertiary amines, **26**, are less reactive than imines lacking the N-substituent, and since unsubstituted imines also reacted further with their secondary amine progenitors, only tertiary amines were selected for kinetic determinations. Furthermore, the two alkyl groups on the nitrogen atom of **26** were kept identical to avoid the occurrence of two competing retro-ene reactions. The homogeneous reactions strictly followed the first-order rate equation, and the results of kinetic determinations on the remaining suitable amine substrates are summarized in Table 3. As in the other two examples of the acetylenic retro-ene cleavage already discussed, the low E_a values suggest energetic assistance to the bond-breaking process from the bond-forming process and the negative $\Delta S^{\neq}$ values are in accord with a cyclic transition state. Comparison of the kinetic data from the propargylic amines with those from analogous propargylic ethers reveals that the amines react at consistently higher rates, due to lower activation

Table 5. Bond dissociation energies (kcal/mol)



Bond		X = O	X = N-CH$_3$	ref.
C_1-X		76.9	72.3	35
C_α-H	anti	93.9	86.6	36
	gauche	102.5	99.8	36

energies whose effects are only partially offset by more negative entropies of activation. The lower activation energies for the amines in part reflect decreased bond dissociation energies of the two bonds which must break in the reaction process, as listed in Table 5. The more negative entropies of activation of the amines reflect the restriction forced upon the non-participating N-substituent by the rigid transition state. Substituents at C_α, the donor site of the migrating hydrogen, cause a larger rate acceleration in the amines than in the ethers, which is an indication of greater charge development in the amines. Unfortunately it has not been possible to utilize a Hammett probe at that site, since the thermolysis of N,N-dibenzylpropargylamine, **31**, gave a large number of products. Similarly, the thermolysis of N-phenyl-N-methylpropargylamine, **32**, also gave a large number of products. Unfortunately, the failures of **31** and **32** to react cleanly thus prevented the determination of charge development either at the site of the migrating hydrogen or at the heteroatom itself. This failure may be attributed to the effect of phenyl substituents in further weakening already weak bonds to the point where homolytic processes can compete with the concerted retro-ene reaction and radical decompositions result.[32]



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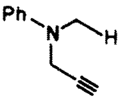

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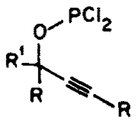

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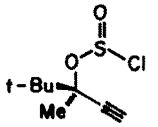

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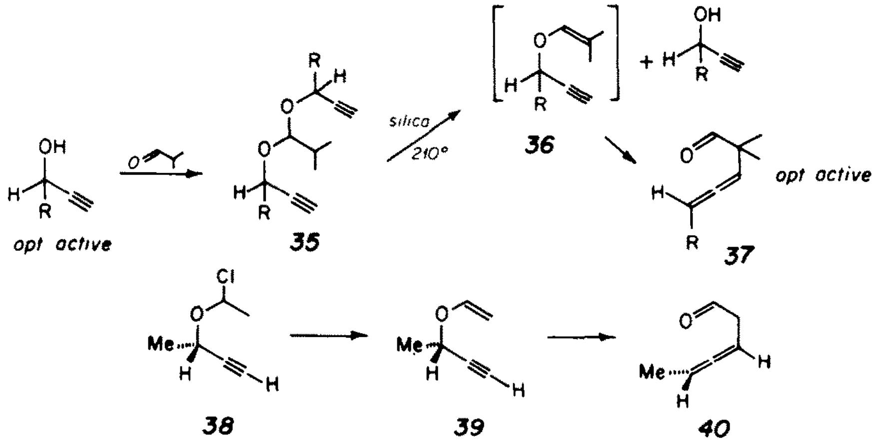
The case for concert in acetylenic retro-ene reactions

The thermal vapor phase cleavages of β-hydroxyacetylenes, propargylic ethers and propargylic amines all share certain properties characteristic of concerted processes: they are all homogeneous, first-order, unimolecular processes; all have activation energies far lower than the bond dissociation energy of their weakest bonds, indicative of bond formation providing energetic assistance to the bond breaking process; all have negative entropies of activation as required by a cyclic transition state; and finally, all show some similarities to the previously known analogous reactions of olefins, which are believed to proceed in a concerted manner.

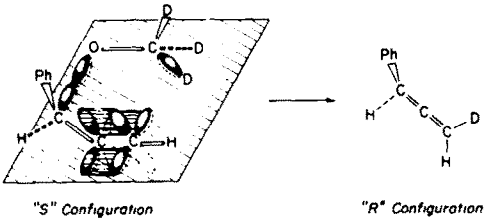
There remains only one additional criterion for concertedness which can be applied: the preservation of stereochemical integrity. This test for concertedness has often been invoked with olefinic substrates and calls for a chiral substrate to provide a chiral product with internal asymmetric induction. Only a few acetylenic derivatives have met this test, and the first example, reported by Jones *et al.*[37] in 1960, is illustrated in Scheme 1. Treatment of optically active propargylic alcohols with isobutyraldehyde



Scheme 1.

gave acetal **35**, which, upon thermolysis over silica at 210°, produced the optically active allenic aldehyde, **37**, presumably via intermediate **36**. The reaction was thought to be a stereospecific Claisen rearrangement of **36**. A very similar reaction sequence, reported by Evans *et al.*[38] in 1965, involved dehydrohalogenation of the α-chloro ether, **38**, of optically active 3-butyn-2-ol. The resulting chiral propargyl ether **39**, rearranged to allenic aldehyde **40**, whose configuration was that predicted on the basis of a concerted process. Some other examples of [2,3] shifts, e.g. in **33**,[39] and a [1,5] sigmatropic chlorine shift in **34**,[40] are discussed in the appropriate sections of the second part of this report.

This criterion for concert has been applied to the acetylenic retro-ene reaction by Viola *et al.*[41] Propargylic ether **41** was chosen as the substrate, since the requisite 1-phenylprop-2-yn-1-ol was commercially available, its resolution and absolute configuration had been reported, and it was known that the polarizable phenyl substituent enhances the optical rotation in the case of isotopic substitution at sp^3 hybridized carbon atoms. Thermolysis of optically active **41**, of known configuration, produced an allene, **42**, which was optically active and which was shown to have the configuration predicted on the basis of the indicated planar transition state (see Fig. 4). Not only did this reaction provide additional evidence for the concert of the acetylenic retro-ene process, but it also illustrated the utilization of the reaction for the formation of a chiral allene of predictable configuration which, in this instance, provided the first reported example of an allene optically active by virtue of isotopic substitution.[41]

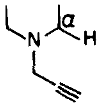


41 42

Fig. 4. Thermolysis of optically active (*S*)-1-trideuteriomethoxy-1-phenyl-2-propyne, **41**.

The case for planarity of acetylenic retro-ene transition states

We have suggested that the transition state for the retro-ene reaction of β-hydroxyacetylenes requires a planar array of all six participating atoms, as illustrated in Fig. 1, in consideration of the minimum distortion of the linear acetylenic bond, the spherical symmetry of acetylenic Π systems, and the relative magnitudes of alkyl substituent effects in β-hydroxyolefins and β-hydroxyacetylenes (*vide supra*). In addition to the fact that alkyl substituent effects in the propargylic ethers and in the propargylic amines were in accord with this interpretation, more specific evidence for such geometric requirements was also obtained from each series.



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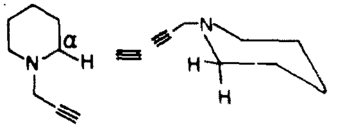

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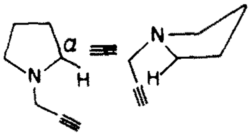

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Both cyclic amines **44** and **45** resemble acyclic amine **43** in terms of the extent of substitution: all three have an alkyl substituent at C_α. Yet their reactivities vary considerably[32] as shown in Table 6. A planar transition state requires that the N-propargyl and C_α–H bonds be eclipsed. This is clearly impossible in **44** if the piperidine ring is to remain in its energetically favored[42] chair conformation. The additional energy required by **44** to achieve a conformation which permits a planar transition state is

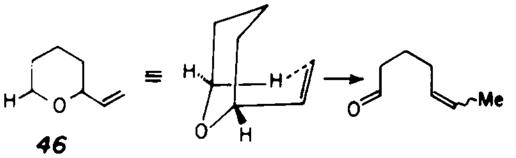
Table 6. Effect of ring strain on thermolyses of propargyl amines at 250°

Compound	E_a(kcal/mol)	$\Delta S^{\ddagger}$ (eu)	k_{rel}
N,N-dimethylpropargyl amine	40.0	-10.5	1.0
N,N-diethylpropargyl amine, 43	35.6	-13.8	55
N-propargylpiperidine, 44	42.6	-6.8	2.3
N-propargylpyrrolidine, 45	38.9	-9.3	22

therefore reflected in the activation energy, and E_a for **44** is 7.0 kcal/mol higher than that for acyclic **43**. If no eclipsing of the bonds in question were required, then only a small difference in activation energies is to be anticipated since only a moderate energetic price would have to be paid to introduce a double bond into the six-membered ring. This price should not exceed the reported[43] strain energy in cyclohexene of 1.4 kcal/mol. A smaller entropy loss for **44** is also expected since one rotor, i.e. N–C_α, which is lost in the transition state for acyclic **43**, is already essentially absent in the ground state of **44**.[32]

Compound **45**, in which the nitrogen atom is part of a five-membered ring, can easily accommodate a planar retro-ene transition state. The N-propargyl and C_α–H bonds are already eclipsed, or nearly so, in the ground state and no deformation of the five-membered ring is necessary. Consequently, the activation energy for **45** is 3.7 kcal/mol lower than that for the six-membered ring compound, **44**. That E_a for **45** is 3.3 kcal/mol higher than for acyclic **43** reflects the strain energy required to incorporate a double bond into the pyrrolidine ring. The smaller entropy loss for **45** again reflects the greater rigidity of the ground state of **45** relative to acyclic **43**. That the entropy loss for **45** is slightly greater than for **44** may reflect more freedom due to pseudorotation in the ground state of **45**. If the retro-ene transition state were not to require eclipsing of the N-propargyl and C_α–H bonds, then piperidine **44** should more readily accommodate that transition state than should pyrrolidine **45** and their reactivities should be reversed, especially since entropic considerations already favor **44**.[32]

The propargylic ether series seems to provide unequivocal proof for the necessity of an acetylenic substrate to assume a planar conformation if the retro-ene reaction is to occur.[44] Molecular models indicate that olefinic ethers **46** and **47** can readily assume the chairlike conformations normally preferred for their retro-ene fragmentations, and indeed both compounds readily cleaved upon flow system, vapor-phase thermolysis at 450–470° to give the expected products at rates commensurate with the degree of alkyl substitution upon the acyclic olefinic substrate.



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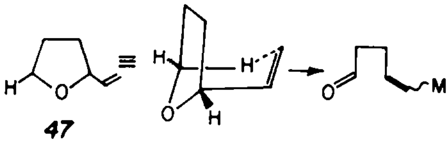

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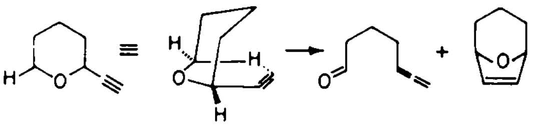

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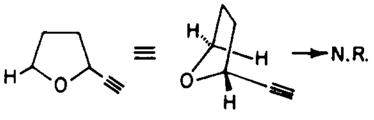

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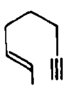
In contrast, the behavior of their acetylenic analogs differs substantially. Models indicate that the six reacting atoms in **48** can assume a planar conformation only at the cost of considerable angle strain within the confining tetrahydropyran structure. As a consequence, **48** was the first substrate in all our studies in which the acetylenic analog did not react faster than the corresponding olefin. Furthermore, the retro-ene fragmentation of **48** is accompanied by a cyclization leading to **49** which was not observed in any acyclic ethers and which can therefore apparently compete with the retro-ene process only when the latter is hindered. This cyclization is discussed further in the second part of this report, under the section dealing with five-membered transition states. Models further suggest that **50** can attain the requisite planar array only at the cost of a prior bond rupture due to the constraints enforced by the tetrahydrofuran ring. Compound **50** proved to be essentially thermally stable at 470°C, with >99% recovery under conditions where its olefinic analog **47** had almost completely reacted. It appears clear, therefore, that the retro-ene reaction of acetylenic substrates is inhibited when structural requirements restrict planarity of the reacting 6-atom system.[44]

The geometric considerations which dictate planarity for transition states of acetylenic retro-ene reactions also apply to any other concerted pericyclic reactions which involve only sigma bonds and acetylenic Π bonds. However, a pericyclic transition state which also involves an olefinic bond cannot be planar since the orientation of the participating olefinic orbitals does not permit such a configuration. Thus, the olefinic portion of the transition state of an acetylenic Cope or Claisen rearrangement cannot be coplanar with the acetylenic component. The transition state of a bis-acetylenic Cope rearrangement, however, should also enjoy the energetic stabilization brought about by maximum orbital overlaps within a planar configuration.

The reactivity of acetylenic substrates

Despite the additional energetic increment required to distort the linear acetylenic bond and permit its incorporation into a cyclic transition state, an abundance of evidence indicates that acetylenes normally react faster in intramolecular pericyclic reactions than do their olefinic counterparts. Thus, in addition to the reactivities for the two components of oxy-Cope systems,[11] summarized in Table 1, β-hydroxyacetylenes were consistently found to react faster in all cases where comparable data on analogous olefins were available: acetylenic reactivity was 1.3–6.9 times that of the corresponding olefin for 5 analogous alcohol pairs in the vapor phase at 350°,[14] and the reactivity ratio was 1.5–1.6 for 7 pairs of aryl substituted compounds utilized for solution phase Hammett studies at 260°.[21] Parallel results were obtained in the ether series,[26] where more data are available for comparisons: for 9 pairs of analogous alkyl substituted ethers, in the vapor state at 300°, acetylenic reaction rates were higher by ratios of 1.3–5.5, and in 9 pairs of aryl substituted ethers, in solution at 270°, the ratios were 2.9–4.7.

In the limited number of reports of related reactions, where comparable data for both olefinic and acetylenic substrates exist, similar results have normally been observed. Huntsman[45] reported in 1962 that the intramolecular ene reaction of **51** proceeds more rapidly than that of its olefinic counterpart **52**. Similar conclusions have more recently been reached by Oppolzer and Snieckus, who report[46] in a review of intramolecular ene reactions that acetylenes participate in such reactions under milder conditions than do analogous olefins. As has been pointed out earlier in this report, such reactions may not require distortion of the acetylenic bond angle and therefore no extra energetic increment for this purpose may be needed.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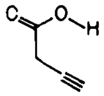

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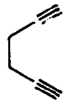
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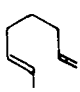
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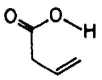

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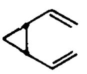
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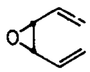

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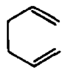
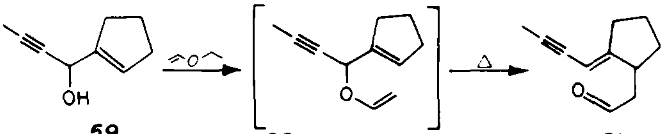

1

In the acetylenic retro-ene cleavage of 3-butynoic acids, discussed in the second part of this report, the triple bond must become part of an intramolecular 6-membered transition state. Yet, in this reaction for which substantial evidence for concert has been presented,[4] acetylenic 3-butynoic acid **53** decarboxylates at a rate 3.9 times that of the analogous 3-butenoic acid **54**.

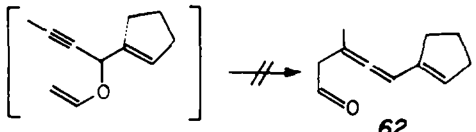
In both compounds **55** and **57** the acetylenic bond angle distortion required for a Cope rearrangement must be even larger than in acyclic cases, since the small internal bond angles of the three membered rings require the indicated external bond angles to be larger than normal. Yet, the kinetic parameters reported for these compounds do not reflect any energetic requirements above those of their olefinic analogs in which little such distortion should be necessary. Brown *et al.*[47] have reported *cis*-divinylcyclopropane, **56**, to undergo an exceedingly facile Cope rearrangement, with $\Delta H^{\neq} = 19.4 \pm 1.8$ kcal/mol and $\Delta S^{\neq} = -5 \pm 7$ eu. For *cis*-ethynylvinylcyclopropane, **55**, Dolbier *et al.*[48] have reported corresponding parameters to be 19.3 kcal/mol and −15 eu respectively. The behavior of oxirances **57** and **58** closely parallels that of the cyclopropanes. The solution phase kinetic parameters reported by Manisse and Chuche[49] for the acetylenic derivative **57**, $\Delta H^{\neq} = 25.1 \pm 1.7$ kcal/mol and $\Delta S^{\neq} = -3 \pm 3$ eu, are very similar to those for the olefinic analog **58** in the gas phase, reported by Vogel and Gunther[50] to be $\Delta H^{\neq}$24.6 kcal/mol and $\Delta S^{\neq} = -11.3$ eu. While it cannot be stated on the basis of these data, gathered from different laboratories and in different phases, that the acetylenes react faster, the reported parameters for analogous olefins and acetylenes are certainly within experimental error of each other, despite the additional distortion required of the acetylenes.

