

Thermal Isomerization of Allylic Alcohols to Saturated Ketones

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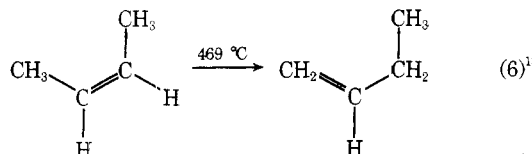
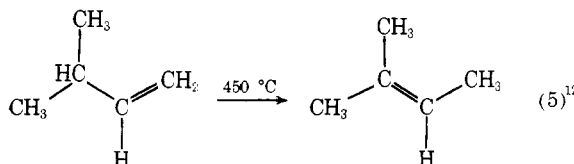
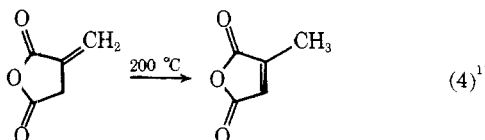
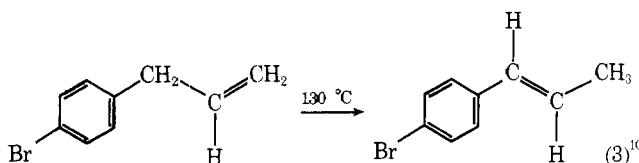
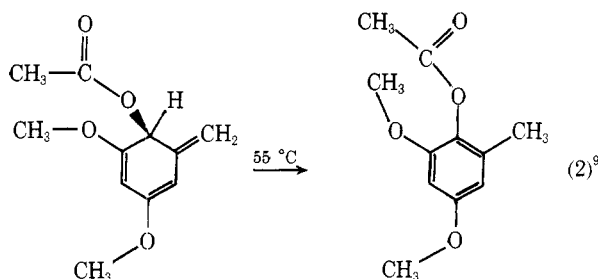
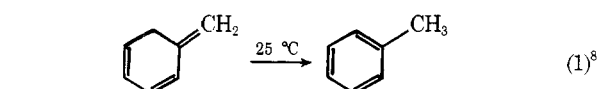
trans-Pent-3-en-2-ol and *trans*-1,3-diphenylprop-2-en-1-ol have been thermally isomerized to the saturated ketones 2-pentanone and 3-phenylpropiophenone. Rearrangements of mixtures of *trans*-2-deuterio- and *trans*-1,1,1-trideuteriopent-3-en-2-ol gave 2-pentanone and recovered starting material, indicative of extensive intermolecularity at some stage in the reaction. Rearrangement of undeuterated and *trans*-1-deuterio-1-pentadeuterio-phenyl-3-phenylprop-2-en-1-ol, however, indicated intramolecular hydrogen transfer.

Sigmatropic migrations of hydrogen atoms must occur with retention of configuration;¹⁻³ they do not have the retention or inversion option available to a migrating carbon atom. The only stereochemical alternatives for a [1,*j*] sigmatropic hydrogen shift concern the system of *j* π electrons.

For thermally activated [1,5] hydrogen transfers,^{4,5} the theoretically required suprafacial utilization of the pentadienyl fragment has been elegantly demonstrated.⁶

The theoretically predicted [1,3] thermal hydrogen migration with antarafacial allylic participation has not been uncovered; it has been considered unlikely by virtue of serious uncoupling within the π framework¹ and inaccessible by virtue of steric constraints.⁷

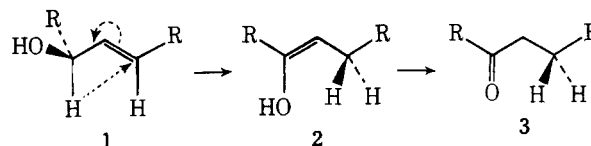
Yet reactions are known which, at least formally, correspond to such simple [1,3] hydrogen shifts (eq 1-6).



However, none of these reactions has been subjected to any sort of mechanistic appraisal. Without some appropriate experimentation, these and other such examples will contribute nothing toward a better understanding of the circumstances necessary for a thermal [1,3] hydrogen shift to occur intramolecularly with either suprafacial or antarafacial allylic participation.

Curiously, photochemical [1,3] sigmatropic shifts of hydrogen¹⁴⁻¹⁷ are well-known, while one transition metal catalyzed [1,3] hydrogen migration is known to be intramolecular as well as stereospecific.¹⁸

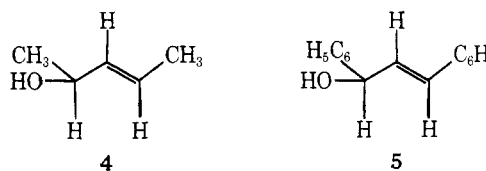
As an initial approach to the study of thermal [1,3] hydrogen migrations we have studied the thermal reactions of two allylic alcohols. By analogy with substrates which undergo oxy-Cope isomerizations,^{19,20} substituted allylic alcohols 1 might isomerize through a [1,3] hydrogen shift to give enols 2 able to isomerize readily to the more stable ketonic tautomers 3.



Once the rearrangement had been established, and intramolecularity demonstrated, work with the optically active and deuterium-labeled substrates necessary for probing reaction stereochemistry would become justified.

Results and Discussion

The two systems chosen for study were *trans*-1,3-dimethyl- and *trans*-1,3-diphenylprop-2-en-1-ol (4 and 5). The first,



more systematically designated as *trans*-pent-3-en-2-ol, was prepared through an