In the case of the bis-acetylenic Cope rearrangement of 1,5-hexadiyne, **3**, still more of an energetic increment for bond angle distortion will be required than for **55** and **57**, since the termini of the reacting 6-atom system are still further apart by virtue of the two linear acetylenic units. Yet, Huntsman and Wristers[51] have reported kinetic parameters, $E_a = 34.4$ kcal/mol and $\Delta S^{\neq} = -9.6$ eu, which are virtually identical to those reported by Doering *et al.*[52] for the Cope rearrangement of 1,5-hexadiene, **1**, $E_a = 34.3$ kcal/mol and $\Delta S^{\neq} = -13.8$ eu.

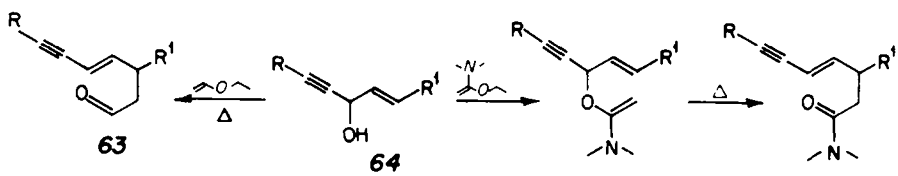
Some contrary results have been reported from Claisen and oxy-Cope rearrangements in which there is direct competition between participation of an olefinic and of an acetylenic unit within the same molecule. Bancel and Cresson[53] have reported several examples of the reaction illustrated for **59**. When that compound is heated with ethoxyethylene, the acetylenic aldehyde **61** is produced, presumably via a Claisen rearrangement of intermediate **60a**. Although a conformer of the same intermediate, **60b**, could lead to an acetylenic Claisen rearrangement, no **62** is reported. The same reaction has also been reported to yield acyclic compounds **63** from **64** for a number of different substituents.[54,55] Moreover, when **64** is transetherified with 1-ethoxy-N,N-dimethylvinyl amine, compound **65** is produced which upon further heating rearranges to amide **66**. Again, no competing reaction of the ethynyl group is observed.[55] Some of these reports contain little experimental detail and therefore structures of some of the claimed products are suspect. Thus, for **61** the structure is based mainly on the fact that the NMR signal of the methyl group is a doublet and not a triplet as would be expected for an endocyclic double bond.[53] Since the methyl group in **62** would also be a doublet, this structure assignment must remain in doubt.



59 60a 61

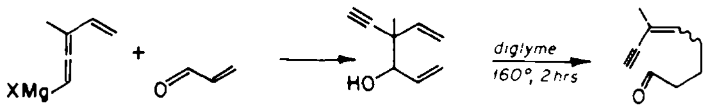


60b 62



63 64 65 66

Equally surprising are a series of reports[56] which deal with oxy-Cope rearrangements of ethynyl substituted substrates. For example, when alcohol **67**, prepared as indicated, was heated in diglyme solution, a mixture of *cis* and *trans* olefinic aldehydes **68** was obtained, and essentially no participation of the acetylenic unit is reported.[56] This reaction has been utilized for the synthesis of the sex pheromone of the pine sawfly.[57] When alcohol **69** was heated in diglyme for 2 h, the rearranged aldehyde **70** was obtained in 82% yield. Catalytic hydrogenation afforded saturated aldehyde **71**, treatment of which with methylmagnesium iodide followed by acetylation gave the pheromone **72**. There are some disturbing aspects to this report. It is difficult to rationalize a rearrangement of **69**, in 82% yield, when not only can there be competition from the acetylenic oxy-Cope process, but also from two retro-ene cleavages. Unfortunately the structure proof of the final product consists solely of a comparison of prominent spectral peaks with those described for the natural product.



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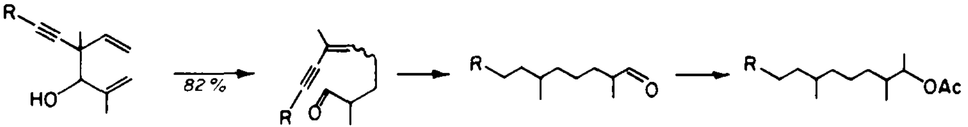
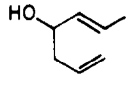


69 70 71 72

Some aspects of these internally competing Claisen and oxy-Cope rearrangements are readily explicable. The rate of the Cope rearrangement is normally depressed by terminal substituents, presumably for steric as well as electronic reasons. For example, the forward reaction for **73** proceeds at a rate about 4 times that of the reverse reaction.[58] Similarly, in the oxy-Cope rearrangement the 1-methyl substituent in **75** slows up the reaction by a factor of about 4, while the two methyl substituents in **76** slow up its rate, relative to the parent compound, about 40-fold.[8] The only information available for acetylenic Cope rearrangements[59] indicates the ratio of the reactivities of **3**:**77**:**78** to be 137:37:1. A substituent on a linear acetylenic bond can be expected to have a larger steric effect than a ***trans*** substituent on an ethylenic bond. Indeed, in the retro-ene reaction of acetylenic ether **79**, the methyl substituent slows up the reaction by a factor of 4, whereas in the corresponding olefin **80** the effect is only a factor of 1.7.[26] Since hydrogen transfer has a lower steric requirement than does the approach of a terminal methylene in a Cope rearrangement, the effect of a terminal alkyl substituent is smaller for the retro-ene reactions. In the β-hydroxyacetylenes, the methyl group in **81** also slows up the rate by a factor of 4,[14] but in amine **82**, where hydrogen transfer involves the larger steric requirement of an approaching secondary carbon, the effect is a factor of 23.[32]


73 74



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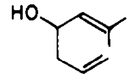

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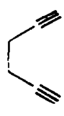
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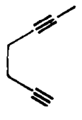
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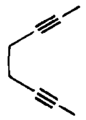
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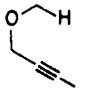

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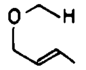

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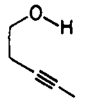

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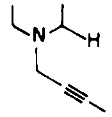


82

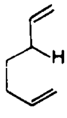
When the rate deceleration caused by a terminal substituent is considered, it is not surprising that in ethynyl substituted Cope and Claisen substrates, when the competition is between a substituted acetylene and an unsubstituted olefin, the reaction of the olefin can predominate. Indeed, in the absence of a terminal substituent in **65**, i.e. R = H, a mixture of a number of products was formed but no product ascribable to the olefinic Cope rearrangement could be detected.[55] However, even when the reactivity of an acetylenic unit is decreased by a substituent, some product formation from that path should still be observable. In the case of substrates **59** and **67**, where competing olefinic and acetylenic units are equally substituted, the results are surprising indeed, and since these appear to be the only reports where olefinic reactivity exceeds that of acetylenes, a reinvestigation may be desirable. This is particularly true in the case of **67**, to which the relative rates summarized in Table 1 are directly applicable.

Polarity in acetylenic transition states

Pericyclic reactions of acetylenic substrates have been studied much less than those of olefins. Consequently, it seems appropriate to consider the development of charge separations in the better-known olefinic reactions and then consider their relationships to their acetylenic analogs.

If a concerted reaction proceeds in a truly synchronous manner, where all bond order changes occur at the same precise rate and time, then no polarity changes are anticipated in the transition state and that transition state will be truly symmetrical. Kwart *et al.* have claimed the retro-ene reactions of β-hydroxyolefins[24] and of allylic ethers,[25] as well as of the acetylenic derivatives, to proceed through such symmetrical transition states. These conclusions were reached on the bases of the supposed identity of the transition state geometries for olefinic and acetylenic substrates, of the lack of substituent and medium effects in the allylic ethers, and of the maximum kinetic deuterium isotope effects in all four types of substrates. Yet on each of these items substantial contrary evidence exists. The difference in olefinic and acetylenic transition state geometries has already been discussed, as have the magnitudes of substituent effects. As of this time, there appears to be considerable disagreement on the implications of maximum kinetic isotope effects,[61] particularly in those cases of proton transfer reactions where pK_a values of donor and receptor sites are not evenly matched.[62]

Are the structures of transition states normally symmetric? McIver has concluded that most probably they are not.[63] The most likely truly synchronous process would be one in which all participating atoms are nearly identical. Yet, even in the Cope rearrangement there appears to be a lag between the bond-forming and bond-breaking processes.[64] When there is a heteroatom within a cyclic transition state, then that state is intrinsically polar, and the greater electronegativity of atoms such as oxygen and nitrogen promises an enhancement of that polarity relative to the ground state. Accordingly, Dewar and Nahlovsky have noted that polar solvents favor the Claisen rearrangement of cinnamyl phenyl ether and have suggested that this pattern should occur in other pericyclic reactions wherein a heteroatom is involved.[65] Along similar lines, Egger and Vitins concluded that the presence of a heteroatom lowers the activation energy of retro-ene reactions.[31] Despite virtual agreement in the dissociation energies of the breaking bonds, E_a for the all-carbon retro-ene reaction of **83** is 9 kcal/mol higher than that of the nitrogen analog, **85**. Consequently, a pronounced polar character was deduced for the transition state of amine **85**. The corresponding ether, **84**, has an intermediate activation energy, presumably with intermediate polarity.[31] Further support for these conclusions comes from a comparison of the bond-weakening effects of a vinyl group on the breaking C–H bonds. This effect is expected to be smaller in a largely synchronous process where there is little polar character in the transition state. The difference in E_a between **85** and **87** was found to be about 6 kcal/mol, that between **84** and **21** about 3 kcal/mol, and that between **83** and **86** was calculated to be less than 3 kcal/mol. Here again the evidence points to the largest degree of polarity in the transition state of the amines, and somewhat less in the ethers.[31]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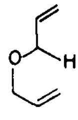
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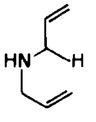
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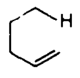
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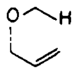
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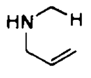
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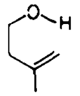
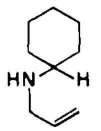

88

For those reactions of olefinic substrates, with which the reactions of acetylenes covered in this report may be superficially compared, there is ample additional evidence for developing polarity in the transition state. Hammett studies for the retro-ene cleavages of β-hydroxyolefins[21,22,66] and of allyl ethers[26,29] are in accord with small charge separations in their transition states. There are alkyl substituent effects in excess of what is to be expected on the basis of steric factors alone in the retro-ene reactions of β-hydroxyolefins,[13] allylic ethers,[26] and allylic amines.[31] Of particular interest in this respect are two reports[67,68] that in the β-hydroxyolefin cleavage of **88**, the 3-methyl substituent, which can have virtually no steric effect on the reaction but can stabilize charge development at C_3, accelerates the reaction by a factor of about 10 at 350°. Finally, on the theoretical side, Dewar and Ford[69] have calculated that in the thermal decarboxylation of 3-butenoic acids a sizeable positive charge develops at C_3 with negative charges at C_2 and C_4. These calculations have recently been verified experimentally by Bigley *et al.*[70]

There is also consistent evidence for developing charge separations in acetylenic transition states, some of which indicates that these transition states are more polar than their olefinic counterparts. As in olefinic retro-ene reactions, alkyl substituent effects are larger than can be accounted for by steric factors alone in those propargylic ethers[26] and amines[32] where eclipsing interactions in a planar transition state are not a factor, and they are larger in the case of amines where the heteroatom is also more basic. Although Kwart *et al.* claim there are no medium effects in the retro-ene reactions of allyl ethers, a statement not completely borne out by the data presented,[25] we have previously reported the medium effects, summarized in Table 7, for the β-hydroxyacetylenes.[14] In each of the three examples cited, the E_a in the liquid phase was on the average of 3 kcal/mol lower than in the gas phase, and was accompanied by a $\Delta S^{\neq}$ about 3 eu more negative, as is to be expected for solvation of a polar transition state. The Hammett studies of the β-hydroxy compounds,[21] taken in conjunction with Huisgen's comments (*vide supra*), imply a greater transition state polarity for the acetylenic series than for the olefinic one. Further evidence for the correctness of this view comes from the Hammett studies of the ethers,[26] where the ρ value for acetylenes is 2.5 times as large as that for the olefins. Finally the

Table 7. Medium effects on thermolysis rates at 250°, 10 k

Compound	Gas Phase (extrapolated)	Xylene (dilute solution)	Neat Liquid
3-Butyn-1-ol	0.818	1.88	2.86
5-Hexyn-3-ol	1.80	----	9.4
2-Methyl-4-pentyn-2-ol	2.03	3.42	5.3



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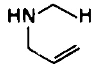

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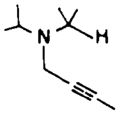

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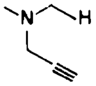


26

difference in activation energies between olefinic amines **89**, where there are two alkyl substituents on C_α, and **87**, where there are none, is 1.2 kcal/mol,[33] whereas the corresponding difference between the acetylenic amines **90** and **26** is 4.2 kcal/mol.[32]

Possible reaction rationales

The various studies described in this report indicate clearly that, in the absence of specific steric constraints, the linear acetylenic unit can not only replace a bent olefinic unit in cyclic, intramolecular transition states, but can indeed react more readily than the corresponding olefinic unit. Bigley and Weatherhead[4] have noted that there can be no thermodynamic driving force for this enhanced reactivity of acetylenic substrates: at 298°K, ΔG_f^0(propyne) = 46.3 kcal/mol whereas ΔG_f^0(allene) = 48.4 kcal/mol. Therefore the different reactivities must reflect kinetic considerations.

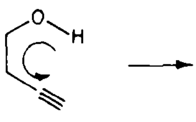
The relative reactivities of acetylenes and olefins in reactions involving their Π systems vary considerably, and have been discussed in March.[71] Acetylenic systems represent a paradoxical situation wherein effects of greater electron deficiency are counterbalanced by an increased electron density. Frequently, but not uniformly, triple bonds are less subject to electrophilic attack and more subject to nucleophilic attack than are double bonds. Thus, in non-conjugated enynes most electrophiles preferentially react with the double bond. The preference for attack by hydrogen halides, however, depends on the degree of substitution and terminal acetylenes are preferred over similar olefins while internal triple bonds are not so favored. A factor which is involved in these reactions is the relative stability of the ionic intermediates produced: additions of electrophiles to acetylenes produce vinyl cations which are less stable than the corresponding alkyl cations formed from additions to olefins; on the other hand, nucleophiles produce vinyl anions from acetylenes which are more stable than the corresponding alkyl anions.[71]

In pericyclic reactions the stabilities of intermediate ionic species are only marginally pertinent, since only those small charge developments need be considered which would result from any non-synchronous nature of such reactions. However, olefins are intrinsically better electron donors than are acetylenes, possibly because the shorter carbon–carbon bond distance in acetylenes results in more tightly held electrons. Thus, the ionization potentials for olefins are about 0.5 eV lower than those for corresponding acetylenes.[72]

In a comparison of the pericyclic reactivities of olefinic and acetylenic substrates, the properties of the other bonds involved must also be considered. In general, allylic bond dissociation energies are 3–4 kcal/mol lower than those of corresponding propargylic bonds,[73] a factor which favors the reactivity of olefinic substrates. The fact that entropic considerations are less favorable for the allylic radicals formed in such dissociations, due to rotational restrictions imposed upon them but not on their propargylic counterparts,[73] does not enter into the case of pericyclic reactions where both moieties remain part of a rigid transition state.

In summation then, acetylenic retro-ene reactions proceed at rates faster than those of their olefinic analogs despite the facts that: an additional energetic increment is required to allow the linear acetylenic unit to conform to a cyclic transition state; there may be additional eclipsing interactions between adjacent substituents in the planar transition state; the more energetic propargylic bond must be broken during the reaction process; and the allenic bond system formed is thermodynamically less stable than its acetylenic precursor. We have suggested that one factor which favors the acetylenes, and thus can help offset some of these increased energetic demands, is their planar transition state geometry. In such a configuration all participating bond orbitals are centered in that plane and maximum orbital interaction, i.e. "aromaticity", results. This is not the case with the corresponding olefins.

Differing transition state geometries, however, do not account for the observed polarity differences between acetylenic and olefinic transition states. As stated previously, the development of polarity is an indication of a nonsynchronous process in which there is a lag between bond-breaking and bond-forming processes. We had initially suggested[14] that part of the greater reactivity of β-hydroxyacetylenes, compared with that of their olefinic analogs, may well be due to the greater nucleophilicity of the triple bond toward the hydroxyl proton. This suggestion was based in part on a report that in the addition of HX to non-conjugated enynes the triple bond coordinated the proton more readily than an equally substituted double bond.[74] Furthermore, the gas-phase reactivities of primary, secondary, and tertiary alcohols, in both acetylenic and olefinic series, increased in the same order as the reported gas-phase acidities[75] of such alcohols. Implicit to this suggestion is that the hydrogen transfers with protonic character; its addition at C_4 would impart a partial positive charge to C_3 and leave behind a partial negative charge on the oxygen atom. Subsequently, we reported the results of a Hammett study[21] which indicated development of a small positive charge at C_1. These events can be readily reconciled if, as was suggested, the progress of proton transfer slightly precedes that of C–C bond rupture. The motion of electrons as depicted in **91** would therefore result, with formation of transition state **92**.



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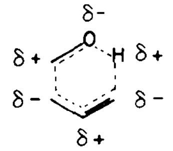

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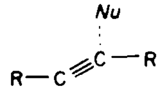

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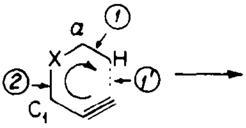
Bigley and Weatherhead questioned this conclusion since no indication existed concerning the electronic nature of transferring hydrogen atoms in pericyclic reactions.[4] Instead, they preferred a bond energy explanation based upon the fact that one of the Π bonds in acetylene is more easily broken, by 9.4 kcal/mol, than that of ethylene.[4] We suggest that a more appropriate view must take into account all of the following energetic considerations. In olefins no net change occurs in the nature of the Π bond, whereas in acetylenes the net change is the above-mentioned 2.1 kcal/mol increase from the initial acetylene to the final allene. At least a part of this increase, and of the 4 kcal/mol difference between the breaking C–C bonds, must be reflected in the transition states. These differences, both of which favor the reactivity of the olefin, are more than offset by the difference in bond energies of the forming C–H bonds: the bond energy of the allylic C–H produced from the olefin is 87 kcal/mol whereas that of the allenic C–H formed from the acetylene is 108 kcal/mol.[19] Whatever portion of this 21 kcal/mol difference is reflected in the transition states helps to defray some of the extra energetic costs of the acetylenic process.

But these energetic considerations still do not pertain to the greater polarity apparently developed in acetylenic transition states. A possible clue to the elucidation of this facet of acetylenic retro-ene reactions comes from recent theoretical studies.[76,77] Houk *et al.* report[76] that in nucleophilic additions to acetylenes, a "*trans*" bending of the acetylene, as indicated in **93**, leads to a substantial decrease in the LUMO of the acetylene. An increased interaction with the HOMO of the nucleophile then results, which more than compensates for the energy required to distort the acetylene from its linear ground state geometry. No similar increase in the HOMO–LUMO interaction occurs with olefins, in which no such distortion is possible.[76] Since there is no corresponding effect with electrophiles, retro-ene reactions in which an acetylenic unit must bend to accommodate the requisite cyclic transition state should be favored by a hydrogen transfer with hydride (i.e. nucleophilic) character.

There are two possible chains of events by which concerted but non-synchronous hydrogen transfer with nucleophilic character could occur. As depicted in **94**, an initial beginning rupture of the C_α-H bond,



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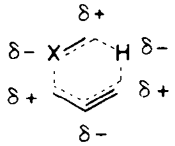

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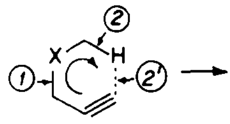

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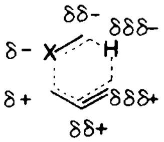


97

with concommitant bond formation between that nucleophilic hydrogen and the terminal acetylenic carbon, events 1 and 1′, leaves a positive charge residue at C_α which then initiates rupture of the C_1-X bond, event 2. The ensuing electron flow is indicated in **94** and would provide a transition state with alternating polarity on adjacent atoms, as shown in **95**. Such charge distribution in transition states has frequently been invoked and was originally proposed by Pople[78] on the basis of INDO and CNDO calculations. Recently, however, Lipscomb *et al.*[79] have reported that such calculations are often in serious disagreement with *ab initio* SCF calculations as well as with experimental values.

There are two factors which are contrary to the scenario considered above. The Hammett probe in the propargylic ethers indicated there to be negative charge development at C_α, and furthermore, *it is not the* C_α*-H but the* C_1*-X bond which is by far the weakest bond in the molecule.* Consequently, it is more likely that events occur as depicted in **96**. Thermal activation triggers an initial bond rupture of the C_1-X bond, event 1, in which the electronegativity of the heteroatom dictates the indicated direction of the electron flow. An inductive negative charge accumulation at C_α then leads to hydrogen migration with hydride character, events 2 and 2'. The resulting charge distribution in the transition state is now represented by **97**, with highest charge densities at the sites of the initial bond rupture and with decreasing densities of like charges on adjacent atoms. The concept of the development of like charges on contiguous atoms, with decreasing charge density as a function of distance from the site of origin of that charge, has been suggested by Stolow *et al.*[80] on the basis of experimental data.

The scenario just specified also accounts for the development of greater polarity in the transition state of amines, as compared with that of ethers. It is not that the nitrogen atom is more basic, since no lone pair involvement is called for in a non-catalyzed process. Rather the difference lies in the strength of the breaking C-X bond which initiates the reaction process. A weaker C-N bond will be more completely broken in the transition state, which, with an electron flow as specified in **96**, results in a greater negative charge accumulation on the nitrogen atom than is the case in the analogous oxygen compound. Further verification of this scenario will require a Hammett probe of the amines, which has not been possible as of this time.

On consideration of all available information, we suggest that a planar transition state, formed by events as depicted in **96**, provides the most consistent rationale for the acetylenic retro-ene reaction of propargylic ethers and amines.

A cautionary note

The energetics of concerted reactions are a summation of the factors involved in a number of bond-breaking and bond-forming steps and those energetics are reflected, in part, in the transition state. However, the fact that there are similarities in the total energetic summations which constitute the kinetic parameters of two reactions does not necessarily imply similarities in the individual components of those reaction processes nor does it imply that the same precise mechanistic pattern is being followed.

Differing transition state polarities suggest differences in the timing of various steps, i.e. the degree of concertedness, as well as the attainment of the transition state, i.e. "early" or "late". Since transition states depend upon the lowest energy potential surface available, their timing will be affected by structural variations in the substrates. Therefore, despite similar activation parameters, the sequence of events in the reactions of acetylenic substrates need not be at all identical to those of olefinic ones, nor do different functionalities within the acetylenic manifold necessarily follow identical patterns. A case in point is the β-hydroxyacetylene cleavage, which does not fit into the pattern just discussed for propargylic amines and ethers: it is difficult to rationalize hydrogen transfer in **91** with hydride character and with positive charge development at C_1. Here the effect of the strong polarity of the breaking O-H bond appears to overshadow the fact that the C_1-C_2 bond is the weakest one in the molecule. Despite the apparent preference of the acetylenic bond for nucleophiles, we agree in this case with Bigley *et al.*[70] that hydrogen transfer with protonic character is the likely event.

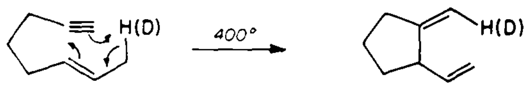
Since substitution will affect the nature of the transition state, particular caution should be exercised with interpretations of effects of aromatic substituents which interact with either developing or disappearing Π systems. In these cases the timing of the transition state could be altered substantially and it is likely that in such Hammett studies the transition state being probed is itself altered by the instrument used for that probe.[81]

One factor remains clear: regardless of the rationales which have been explored in the first part of this report, acetylenes can participate in intramolecular pericyclic reactions, and in most instances, do so more readily than their olefinic analogs.

A SURVEY OF PERTINENT REACTIONS OF ACETYLENIC COMPOUNDS

In this section we will survey nominal pericyclic reactions of acetylenes in which the acetylenic unit becomes part of an intramolecular transition state. In many of these examples neither concertedness nor intramolecularity has been established, and consequently the suggested mechanisms must remain conjectural although they are eminently reasonable in light of present day understanding of such processes. It should be emphasized, though, that alternate mechanistic pathways are possible and, particularly in liquid phase reactions, intermolecular steps have been identified in a few cases. Many of these examples do not by themselves provide concrete evidence for the ability of acetylenic bonds to participate in concerted intramolecular processes, but collectively they indicate the extent and potential utility of reactions which nominally fall into this category.

The questions addressed by this report are if and how acetylenic bonds can participate in intramolecular, cyclic transition states which require a considerable distortion of the linear sp bond angle. Since not all intramolecular reactions of acetylenes are in this category, only those reactions will be considered which involve a contiguous array of participating bonds in the transition state. For example, the numerous reported intramolecular acetylenic ene reactions, as exemplified by **51**, do not fall within the intended scope of this report. The thermolyses of 6-alken-1-ynes, such as **51**, were first reported by Huntsman in 1962 and the evidence presented leaves little doubt about the concerted nature of the process.[45,59] However, the six participating atoms are not contiguous and the two reacting components, which are separated by a three-carbon bridge, merely co-exist within the same molecule. The same consideration applies to the more recently reported rearrangements of **98**[82] and **99**[83] where the leeway afforded by that three-atom bridge largely negates any steric influence by the substituents α to the acetylenic bond. Another version of this reaction, the acetylenic enolyne rearrangement of **100**, affords the indicated mixture of cyclized products.[84] These reactions require little if any distortion of the acetylenic bonds and should resemble, energetically, normal bimolecular ene reactions which enjoy the entropic advantage of having both reaction components located within the same molecule. Similarly, there are no involvements of contiguous arrays of bonds in the elegant nonenzymatic biogenetic-like olefinic cyclizations, in which some acetylenic derivatives have been employed.[85] Such reactions, which do not fall within the scope of this report, will not be considered further.



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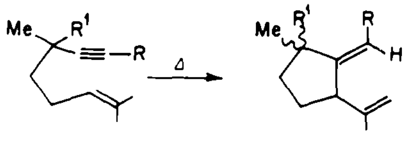
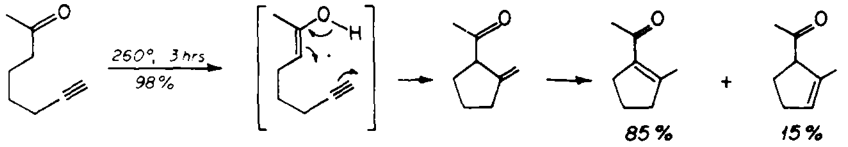


98 $R = COOMe$ or Me; $R^1 = H$
99 $R = H$; $R^1 = OH$



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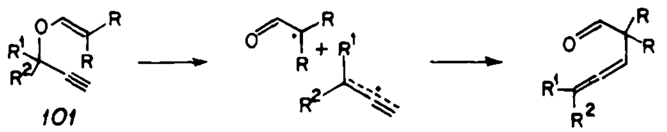
Reactions via six-membered transition states

Acetylenic Claisen rearrangements.[60,86,87] There is general agreement on the first step in these rearrangements: a [3,3] sigmatropic shift to an allenic derivative. Subsequent reactions of these allenes appear to be highly dependent upon substitution and, possibly, reaction conditions. It is the initial step, involving the acetylenic bond, which is of main interest in this report.

The aliphatic acetylenic Claisen was reported by Black and Landor[88] in 1965. Vapor or liquid phase

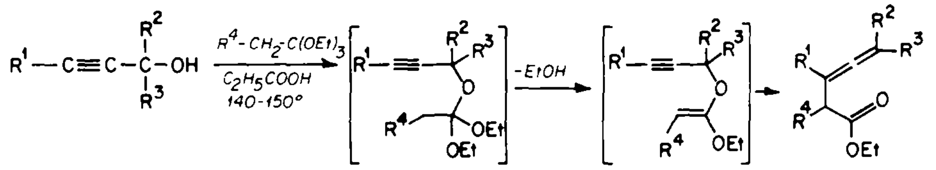


101 **102**

R	*R¹*	*R²*	*PHASE*	*TEMP.*	*YIELD*
H	*H*	*H*	*vapor*		
H	*Me*	*H*	*vapor*	*200°*	*20%*
H	*Me*	*Me*	*vapor*	*250°*	*10 %*
Me	*H*	*H*	*liq.*	*140°/4 hr*	*70 %*
Me	*Me*	*Me*	*liq.*	*140°/15 min*	*76 %*

thermolyses of vinyl propargyl ether and several methyl derivatives, **101**, yielded the corresponding 3,4-pentadienals, **102**, in a process completely analogous to the non-aromatic Claisen rearrangement. Since considerable polymerization occurred and since methyl substitution accelerated the reaction, a mechanism involving a "1 electron shift" was postulated with partial radical formation. A concerted pericyclic mechanism now seems more likely with methyl substituents aiding the reactions via energetic and entropic contributions.

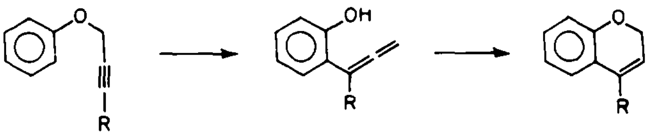
Two earlier reports,[37,38] which postulated stereospecific Claisen rearrangements in the formation of optically active allenes, have been discussed in the first part of this report (see Scheme 1). Crandall and Tindell[89] have reported a nominal aliphatic Claisen rearrangement as an intermediary step in a general



103 **104**

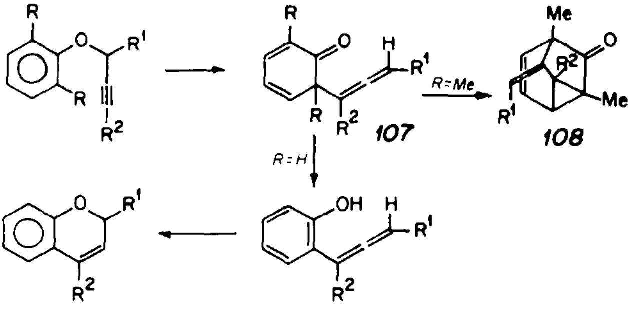
synthesis of β-allenic esters, **104**, from propargylic alcohols, **103**. In the absence of isolation of the suggested intermediates, the mechanism for this liquid-state conversion must be considered conjectural.

There are conflicting reports about the final products of acetylenic aromatic Claisen rearrangements. Iwai and Ide[90] have reported formation of benzopyrans, **106**, from the thermolyses of phenyl propargyl



105 **106**

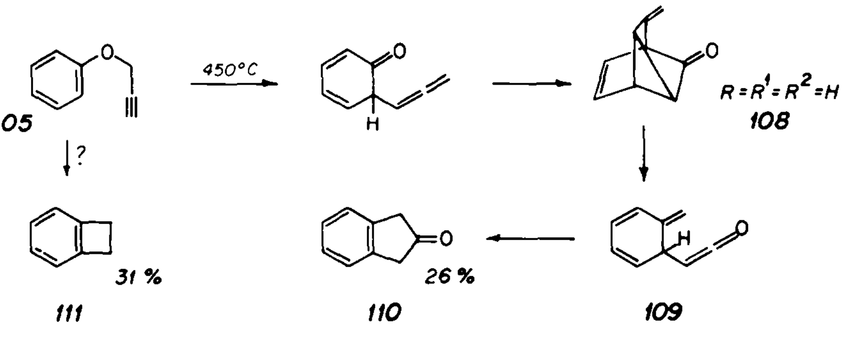
ethers, **105**. Schmid *et al.*[91] have reported the same liquid phase reaction, **105**→**106**, but only when the ortho positions on the phenyl ring are unoccupied. With di-ortho alkyl substituents, the intermediate **107**



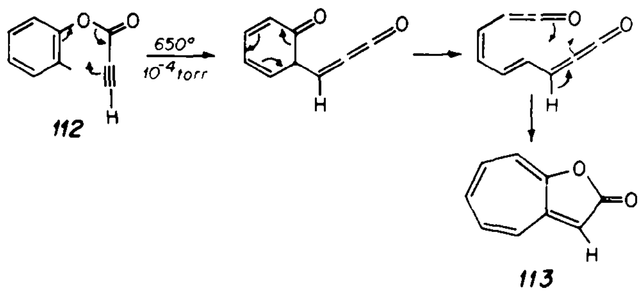
107 **108**

cannot use enolization as a return to aromaticity and an internal Diels–Alder reaction ensues to afford tricyclic **108**. With di-ortho halogen substituents, halogen migration occurs.[92]

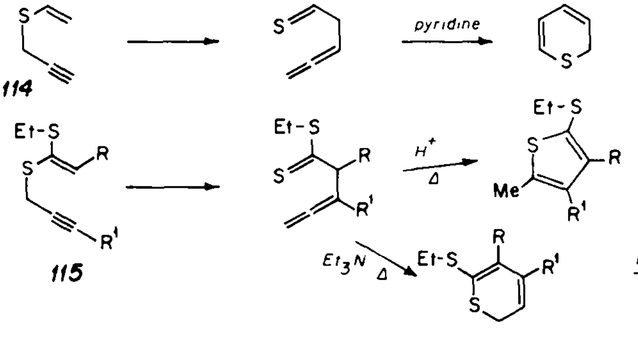
Trahanovsky and Mullen,[93] on the other hand, report the vapor phase thermolysis of unsubstituted phenyl propargyl ether, **105** (R = H), to produce 2-indanone, **110**, via the following sequence. Formation of the tricyclic product, **108**, is followed by ring opening to yield ketene **109**, which itself cyclizes to **110**. This mechanistic sequence is in accord with a deuterium tracer study, but is complicated by the fact that benzocyclobutene, **111**, is also produced. The formation of **111** must involve an unknown alternate pathway, since it is formed under conditions where **110** is stable.



Still another secondary process has been reported by Trahanovsky *et al.*[94] in the flash vacuum pyrolysis of aryl propiolates, **112**, wherein an initial suspected Claisen rearrangement is followed by a series of pericyclic processes which terminate with formation of cyclohepta[*b*]furan-2-ones, **113**. The reason for the difference in this path, from that followed by aryl propargyl ethers, is not clear, but the authors suspect that the pyrolysis temperature required for esters, which is ~200° higher, could be an important factor. An alternative mechanism, based upon this fact, is suggested in Section D, of the second part of this report.

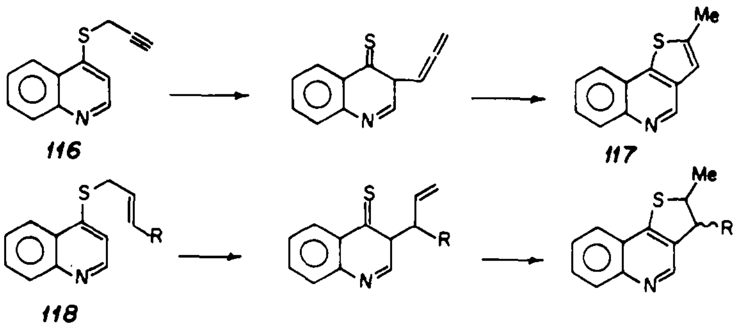


Brandsma and Schuijl have reported the aliphatic thio-Claisen rearrangement[95] of **114**, as well as the analogous reaction[96] of **115**, together with the indicated kinetic data. Although the low activation energies suggest energetic assistance to the bond breaking process, the large difference brought on by terminal methyl substitution is suspect, and alternate mechanistic paths should not be ruled out.

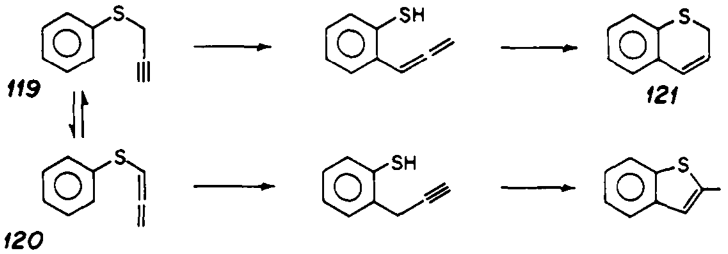


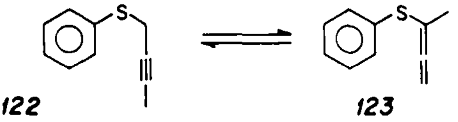
E_a(kcal/mol)	R	R^1
20.7	H	H
26.2	H	Me
23.2	Me	H

Makisumi and Murabayashi[97] have reported the aromatic thio-Claisen rearrangement of **116** to yield

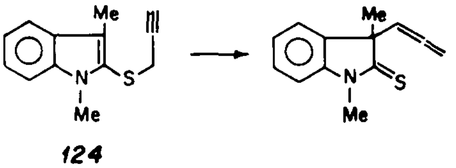


thiophene **117**, a reaction which appears to bear close analogy to the behavior of the corresponding allylic compound, **118**. However, the conversion of **116**→**117** may not really represent an acetylenic Claisen rearrangement, since Kwart and George[98] report phenyl propargyl sulfide, **119**, to undergo a [1,3] sigmatropic shift to phenyl allenyl sulfide, **120**. Each of these substrates then gives rise to its own Claisen product, and the final product **121**, which arises from the true acetylenic Claisen rearrangements, corresponds to pyran derivative **106** formed from the oxygen analog. Although these reactions were observed in solution and not in the vapor phase, a prototropic shift for the interconversion of **119**→**120**



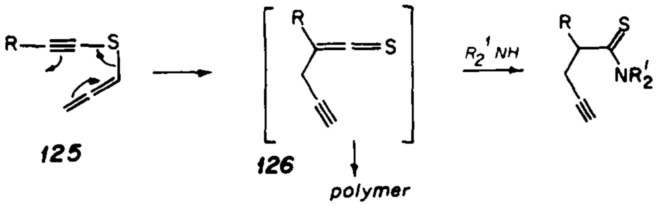


was ruled out by the thermal equilibration of **122**→**123**. The occurrence of this [1,3] sigmatropic shift, which will be discussed later under four-membered transition states, throws doubt on the kinetic data reported for thio-Claisen rearrangements. Thus, Bycroft and Landon[99] had reported the rearrangement of **124** to proceed with an activation energy of 23.8 kcal/mol and an entropy of activation of −6.3 eu.



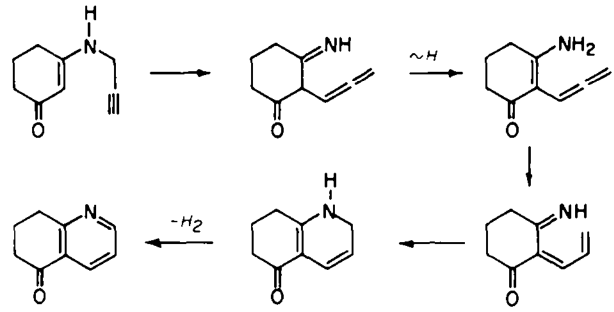
Although these kinetic parameters are in accord with a cyclic transition state, the possibility of complications from an unobserved [1,3] shift beclouds the data. The same possibility also arises in regard to the kinetic data reported for **115** and may account for the discrepancies noted above.

Meijer and Brandsma[100] have reported the somewhat different thio-Claisen rearrangement of ethynyl



allenyl sulfide, **125**. The product of this rearrangement, **126**, is not only itself still an acetylene, but also a highly reactive thioketene. In the absence of a suitable trapping agent, polymerization occurs.

Berg-Nielson and Skattebøl have reported[101] the acetylenic aliphatic amino-Claisen rearrangement of several compounds, as exemplified by **127**, to give intermediates **128**, which correspond to the final products, **106** and **121**, obtained from the oxygen and sulfur analogs. Unlike the latter two products, **128** can undergo dehydrogenation to give the final observed aromatic product, **129**. Cresson and Corbier have reported[102] another example of this version of the Claisen rearrangement, the very facile reaction of **130** under conditions of hydrolysis. Although the concerted nature of this reaction must remain conjectural, the 3,4-pentadienals, **132**, obtained are the expected hydrolysis products from the rearranged iminium ions, **131**. A possible reason for the ease of this reaction, at only 80°, is the fully positively charged quaternary nitrogen, whose presence should result in an electron flow toward that nitrogen atom in the initial reaction step, the cleavage of the N-C bond. This directionality of the electron flow provides a nucleophilic olefinic component whose interaction with the acetylenic unit thereby becomes highly favorable.



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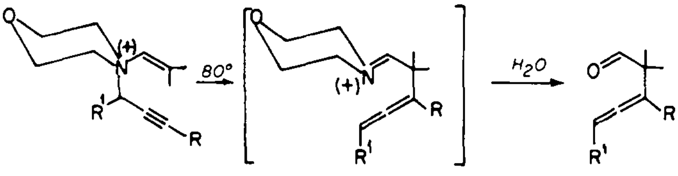
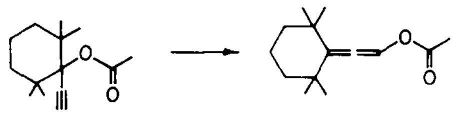
129 **128**



130 **131** **132**

Closely related to the Claisen rearrangement is the [3,3] sigmatropic rearrangement of propargylic esters. This reaction of **133** was first reported by Landor and Landor[103] in 1956. More recently, Trahanovsky and Emeis[104] have suggested it as a general method for the preparation of α,β-unsaturated ketones from propargylic esters **134**. A practical limitation is that R and R^1 may not contain any β-hydrogens, since otherwise the competing ester pyrolysis predominates to the extent of 60–80% of the



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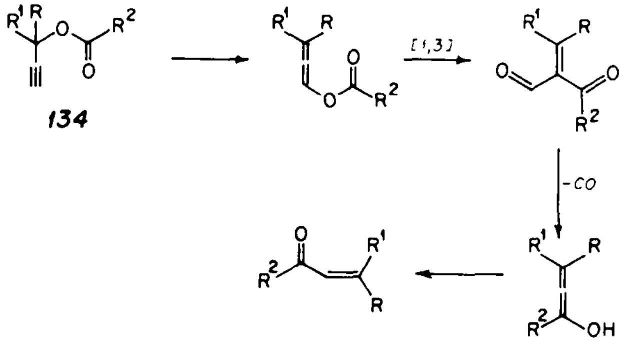

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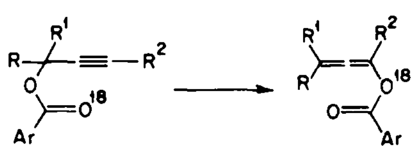
total reaction. This observation places a lower limit on the activation energy for this version of the acetylenic Claisen: somewhat in excess over the E_a of an aliphatic ester pyrolysis which is decreased by the bond weakening effect of an α propargylic substituent.

That the reactions of **133** and **134** actually represent [3,3] sigmatropic shifts and not [1,3] oxygen shifts has been demonstrated[105] by means of carbonyl labelled ^{18}O esters, **135**, which establish the



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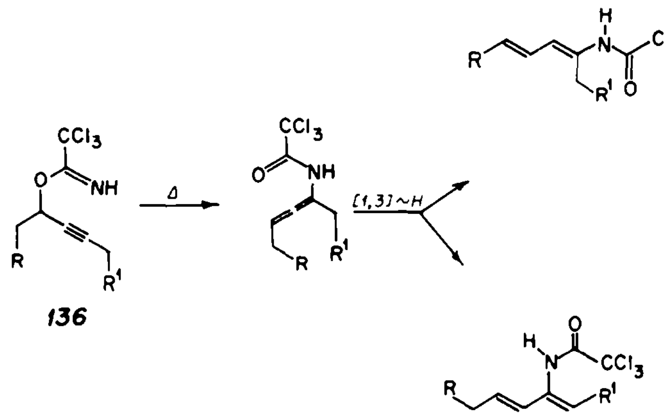
"inversion" of the ester group. Two other similar [3,3] rearrangements have seen synthetic application. Overman *et al.*[106] have utilized imidates **136** in the preparation of activated 1,3-dienes, **137** and **138**, and



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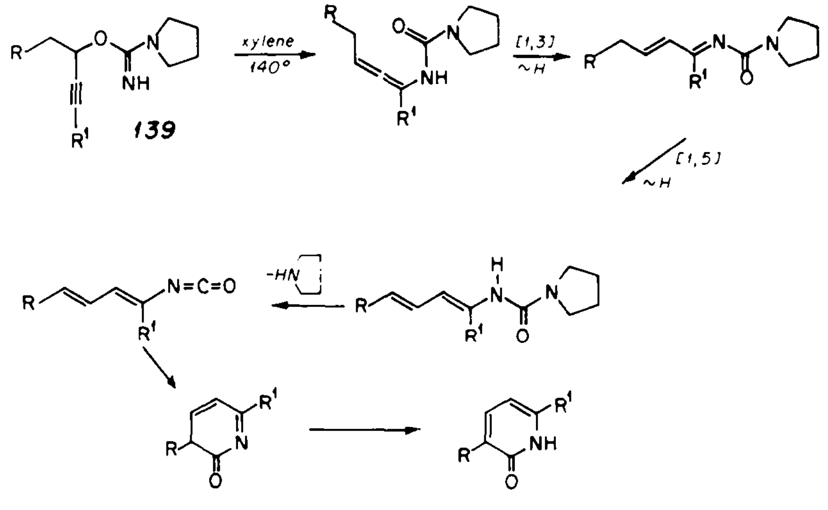
have converted pseudoureas **139**[107] to substituted 2-pyridones, **140**. In both of these cases there is an



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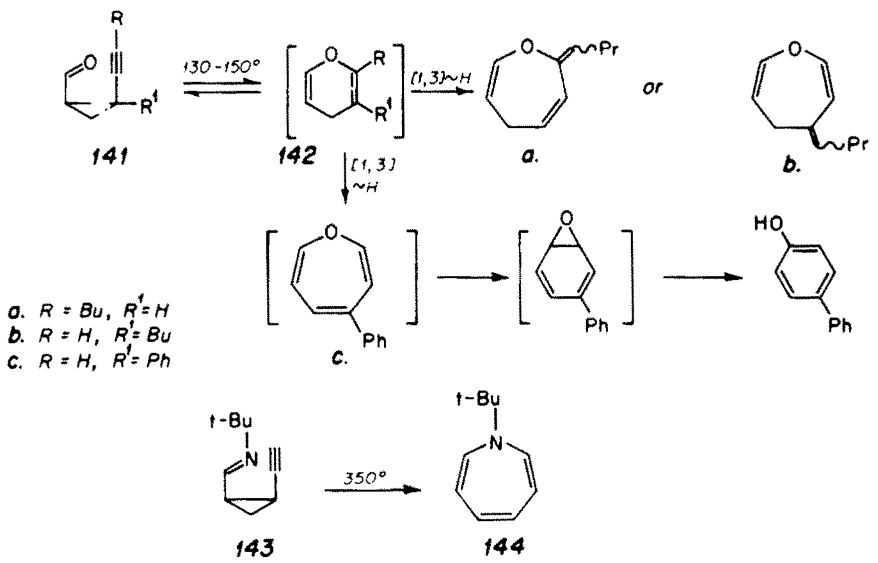
obvious "inversion" in the nitrogen analog of the ester unit, which again implicates a [3,3] sigmatropic shift and rules out a [1,3] oxygen shift.

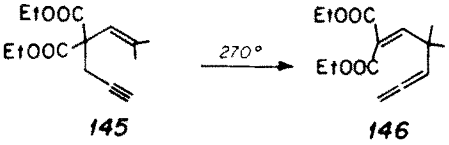
An intriguing example of an acetylenic retro-Claisen rearrangement has recently been reported by Chuche *et al.*[108] The rearrangement of **141** (see Scheme 2) at 130°–150°C occurs only in the liquid phase

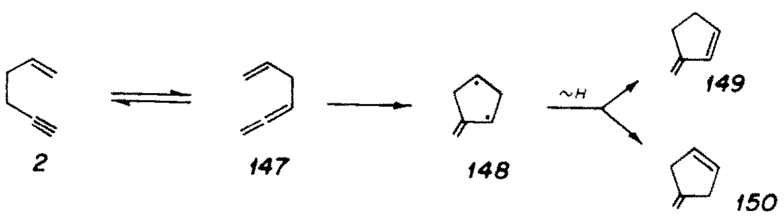


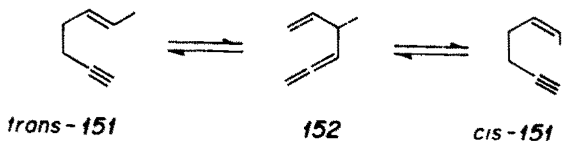
Scheme 2.

and there is no reaction in the gas phase. The authors therefore assume a **141**⇌**142** equilibrium which highly favors **141**. The removal of **142** via catalyzed hydrogen shifts is required to shift the equilibrium in that direction. It is not clear how this equilibrium reflects the high strain energies of **141** and **142**, but no reactions of higher homologs of **141** are reported. Manisse and Chuche[49] have also reported the nitrogen analog of this reaction: flow pyrolysis of **143** leads to the azepine **144**. These reaction manifolds can also be approached via vinylethynyl-oxiranes and -aziridines as shown in Scheme 3 in the next section.

Acetylenic Cope rearrangements.[87] Black and Landor[88] first reported acetylenic bond participation in a classical Cope rearrangement in 1965. The liquid phase thermal conversion of **145** to **146** was accompanied by considerable polymerization, which prompted the authors to suggest a "one-electron process" as described for the Claisen rearrangement of **101**. As in numerous Cope rearrangements of 1,5-hexadienes, the two electron-withdrawing substituents, which greatly stabilize **146**, essentially render this reaction irreversible. In the absence of such stabilization, Huntsman *et al.*[109] found a reversible rearrangement to occur, as illustrated by **2**⇌**147**. At temperatures somewhat higher than those required for the Cope rearrangement, an irreversible cyclization sets in which leads to a mixture of methylenecyclopentenes **149** and **150**, presumably via the 1,3-diradical intermediate **148**. That the

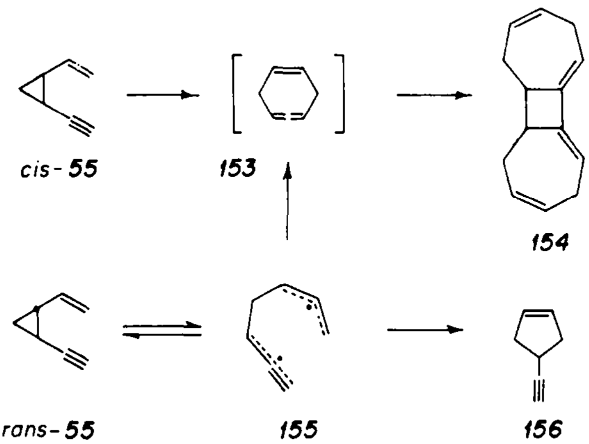




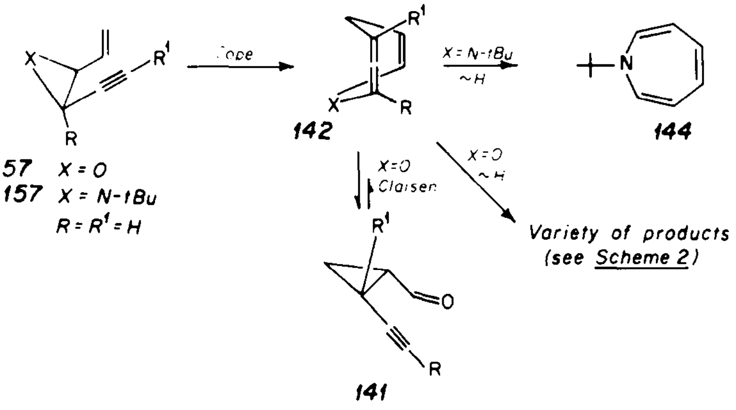


transformation of $2 \rightarrow 147$ results from a Cope process, and not from a thermal acetylene–allene isomerization, was demonstrated by the thermolysis of several methyl-substituted compounds such as 5-hepten-1-yne, **151**, which afforded 4-methyl-1,2,5-hexatriene, **152**, and not a heptatriene.[109] Furthermore, the Cope rearrangement of **151** was accompanied by geometrical isomerization: *cis*-**151** as well as the triene appeared rapidly when *trans*-**151** was heated.[59] This isomerization is due to the fact that the methyl group has only a small conformational preference for either possible orientation in the cyclic transition state.

It is well known that the Cope rearrangement is facilitated by ring strain relief when the C_3–C_4 bond is part of a three-membered ring.[47] Similarly, several rearrangements of three-membered ring derivatives with vinyl and ethynyl substituents have been reported. Dolbier *et al.*[48] have found 1-ethynyl-2-vinylcyclopropanes, **55**, to undergo Cope processes, albeit under somewhat different conditions. The *cis* derivative rearranges at lower temperatures to give the assumed Cope product, 1,2,5-cycloheptatriene, **153**, with activation parameters indicative of a concerted process. The *trans* derivative requires higher temperatures, and appears to react in a non-concerted manner via diradical **155**, which can ring close to either **153** or to 4-ethynylcyclopentene **156**. In either case the cyclic allene was detected only as the dimer, **154**.



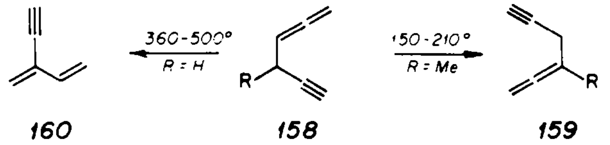
The rearrangements of oxirane and aziridine derivatives, reported by Chuche *et al.*[49,110] are summarized in Scheme 3. The disappearance of vinyl ethynyl oxirane, **57** ($R = R^1 = H$), follows the first-order rate equation over the range of 110–130° and affords ethynylcyclopropanecarboxaldehyde, **141**.[49] Under similar conditions, the aziridine **157** gives azepine **144**. The difference in behavior of the two substrates was ascribed to the greater basicity of the nitrogen atom, which helps to catalyze the [1,3] shift.[49] Suitably alkyl substituted oxiranes **57** partake in liquid phase rearrangements wherein the initial Cope process, which yields suspected intermediate **142**, is followed by nominal [1,3] shifts, either within the ring structure to yield oxepins or involving the alkyl substituents to afford alkylidene derivatives.[110] This process allows another entry into the reaction manifold previously discussed for the retro-Claisen rearrangements of **141** and **143**, described in Scheme 2 in the preceding section. In the gas phase no

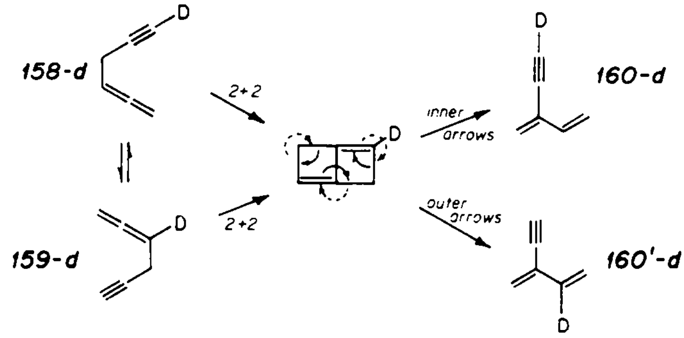


Scheme 3.

catalyzed [1,3] shifts can occur and **142** undergoes only the reversible Claisen rearrangement to afford **141**.[110] It is not clear why some liquid phase [1,3] shifts should occur in the oxygen series while others do not and the concerted nature of these reactions, particularly under liquid phase conditions, remains unproven.

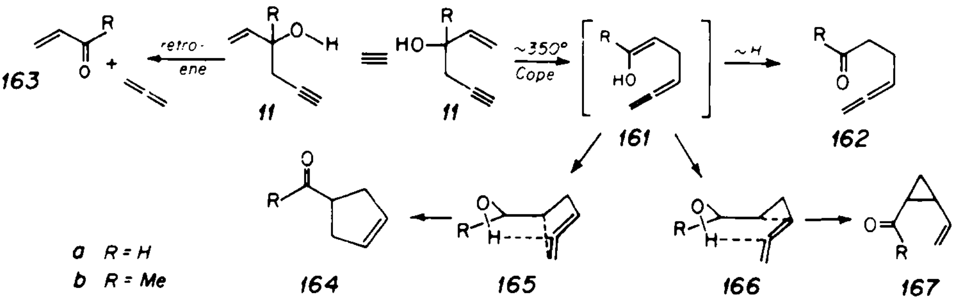
Hopf has reported[111] the Cope rearrangement of several hexa-1,2-dien-5-ynes, **158**. At lower temperatures the allenic and acetylenic termini of molecules such as **158** and **159** exchange places, with activation parameters, $E_a = 30.8 \pm 0.3$ kcal/mol and $\Delta S^{\neq} = -17$ eu, which are in accord with a cyclic transition state. At higher temperatures **160** is produced via an unknown process, although a mechanistic scheme, based upon a deuterium tracer experiment, has been proposed (see Scheme 4).[112] An alternative pathway will be suggested in the section dealing with 3-membered transition states (see Scheme 11).





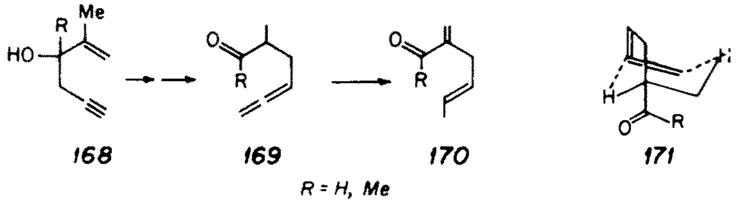
Scheme 4.

Acetylenic oxy-Cope rearrangements. Viola and MacMillan[9] have reported the vapor phase thermolysis of 1-hexen-5-yn-3-ol, **11a**, to give a mixture of 4,5-hexadienal, **162a**, 3-cyclopentenecarboxaldehyde, **164a**, acrolein, **163a**, and allene, as shown in Scheme 5. In the vapor phase, the expected Cope product, enol **161**, cannot ketonize since the requisite concerted [1,3] hydrogen shift is orbital symmetry-forbidden. Only in the condensed phase can this catalyzed intermolecular process provide **162**. However, the allenic enol **161** can react further via cyclic transition state **165** to yield **164**. The Cope process of **11a** competes with the retro-ene cleavage which yields acrolein, **163a**, and allene. For **11b**, which has a 3-methyl substituent, there were two initial conflicting reports,[113,114] although both agreed on the formation of hepta-5,6-dien-2-one, **162b**, and the retro-ene products allene and but-3-en-2-one, **163b**. Wilson and Sherrod[113] reported vinyl acetylcyclopropane, **167b**, to be also formed whereas Chuche and Manisse[114] found 3-acetylcyclopentene, **164b**, to be the only other product. In a reinvestigation of the thermolysis of **11b**, Viola and MacMillan[115] found both **164b** and **167b** to be present and suggested competing pathways via cyclic transition states **165** and **166**. A subtle steric effect, brought on by the alkyl substituent, results in formation of only **164a** when R = H, but slows up that process when R = Me so that formation of **167b** can compete. A further complication, the **167**→**164** interconversion via the

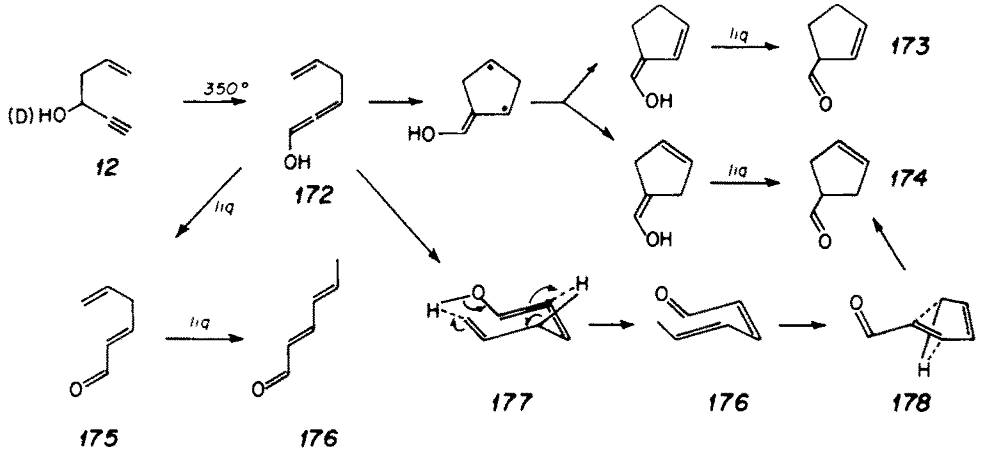


Scheme 5.

thermal vinyl cyclopropane rearrangement, constitutes a higher energy path which contributes only under more drastic conditions of temperature or heating time. When there is a 2-methyl substituent, as in **168**, Chuche and Manisse[114] also report the formation of methylene derivative **170** in addition to the expected oxy-Cope product, **169**. Neither cyclic product, corresponding to **164** or **167** is now produced, which may reflect hindrance to cyclization in transition states **165** and **166** by the 2-methyl substituent at the site of ring closure. Although the authors favor[114b] formation of **170** via an intermediate corresponding to **167**, the absence of this latter substance from the product mixture militates against that pathway. We suggest that formation of **170** may occur from the carbonyl species **169**, formed by surface catalyzed steps in the reactor. This process, via transition state **171**, closely resembles the intramolecular double hydrogen migration in unsaturated benzylic alcohols which has recently been reported by Viola and Madison.[116]

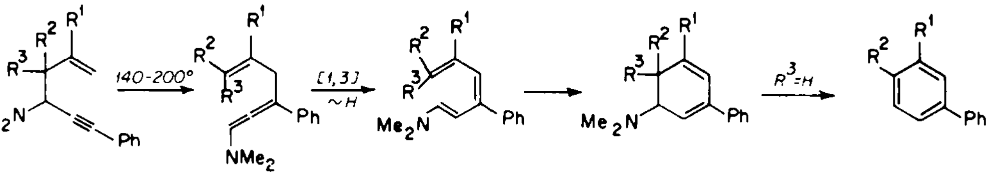


Viola and MacMillan have also reported[10] the vapor phase thermolysis of 5-hexen-1-yn-3-ol, **12**, which corresponds to an interchange of the vinyl and ethynyl groups as they are in **11**. The resultant reactions are outlined in Scheme 6. The initial Cope step provides **172**, which was designated as an "allenol". Ring closure via the 1,3-diradical path originally suggested by Huntsman[109] for 1,2,5-hexatrienes **147**, leads to **173** and **174**. Ketonization in the condensed phase affords the non-conjugated 2,5-hexadienal, **175**. A pericyclic reaction can also be envisaged which involves transfer of a hydrogen from C_4 to the central allenic carbon, as well as of the enolic hydrogen, as depicted in transition state **177**. The two possible configurations of **177** can give rise to the *cis,trans* and *cis,cis* isomers of the conjugated hexadienal **176**. Since the various geometric isomers of **176** are thermally interconvertable, the distribution observed is no measure of the rate of formation of any individual isomer. However, it was postulated that the 4,5-*cis* form, **178**, can undergo the cyclization indicated to produce **174** by an alternate path. Thermolysis of 5-hexen-1-yn-3-ol-0-*d*, **12d**, provided a deuterium distribution in accord with this scheme. Since the retro-ene β-hydroxyolefin cleavage, which normally competes with the Cope process in oxy-Cope reactions, was completely absent in this case, as discussed in the first part of this report, the kinetics of the disappearance of **12** could be determined. The reaction strictly followed the first-order rate law and the Arrhenius parameters, $E_a = 30 \pm 2$ kcal/mol, $\Delta S^{\neq} = -14$ eu, were indicative of a concerted process. Fujita *et al.*[117] have recently applied this reaction to the syntheses of pseudoionone analogs. They report that in liquid phase thermolyses of suitable derivatives of **12** there is not only a solvent acceleration, but the facile ketonization of the initial Cope product prevents any further



Scheme 6.

reactions of the allenol. Formation of the product corresponding to **175** then becomes essentially the only functioning process.

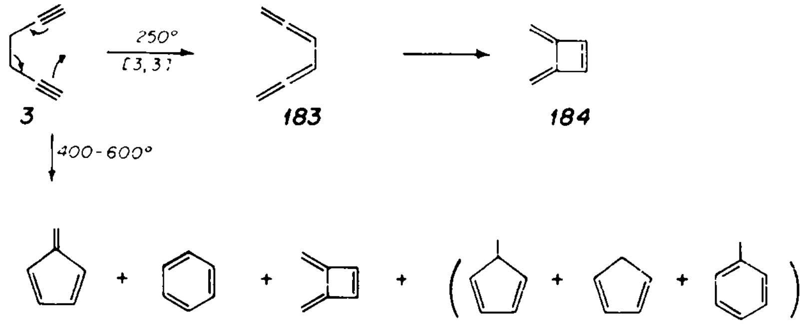


179 180 181 182

Jemison *et al.*[118] have reported a nitrogen analog of the oxy-Cope rearrangement of **12**. When **179** is heated at 140–200° for a period of 1 hr to 7 days, depending upon the nature of the substituents, a Cope rearrangement to **180** occurs. Since this is a liquid state reaction, a catalyzed [1,3] hydrogen shift followed by the analog of a hexatriene-cyclohexadiene electrocyclization affords **181**. If $R^3 = H$, thermal elimination of Me_2NH gives aromatic product **182**.

Reactions of 1,5-*hexadiynes*. If, as shown in the preceding section, one acetylenic bond aids the Cope rearrangement, then might not a similar reaction with two such bonds be possible? Indeed, the thermolyses of a number of 1,5-hexadiynes have been investigated.[59,60]

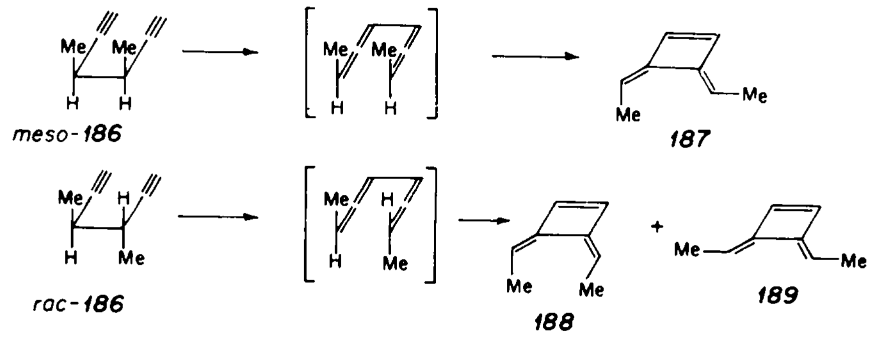
Huntsman and Wristers[119] first reported in 1963 that 1,5-hexadiyne, **3**, rearranges smoothly and in



3 183 184

185 184

high yield to 3,4-dimethylenecyclobutene, **184**. Arrhenius parameters, determined over the range of 210–297° ($E_a = 34.4$ kcal/mol and $\Delta S^{\neq} = -9.4$ eu) were indicative of a concerted process.[51] A number of substituted 1,5-hexadiynes were subsequently reported to behave in an analogous manner[51] and the reaction mechanism suggested[51,120] consists of an initial [3,3] sigmatropic shift to give 1,2,4,5-hexatetraene, **183**, followed by a rapid butadiene-cyclobutene electrocyclization. This sequence received further credence from the observations[121] that several derivatives of **183** cyclize readily to the corresponding derivatives of **184** and Hopf has reported[122] that the parent compound, **183**, cyclizes at a rate much greater than the rate of rearrangement of **3**. In addition, Huntsman and Wristers report[51] that *meso*-3,4-dimethyl-1,5-hexadiyne, **186**, gives solely *syn,anti*-3,4-diethylidenecyclobutene, **187**, whereas



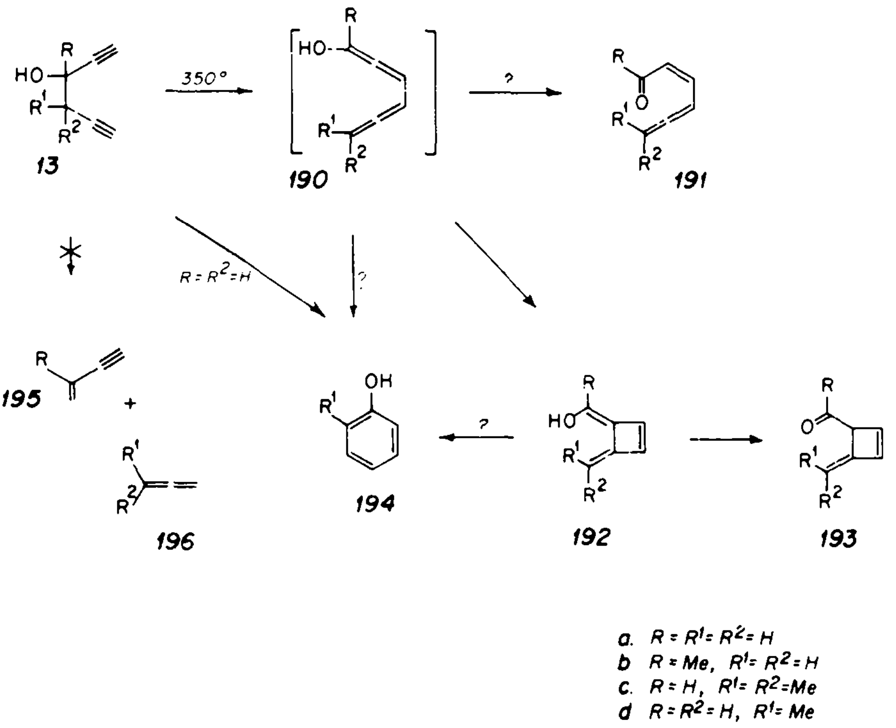
meso-186 187

rac-186 188 189

racemic-**186** provides a mixture of the *syn,syn*- and *anti,anti*-cyclobutene derivatives, **188** and **189**, which indicates that the electrocyclization follows the conrotatory path dictated by orbital symmetry control. We suggest that the [3,3] shift must therefore leave the methyl groups in their same relative orientation which they held in **186**, and a fairly planar transition state would best accommodate the bis-acetylenic Cope process.

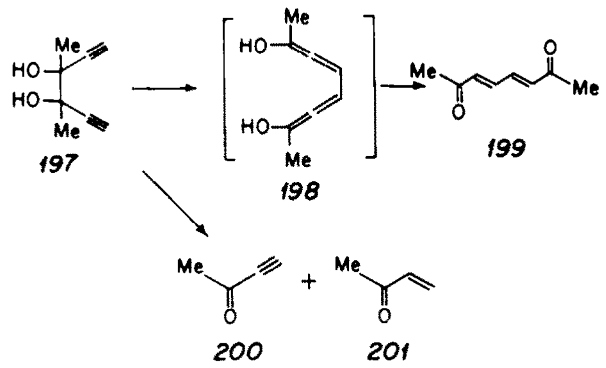
When the thermolysis of **3** was carried out at higher temperatures, Jones *et al.*[120] found fulvene, **185**, and benzene in the product mixture along with **184**. Despite the fact that this is accompanied by some radical fragmentation leading to small amounts of cyclopentadiene, methylcyclopentadiene, and toluene, it is claimed to be one of the better preparations of fulvene, which is obtainable in about a 30% yield. Henry and Bergman, however, found that dimethylenecyclobutene, **184**, rearranges to benzene and fulvene at 620°, and by means of a deuterium tracer study, implicated a reversible **184**→**183** transformation in which the tetraene **183** is responsible for benzene and fulvene formation.[123] Although the mechanisms of benzene and fulvene formation remain in doubt, they evidently do not represent primary reaction pathways of 1,5-hexadiyne.

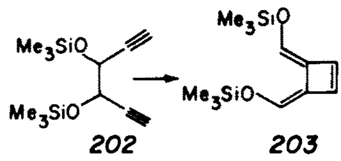
The oxy-Cope version of several diacetylenic analogs has been investigated by MacMillan[12] and the results are summarized in Scheme 7. Thermolyses of 1,5-hexadiyn-3-ols, **13a–d**, led to the carbonyl derivatives of methylenecyclobutene **193a–d**, presumably via the same mechanism described for **3** above. Electrocyclization of **190** in these cases produces enols **192** which ketonize in the condensed phase to form **193**. Ketonization of the initial Cope product, **190**, should yield **191**, but no such products were observed. Either the **190**→**192** transformation is too fast and no **190** survives, or these highly unsaturated carbonyls are too unstable and polymerized before their possible identification. There were substantial amounts of polymeric materials produced, although the final product, **193**, was also unstable and polymerized rapidly. In the case of **13a** and **13d**, the corresponding phenols **194** were also formed. It is of interest that formation of aromatic compounds occurs only when there is no geminal disubstitution at either C_3 or C_4 of **13** and that in the presence of the hydroxyl function aromatization occurs at a temperature some 200° below that reported in its absence. This fact, however, reflects on the influence of a hydroxyl function on pericyclic reactions and is not concerned primarily with reactions of acetylenes. The mechanism of phenol formation remains unknown. No fulvene derivatives were found, although it is unlikely that such unstable substances could have been isolated under the reported conditions. As mentioned in the first part of this report, no trace of retro-ene cleavage products **195** or **196** could be detected, which reflects on the surprising facility of a Cope process involving two acetylenic bonds.



Scheme 7.

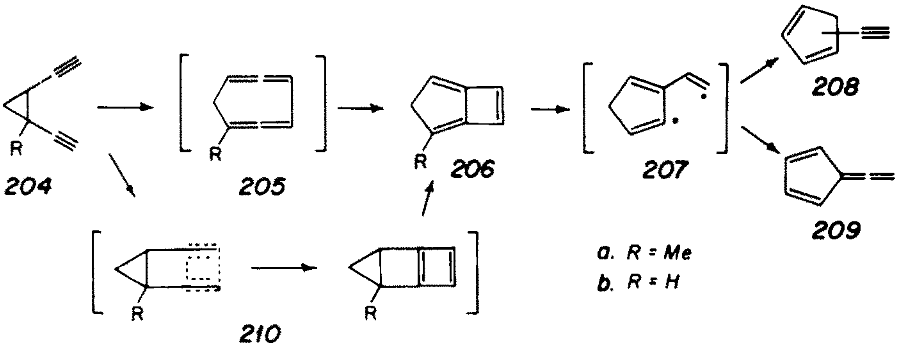
The bis oxy-Cope rearrangement of **197** has been reported by Chuche and Manisse.[114a] Strangely, the





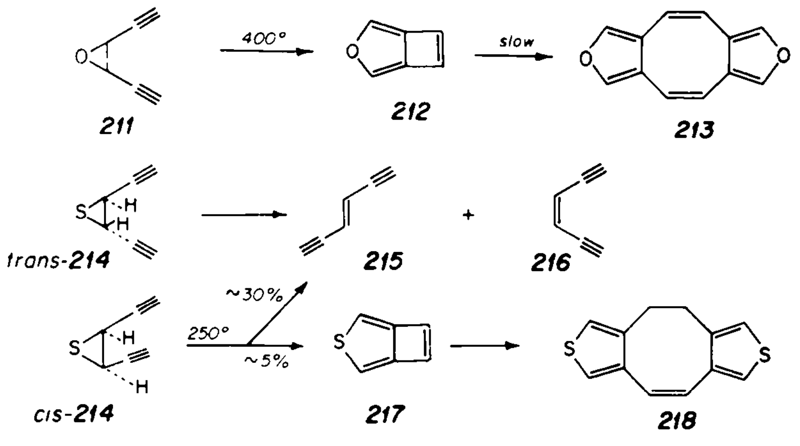
only products reported are the retro-ene cleavage products **200** and **201**, and the product of ketonization, **199**, from the initial Cope product **198**. We question the correctness of the structure assignment of **199**, which appears to be based only on NMR and IR spectra, since the corresponding spectra of the anticipated diacetylcyclobutene were not available for comparison. The structure assignment of **199** is further clouded by the later report of Manisse and Chuche[124] that the di-trimethylsiloxy-Cope rearrangement of **202** affords only the expected dimethylenecyclobutene **203**. Why the retro-ene cleavage can compete with the Cope process of **197** but not in the case of **13** also remains unclear.

The thermal reactivities of diethynylcyclopropanes, **204**, and their heterocyclic analogs, have been investigated by Bergman *et al.* as precursors to 1,4-dehydrocycloheptatrienyl systems.[125] Pyrolysis of



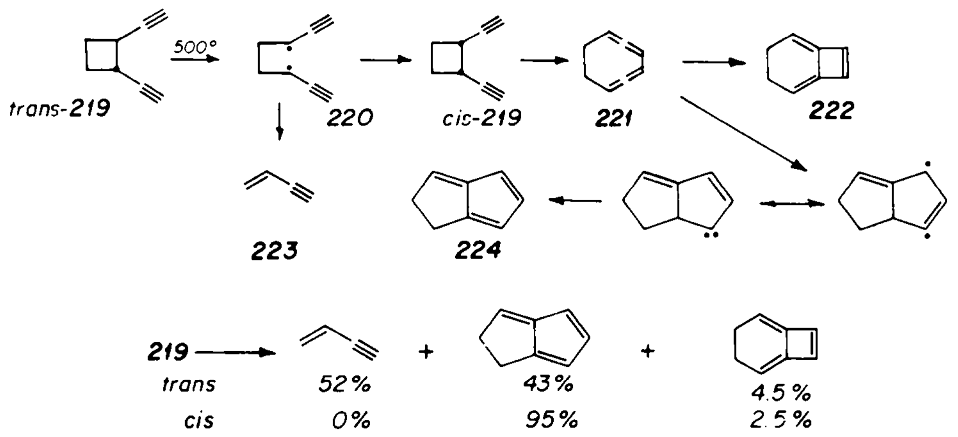
204a, in either a static reactor at 200–240° or in a gas-phase flow system at 480°C, gives triene **206a** cleanly.[126] The presumed intermediate is **205a**, although other species, e.g. **210**, which represent differences in the degree of internal bonding, are possible. Thermolysis of **204b** similarly leads to **206b**, but at low pressures increasing amounts of **208** and **209** are also observed.[127] On the basis of group equivalent calculations, the authors argue that **206** is initially produced in a vibrationally excited state from which it can rearrange to other products in time, i.e. under conditions of low pressure where fewer deactivating collisions occur. In support of this hypothesis, it was observed that triene **206**, although surprisingly unreactive, also yields **208** and **209** upon pyrolysis but at temperatures much higher (~580°C in the flow system) than those needed for their formation from **204**. Further evidence for this mechanism was provided by a deuterium tracer study,[123] whose results were totally in accord with this scheme and which implicated vinyl–vinyl bond rupture in **206**, leading to diradical **207**, in the formation of both **208** and **209**. It is not surprising that the *cis* isomer of **204** rearranges at temperatures as low as 100°, whereas *trans*-**204** requires about 250°.[128] It would appear to us that these widely different conditions suggest a difference in mechanism for the reactions of the two geometric isomers of **204**. The termini of the two ethynyl substituents of the *cis* isomer can be brought within bond forming distance of each other by a limited amount of bond angle distortion, while a cyclopropane C–C bond rupture appears necessary before such proximity can be attained in the *trans* isomer. Therefore it seems likely that the *cis*-**204** → **205** conversion proceeds in a concerted fashion whereas that of *trans*-**204** does not.

The difference in behavior between *cis* and *trans* diethynyl derivatives was borne out in two other reports by Vollhardt and Bergman,[129,130] which concern the thermolyses of the heterocyclic analogs of cyclopropane **204**: oxiranes **211** and thiiranes **214**. Both *cis*- and *trans*-**211** were converted to **212** upon



vapor phase flow thermolyses at 400°.[129] The difference in reactivities between the two isomers is indicated by the fact that the half-life of *cis*-**211** at 270° was equalled by *trans*-**211** only at 370°. The product of the thermolyses is 3,6-dehydrooxepin, **212**, and 8Π-electron furan analog of benzocyclobutadiene, which was found to be highly unstable to air, glpc and tlc, and which on standing in dilute solution slowly dimerized to **213**. The thiiranes showed an even more marked difference in their thermal behavior.[130] Both *cis*- and *trans*-**214** followed only a desulfuration path upon solution thermolysis at 100° to yield mixtures of *trans*- and *cis*-diethynylethylene, **215** and **216**. In a vapor-phase flow system at 395° *trans*-**214** still produced only **215** and **216**, whereas *cis*-**214** at 250° gave a 5% conversion to **217** mixed with the products of a 30% conversion to **215** and **216**. Parallel to the behavior of **212**, the extremely sensitive thiophene analog of benzocyclobutadiene, **217**, dimerized slowly in dilute solution to give **218**.

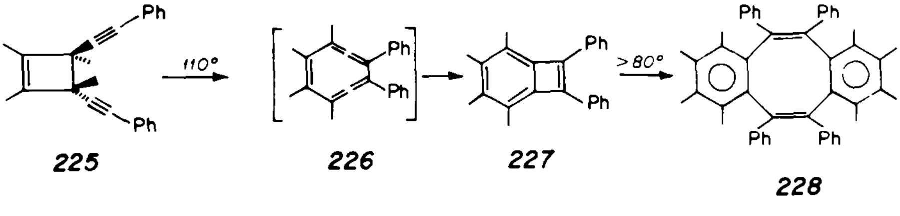
Hopf has suggested[131] a scheme for the thermolytic behavior of 1,2-diethynylcyclobutanes, **219**, which is similar to that proposed by Bergman for the corresponding cyclopropyl derivatives. The suggested reaction paths and the product distribution from the gas phase pyrolyses of *cis*- and *trans*-**219** are indicated in Scheme 8. Under the harsh conditions used, a contact time of 28 s at 500°, *trans*-**219** undergoes a ring rupture to form diradical **220**, which can either ring close to *cis*-**219** or cleave to give the nominal cycloreversion to **223**. A Cope rearrangement converts *cis*-**219** to bis-allene **221**. This bis-allene can ring close, either in the manner analogous to that previously observed for acyclic and cyclopropane derivatives to produce cyclobutene derivative **222**, or in the other manner indicated to produce pentalene derivative **224**. From the product distribution it is concluded that cycloreversion via diradical **220** competes favorably with ring closure to *cis*-**219**, but that the Cope process for *cis*-**219** is too facile to permit cycloreversion from that substrate.[131] It appears to us that under these conditions diradical **220** can ring close directly to **221** without prior formation of *cis*-**219**. Hopf has also reported[131] the yield of cyclobutene derivative **222** to increase at low pressure, at the expense of pentalene derivative **224**, and has interpreted this fact to suggest formation of bis-allene **221** in a vibrationally



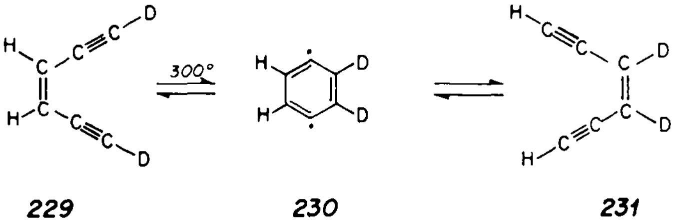
Scheme 8.

excited state. The excess energy must be used in the path leading to **222**, since collisional deactivation favors formation of **224**. However, it appears to us that, if parallel energetic considerations apply to the formation of the analogous bis-allene intermediate **183**, formed from 1,5-hexadiyne, then formation of fulvene, **185**, should also be favored over that of dimethylenecyclobutene, **184**. Since this is the reverse of the actual observation, it appears that some questions about this mechanistic scheme need yet to be resolved.

A diethynylcyclobutene version of this rearrangement has been reported by Straub.[132] When the *trans* isomer of 1,2,3,4-tetramethyl-3,4-diphenylethynylcyclobutene, **225**, is heated to 110°, 3,4,5,6-tetramethyl-1,2-diphenylbenzocyclobutadiene, **227**, begins to crystallize within a few minutes. Although **227** decomposes even in solution at room temperature, it is stable in the crystalline form in which it dimerizes slowly to **228** only when heated above 80°.[132] Although the mechanism for the **225**→**227** transformation is not discussed, the cyclooctapentaene, **226**, seems a likely intermediate. It is unlikely that the termini of the *trans* ethynyl units in **225** can interact to produce **226** in a concerted manner, but the presence of the double bond in **225** further weakens the C_3–C_4 bond and a diradical analogous to **220** should form more readily than from **219**. Formation of **226** via a nonconcerted, two step process is therefore energetically enhanced, in comparison with **221**, by the presence of the double bond and the reaction occurs under much milder conditions. The *cis* isomer of **225** was not mentioned.

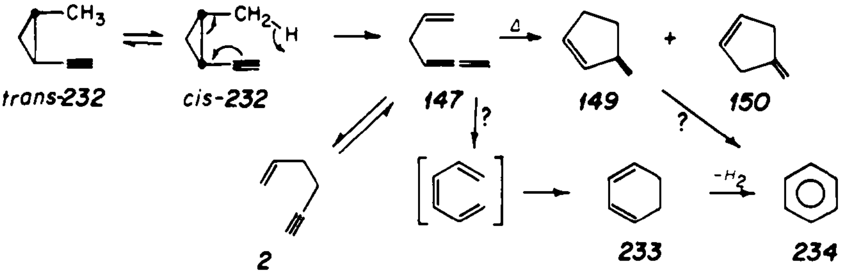


Perhaps the clearest differentiation in the reactivities of *cis*- and *trans*-1,2-diethynyl derivatives comes in a report by Jones and Bergman.[133] When *cis*-1,6-dideuteriohex-3-ene-1,5-diyne, **229**, is heated at 300°, rapid exchange of the deuterium label occurs exclusively to the 3,4-dideuterio isomer **231**, with no other detectable scrambling. When *cis*-hexenediyne is heated in solvents, products of typical radical reactions are observed: alkane solvents lead to benzene formation, toluene yields diphenylmethane and carbon tetrachloride gives p-dichlorobenzene. On the bases of these results, it is concluded that the intermediate formed is p-benzyne, **230**. In contrast to the behavior of the *cis* isomer, *trans*-**229** is completely unreactive.[133] Although these molecules are undoubtedly planar, inability of the termini of the ethynyl units of the *trans* isomer to come into proximity, either via bond angle distortion or via 3,4-bond rupture, precludes occurrence of any intramolecular process, concerted or otherwise, for that isomer.



Acetylenic retro-ene reactions. No pericyclic reaction of acetylenic substrates has received more attention than the retro-ene reaction. Since reactions of β-hydroxyacetylenes, propargylic ethers and propargylic amines have already been discussed in the first part of this report, they will not be further surveyed here.

Dalacker and Hopf[134] have reported a rare example of an all-carbon retro-ene reaction, which also involves an acetylenic link and brings into play the acetylenic Cope reaction already described. Results of pyrolyses of 1-methyl-2-ethynylcyclopropane, **232**, are depicted in Scheme 9. The reaction was carried

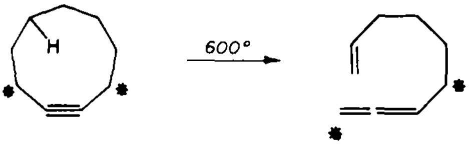


Temp °C	Conversion %	Product Composition (%) 147	149	150	2	233	234
340	67	58	4	3	20	15	0
370	74	46	9	5	20	20	0
530	100	0	38	29	0	30	3

Scheme 9.

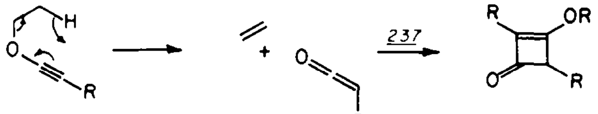
out in the vapor phase, in a tube filled with Raschig rings, with a contact time of about 35 s. Again, the *trans* isomer must first isomerize to the *cis* before a reaction can occur. In *cis*-**232** the retro-ene reaction can proceed smoothly to give initially 1,2,5-hexatriene, **147**, which then reacts further as previously indicated in the section on the acetylenic Cope rearrangements. Under the more rigorous conditions utilized here, cyclohexadiene, **233**, and benzene, **234**, are also produced, presumably via a surface catalyzed 1,3-shift from **147**. The variation in product composition with temperature provides an insight into the energetics of the various processes involved.

Another all-carbon retro-ene reaction has been cited by Baxter and Brown.[135] Pyrolysis of cyclononyne, **235**, at 600°C gave 1,2,8-nonatriene, **236**. The mechanistic assignment is predicated largely



235 **236**

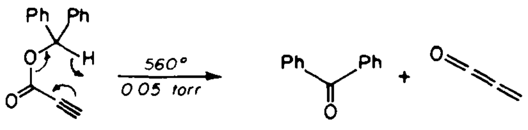
on the fact that deuterium labeling of the position α to the acetylene provided only the indicated deuterium distribution in the triene.[135] In both of these all-carbon retro-ene reactions, the process is undoubtedly aided considerably by relief of bond angle strain: in the case of **232**, cyclopropane ring strain and, in **235**, strain due to the incorporation of the acetylenic unit within the nine-membered ring.



237 **238** **239**

The acetylenic retro-ene cleavage of ethynyl ethers, **237**, was first observed by Ficini[136] in 1954, although the reaction mechanism was only realized later by Arens *et al.*[137] The scope of the reaction has been established by Olsman,[138] and examples with thioether analogs have also been reported.[139] The factor which complicated early attempts to elucidate the reaction path is that the initially produced ketene, **238**, undergoes a [2 + 2] cycloaddition with another molecule of ethynyl ether to form 3-alkoxy-2-cyclobutenones, **239**. The reaction has seen considerable use in the preparation of such derivatives.[137,138]

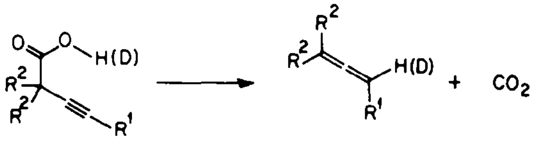
An interesting example of the retro-ene reaction has been utilized in the preparation of methylene-



240 **241**

ketene.[140] When propiolic ester **240** is pyrolyzed at 560° and 0.05 torr, the indicated retro-ene reaction occurs to give benzophenone and methyleneketene, **241**. Under more rigorous conditions, e.g. 640°C/0.1 torr, other reactions of indeterminant nature also occur and a multiplicity of products is seen.

Bigley and Weatherhead[4] have studied the gas-phase pyrolysis of β,γ-acetylenic acids, **53**. The

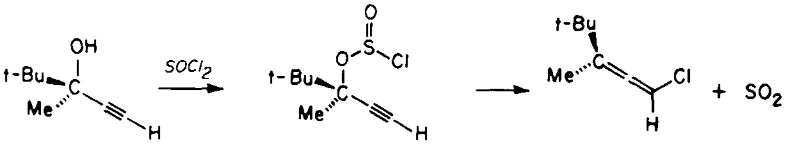


53

R^1	R^2	T(°C)	$\Delta H^{\ddagger}$(kcal/mol)	$\Delta S^{\ddagger}$(eu)
H	H	340-375	36.7 ± 1.5	-10.1 ± 2
H	Me	307-357	35.3 ± 1.5	-10.0 ± 2
Me	H	345-390	37.3 ± 1.5	-10.0 ± 2

reactions are essentially quantitative in a flow reactor, except for a small amount of lactone produced with $R^2 = Me$. The evidence for a concerted reaction, via a cyclic transition state, consists of the facts that the reactions are homogeneous and strictly first-order, the low $\Delta H^{\neq}$ and negative $\Delta S^{\neq}$ values, and the fact that the deuterio acid yields solely the indicated deuterated allene with a substantial deuterium isotope effect. Methyl substituent effects parallel those discussed in the first part of this report for other retro-ene reactions: α-substitution decreases $\Delta H^{\neq}$ and renders $\Delta S^{\neq}$ less negative; γ-substitution increases $\Delta H^{\neq}$. This reaction does not appear to be completely general for such acids, however, since other pathways were also observed when $R^1 = Et$ or Pr.

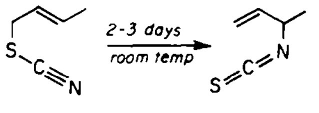
Miscellaneous six-center reactions. When optically active propargylic alcohol **242** was heated with $SOCl_2$, the resultant chlorosulfite **34** decomposed with an apparent [1,5] sigmatropic chlorine shift to yield



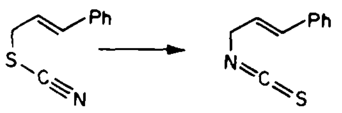
242 *34* *243*

allene **243**.[40] The fact that the optically active allene produced has the expected configuration is excellent evidence for concert. This report, one of the earliest indicative of the ability of acetylenes to fit into six-centered transition states, is not too surprising since two of the six atoms are period 3 elements, whose larger sizes reduce the necessary acetylenic bond angle distortion.

Since nitriles are isosteric with acetylenes, although of quite different polarity, it is not surprising that there are reactions of nitriles which superficially resemble the pericyclic reactions of acetylenes discussed herein. The number of such reported examples is small, however, and the nature of such reactions may indeed be quite different. Mumm and Richter[141] reported a reaction involving a nitrile group, which would now be considered a nominal [3,3] shift, at a time, in 1940, when the Cope

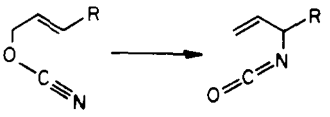


244 *245*

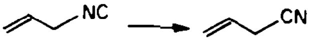


246 *247*

rearrangement was itself first described. Crotyl thiocyanate, **244**, upon standing at room temperature for 2 to 3 days, rearranged to the isothiocyanate **245**. Cinnamyl thiocyanate, **246**, however, rearranged to cinnamyl isothiocyanate, **247**, in what would now be classified as a [1,3] sigmatropic shift. No further evidence for concert is available on these reactions and no conclusions can be drawn about the different effects of a phenyl vs a methyl substituent. More recently, Christophersen and Holm[142] have reported crotyl cyanates, **248**, to rearrange to isocyanates, **249**, in what appears to be a [3,3] shift, as evidenced by the inversions of the allylic moiety as well as the cyanate portion of the molecule. Very little definitive data have as yet been reported on such reactions of nitriles and their mechanisms remain largely undefined, as will be further exemplified in the next section.



248 **249**

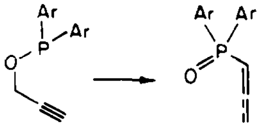


250 **251**

Reactions via five-membered transition states

Acetylenic [2,3] *sigmatropic shifts.*[60] Since isonitriles can be thermally rearranged to nitriles, Glionna and Pritchard[143] have recently studied the kinetics of the thermal isomerization of allyl isocyanide, **250**, to allyl cyanide, **251**. The Arrhenius parameters for the first-order process indicate that the allyl moiety does not assist in the reaction: $E_a = 40.8$ kcal/mol is about 2.4 kcal/mol higher than that for the corresponding isomerization of methyl- or ethyl-isocyanide, and $\Delta S^{\neq} = +5.8$ eu is too positive for a cyclic head-to-tail transition state. Consequently, the authors conclude that this is not a [2,3] sigmatropic rearrangement.

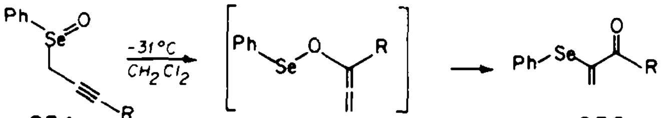
Several other examples of nominal [2,3] sigmatropic shifts have also been observed. Boisselle and Meinhardt[144] have reported a conversion of trivalent phosphorus to the pentavalent state, under very mild conditions, wherein propargyl phosphites, **252**, rearrange to allenic phosphine oxides, **253**.



252 **253**

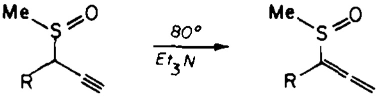
However, since the presence of an organic base is required, the mechanism of this liquid state reaction remains uncertain.

The reverse arrangement of heteroatoms seems to be favored in the case of selenium, since Reich and Shah[145] found selenoxides **254** to rearrange in a clean first-order process to **256**, presumably via



254 **255** **256**

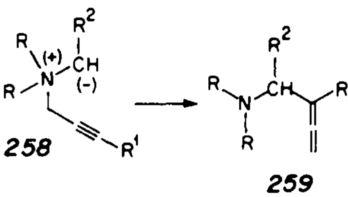
intermediate **255** which then undergoes a [1,3] shift. However, this process has an intermolecular component, since the reaction of a mixture of selenoxides gave a crossover product. The propargylic methyl sulfoxides, **257**, were found[145] to undergo only the prototropic acetylene–allene conversion, in



257

low yield, at substantially higher temperatures and only in the presence of triethylamine. The authors ascribe this difference in behavior to the greater stability of selenate vs selenoxide whereas sulfoxides are normally more stable than sulfenates.

With nitrogen, two examples of [2,3] shifts have been reported. Ollis *et al.*[146] have found that ylide **258** rearranges to **259**, but the reaction is not concerted. Craig *et al.*[147] on the other hand report that amine oxide **260** rearranges to **261** in what appears to be a concerted [2,3] shift. Although no kinetic data were reported, the reaction appears to be an intramolecular process. When a mixture of deuterium labeled substrates was reacted, no crossover products could be detected; the "inversion" of the propargyl moiety was demonstrated with R = Me; and finally, the absence of any detectable **262** indicates the lack of radical or ionic intermediates, since under such conditions **262** would predominate.[147]



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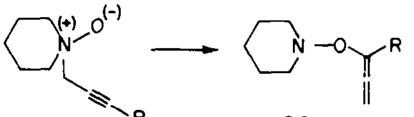

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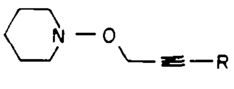
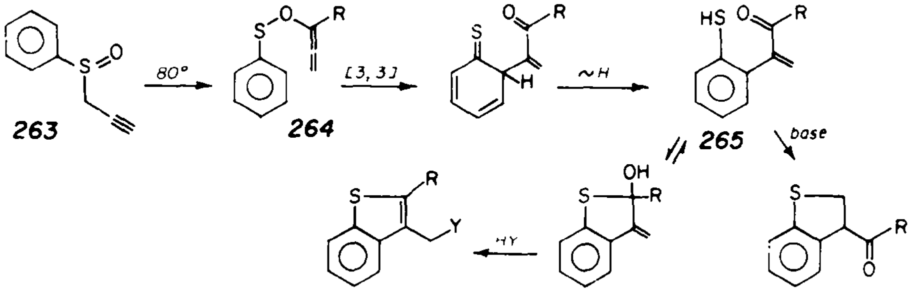


262

A variety of results have been observed with sulfur derivatives. As mentioned above, methyl sulfoxides **257** are apparently thermally stable. However, Makisumi and Takada[148] found phenyl sulfoxides **263** to rearrange in protic media to afford benzothiophenes **266** and in basic media to provide **267**. The authors suggest that an initial [2,3] shift to **264** is followed by a Claisen rearrangement, which affords thiophenol **265**. In the presence of base the resulting thiopenoxide ring-closes via a Michael addition to form **267**. In protic media the thiohemiacetal, which is in equilibrium with **265**, undergoes addition-elimination to give **266**.[148] In our opinion, the occurrence of the [2,3] shift is conjectural since the initial product, **264**, was not detected and the role of the medium on the initial step, as well as the reasons for the different reactivities of phenyl and methyl derivatives, are not known.



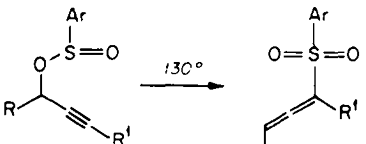
263

264

266

267

The thermal rearrangement of propargyl sulfinates **268** to allenyl sulfones **269** was reported by Braverman and Mechoulam[149] to proceed with a negative entropy of activation, in accord with a cyclic transition state. Smith and Stirling[150] have shown that no scrambling occurs when $R' = {}^2H$, and have provided the best evidence for concert in [2,3] shifts involving sulfur derivatives: optically active sulfinate, **268** (R = Me, R′ = H) yields an optically active allene with the configuration predicted on the basis of a concerted reaction. A similar reaction has been reported[151] by Braverman and Stabinski: the treatment of propargylic alcohols **270** with arylsulfenylhalide affords allenic sulfoxides **272**, presumably via sulfenate **271**. Here again, Smith and Stirling have reported[150] that use of optically active **270** gives an optically active allene, whose activity was shown to be due to the allenic moiety and not to the sulfoxide.



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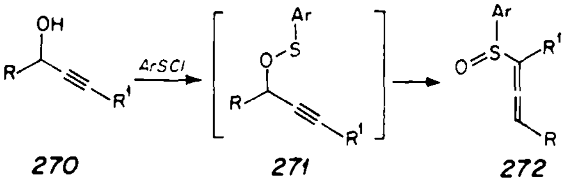

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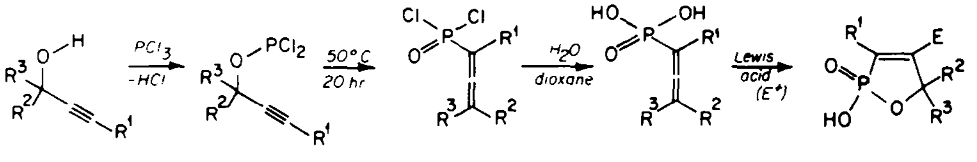
271

272

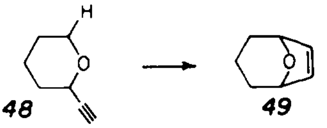
It should be pointed out that these last two examples involve migration from oxygen to sulfur and not the reverse, as was the case with **257** and **263**. The best evidence for concert, therefore, is found in those cases where the donor atom is a Period 2 element, N or O, without the possible complications of d-orbital involvement.

Macomber *et al.* have reported another [2,3] sigmatropic shift, involving migration from oxygen to phosphorus,[152] which proceeds with preservation of stereochemical integrity.[39] When propargylic alcohols **273** are treated with PCl_3, there is an immediate formation of the dichlorophosphites **33**. After efficient removal of the liberated HCl, the thermal rearrangement to **274** proceeds smoothly and hydrolysis in aqueous dioxane followed by treatment with a suitable Lewis acid (electrophile E^+) provides a convenient route to 4-substituted 1,2-oxaphosphol-3-enes, **275**.[152] The claim for concertedness, in the rearrangement step from propargyl phosphite to allenic phosphonate, rests on the fact that optically pure **273** ($R^1 = R^2 =$ t-Bu; $R^3 = H$) afforded a sample of **274** believed to be optically pure.[39] Moreover, the configuration of **274**, based upon the application of the Brewster–Lowe rules to the sign of the optical rotation, agrees with that predicted on the basis of a concerted [2,3] shift.[39]

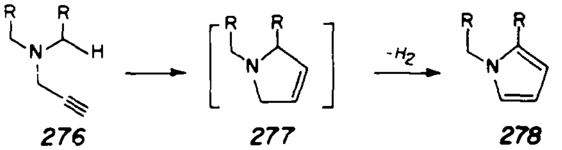


273 *33* *274* *275*

A [2 + 2] *reaction within a five-membered transition state.* The ability of an acetylenic bond to distort sufficiently for its inclusion in a six-atom bicyclic transition state, wherein the acetylenic unit becomes part of a five-membered ring, has been the subject of a report from our laboratory.[153] The reaction in question resembles an intermolecular [2 + 2] addition, which enjoys the entropic advantage that the reacting components are located within the same molecule. Unlike other similar reactions which are excluded from discussion herein, exemplified by the ene reactions of **51** and **100** mentioned in the introduction to the second part of this report, there must be considerable distortion of the acetylenic bond angle in this case. This results from the facts that only a two atom bridge separates the reacting components and that a bicyclic [2.1.1] framework, exemplified in Fig. 5, is involved in the transition state. In the thermolysis of 2-ethynyltetrahydropyran, **48**, as mentioned previously, the retro-ene reaction is encumbered by steric constraints due to the ring structure. Under these circumstances another thermal reaction competes with the retro-ene cleavage and the formation of 8-oxabicyclo[3.2.1]oct-6-ene, **49**, accounts for 30% of the reacted starting material. Similarly, during thermolyses of propargyl amines **276a–e** the retro-ene cleavage was accompanied by 3–7% of pyrrole formation. Cyclization of the amines must initially yield pyrrolines **277**, with subsequent hydrogen elimination to afford pyrroles **278**. Intermediacy of **277** was established by the reaction of **276d**, wherein the usually more facile hydrogen elimination is sufficiently encumbered to permit isolation of pyrroline **277d**. The reaction failed with geminal substitution, as in **279**, which would block hydrogen elimination and arrest the reaction process at the pyrroline stage.

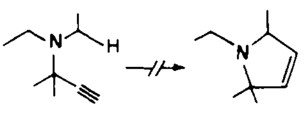


48 *49*



276 *277* *278*

a. R = H
b. R = Me
c. R = Et
d. $R + R = -(CH_2)_2-$
e. $R + R = -(CH_2)_3-$



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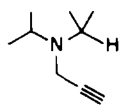

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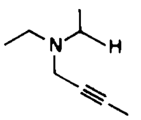

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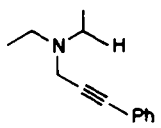

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Although the concerted nature of this process can only be inferred in the absence of thorough kinetic data, there are strong indications pointing in that direction. Energetically, the cyclization competes with the more facile retro-ene cleavage and product ratios imply a free energy of activation of about 4 kcal/mol above that of the latter concerted process. Radical pathways are unlikely since the reaction appears to be homogeneous, does not afford radical abstraction products in the presence of suitable diluents, gives no products involving the highly activated propargylic site, has never been observed in olefinic analogs, and is not found for substrates such as **279**, **280**, **281** or **282** which contain either geminal or terminal substituents. Such substituents should stabilize potential radical intermediates but would sterically hinder a tight, concerted transition state. A concerted reaction would correspond to a $[2_s + 2_a]$ addition of a C–H bond to an acetylenic Π-bond and maintenance of orbital symmetry requires the antarafacial participation of the Π-system.[18] Models indicate that the participating bonds in **48** can assume the requisite orthogonal orientation with a moderate deformation of the sp bond angle, as depicted in Fig. 5. This cyclization may therefore be indicative of the inherent ability of acetylenes to act as $_{\Pi}2_a$ donors, which would add acetylenes to the select group consisting of singlet oxygen, allenes, ketenes, and isocyanates, all of which possess an unhindered linearity, free of interfering hydrogen atoms, such as to permit antarafacial participation in addition processes. It should be noted that the cyclizations of **48** and **276** are aided by the fact that antarafacial involvement of the acetylenic unit permits the tight, congested transition state to be formed. Since the addition to the acetylenic unit must be *trans*, we suggest that the addition process can be aided by the requisite *trans* bending of that unit, and that consequently the hydrogen atom may trigger the reaction by transferring with hydride character in a non-synchronous concerted process.

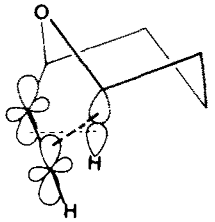
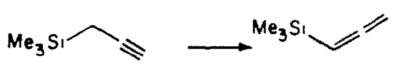


Fig. 5. Schematic illustration of proposed transition state for intramolecular $[_{\Pi}2_a + _{\sigma}2_s]$ addition in 2-ethynyltetrahydropyran, **48**.

Reactions via four-membered transition states

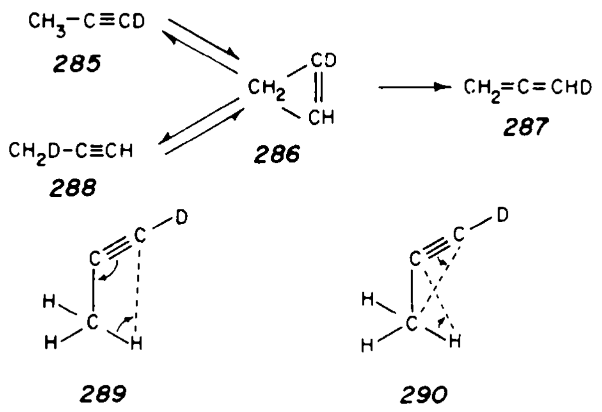
It is difficult to conceive an acetylenic bond angle distortion of sufficient magnitude to permit the normally linear three atom unit to fit into such small cyclic arrays. Yet, some reactions which appear to fall into this category have been reported. In four-membered transition states, the larger size of a third-period element will alleviate some of the bond angle distortion otherwise required of the acetylenic unit. The solution-phase rearrangement of phenyl propargyl sulfides **122** to phenyl allenyl sulfides **123** has already been mentioned. Here the altered location of the terminal methyl group clearly rules out a simple prototropic acetylene/allene interconversion,[98] but an intermolecular process remains a possibility in the liquid phase. However, a kinetic investigation of a silicon analog of this reaction in the gas phase, has also been reported by Slutsky and Kwart.[154] The unimolecular, first-order conversion of trimethylsilyl-2-propyne, **283**, to trimethylsilylallene, **284**, proceeds with $E_a = 50$ kcal/mol and $\Delta S^{\neq} = -4$ eu at 500°. Although these data do not establish a concerted process, the activation parameters closely approximate those of the analogous olefinic derivatives, in which inversion of the silicon atom is implicated.[98] Inversion of the migrating atom is one way to maintain orbital symmetry in a suprafacial, concerted [1,3] sigmatropic shift.[18]

122 *123*



283 *284*

Another intriguing example, reported by Hopf *et al.*,[155] concerns the thermal allene-propynne interconversion shown in Scheme 10. Propyne-1-*d*, **285**, rearranges to allene-*d*, **287**, over the range of 500–750°,

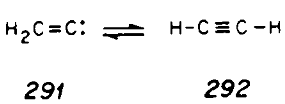


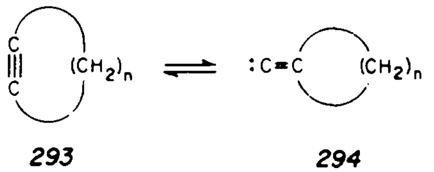
Scheme 10.

but cyclopropene, **286**, and propyne-3-*d*, **288**, are also observed. On the bases of some rough rate estimates, the authors suggest that from 50–100% of the allene produced comes via cyclopropene, although no possible mechanistic pathways were suggested. It appears to us that a [2 + 2] mechanism, similar to that discussed in the previous section for formation of cyclic ether **49** and pyrroles **278**, can account for the transformation of propyne **285** to both allene **287** and cyclopropene **286**. The [2 + 2] transition state, suggested in **289**, would lead to allene formation. This mode of orbital interactions appears to be a symmetry-forbidden, suprafacial [1,3] shift, but at the high temperatures utilized such a higher energy pathway cannot be ruled out. The opposite mode of orbital interactions, as suggested in **290**, leads to cyclopropene. Furthermore, since the two newly formed bonds in **286**, C–C and C–H, must be *trans* relative to the remaining Π-bond, a symmetry-allowed antarafacial involvement of the reacting Π-bond is necessitated. The twisted acetylenic unit must become part of a four-membered ring in transition state **289** and part of a three-membered ring in transition state **290**. Such distortions, if indeed this is the mechanistic path followed, could only come about at the high temperatures utilized.

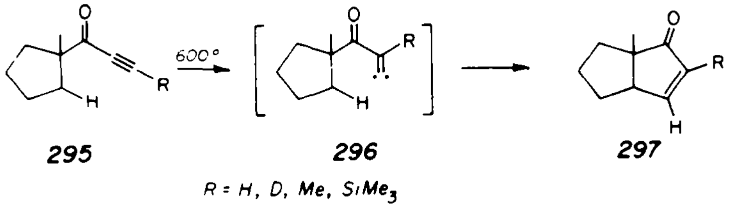
Reactions via a three-membered transition state

Ultimately, a three membered transition state must be involved in the methylenecarbene⇌acetylene interconversion, **291**⇌**292**, which corresponds to a [1,2] shift. The formation of acetylenic compounds from methylenecarbene precursors has been known for quite some time,[156] and is aided by the fact that acetylene, **292**, is between 38–46 kcal/mol more stable than the carbene, **291**.[157] Evidence for the reverse reaction, which occurs only at elevated temperatures, is of much more recent vintage.[158] The high temperature required for acetylene → methylenecarbene conversion undoubtedly reflects the very considerable bond angle distortion required for the migrating substituent on the acetylenic unit to approach the transition state from the direction of the acetylenic ground state. Several examples of possible contributions from this reaction pathway will be considered.



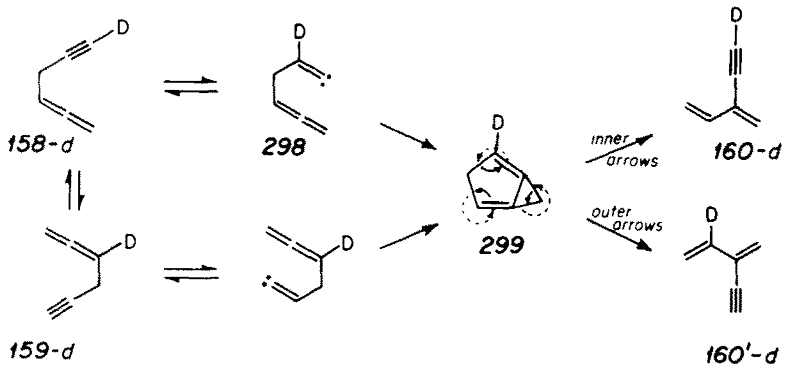


The retro-ene reaction of **235**, discussed earlier, was found during an investigation of the effect of ring strain in **293** on this process.[135] As *n* decreases, formation of the exocyclic carbene **294** should be favored. This rearrangement has also been invoked by Karpf and Dreiding[159] in the cyclization of a series of α-ketoacetylenes, such as **295**. A variety of groups attached to the terminal acetylenic atom can undergo a [1,2] migration to give methylene–carbene **296**, which then ring closes to **297** via C–H



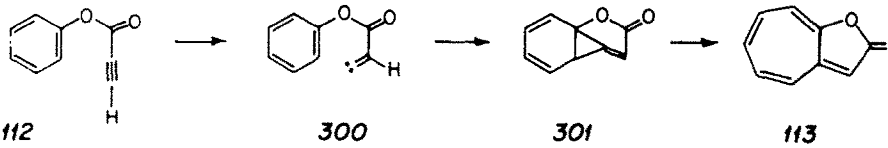
insertion. As stated above, these reactions, which are favored by α-unsaturation,[159] require relatively high temperatures. Since such a carbene reaction path could account for the transformation of propyne **285** to cyclopropene **286**, but cannot lead to allene **287** directly, it may also contribute to the reactions of Scheme 10.

A further possible involvement for the acetylene-methylenecarbene rearrangement is illustrated in Scheme 11. Hopf[112] has proposed a mechanism for the formation of **160** during the thermolysis of **158**, as depicted in Scheme 4, which accounts for the observed distribution of the deuterium label from **158d**. However, this proposed mechanism requires a $[_{\pi}2_a + {}_{\pi}2_s]$ cycloaddition process, which appears unlikely for this molecule. As an attractive alternative, we suggest the involvement of an acetylene-methylenecarbene pre-equilibrium to form **298**, whose geometry is highly favorable for ring closure to **299** via carbene addition to an allenic Π-bond. The indicated pericyclic ring openings, which are actually retro-Diels Alder reactions, would then provide the observed deuterium labeling in the product mixture, **160d** and **160'd**.



Scheme 11.

Yet another reaction in which the possibility of an acetylene–methylenecarbene rearrangement should be considered is the conversion of **112** to **113**.[†] The mechanism originally proposed for this reaction by Trahanovsky,[94] discussed in the section on acetylenic Claisen rearrangements, requires two methylene-ketene intermediates as well as an unlikely cyclization process. However, the high temperature of 650° used for this flash vacuum pyrolysis, as well as the presence of unsaturation at the position α to the acetylene, are uniquely suited for an acetylene–methylenecarbene rearrangement leading to **300**. Carbene addition to the phenyl ring then affords norcaradiene derivative **301**, whose valence tautomer is the final product **113**. This mechanism offers the advantage of utilizing only well-known processes, but, if correct, implies that this reaction is not a Claisen rearrangement.



These examples have illustrated possible participation of the acetylene–methylenecarbene rearrangement in several nominal pericyclic processes of acetylenic compounds. We suggest that such pathways should be given consideration in other suitable reactions of acetylenes which are carried out at high temperatures, since such conditions particularly seem[159] to favor this process.

Reactions via larger-membered transition states

The greater the number of atoms involved in a cyclic transition state, the less angle strain the involvement of an acetylenic unit should require. With eight atoms there is sufficient leeway so that virtually no steric differences should exist between incorporation of olefinic or of acetylenic units. Yet, evidence for such reactions remains inconclusive.

Mitchell and Sondheimer[160] have reported an 8-electron electrocyclization of octa-3,5-diene-1,7-diyne, **302**, to afford benzocyclobutadiene, **304**, via cyclic bisallene intermediate **303**. There is little

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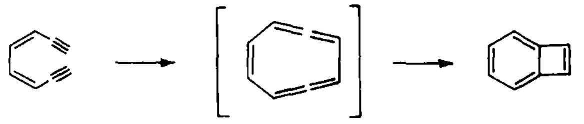
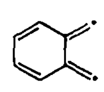
[†] *Note added in proof*: This mechanistic pathway has independently been proposed recently. See R. F. C. Brown and F. W. Eastwood, *J. Org. Chem.* in press (1982).



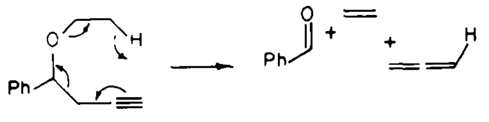
302 303 304



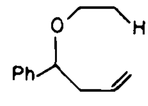
305

evidence in support of a concerted pathway, however, and it would appear that a non-concerted [2+2] cycloaddition, via intermediate diradical **305**, could account for the observed results.

Another perplexing report[161] originated from our laboratory in 1974. Thermolysis of the homopropargylic ether **306** over the range of 330–360° resulted in a homogeneous, first-order, unimolecular



306



307

fragmentation. The indicated products are in accord with a [1,7] hydrogen transfer and the activation parameters, $E_a = 40.9$ kcal/mol and $\Delta S^{\neq} = -14$ eu, implicate a concerted process. The analogous homoallyl ether **307** behaves in a totally corresponding manner, with $E_a = 43.4$ kcal/mol and $\Delta S^{\neq} = -10$ eu. Moreover, the reaction rates of **306** and **307** were virtually identical. Yet despite the fact that these convincing results have found their way into a popular textbook,[162] serious doubts remain, for in the intervening years we have not been able to find a single additional unequivocal example of this reaction pathway, despite thermolyses of more than 35 compounds with a wide variety of appropriate structural features.[163]

At the present time the operation of such reaction mechanisms involving higher order pathways must be considered questionable. At stake is a decision between two divergent claims. On the one hand, Woodward and Hoffman[164] consider symmetry-allowed many-component fragmentations unlikely, since each sigma bond which is transformed into a Π bond involves an endothermicity of some 20 kcal/mol. On the other hand, Schakel *et al.*[165] claim that where competitive thermal sigmatropic migrations are possible, higher order pathways may have intrinsically lower activation energies and are frequently preferred. The number of reported examples of higher order reactions in which acetylenes are involved is still too small to permit a definitive conclusion at this time.

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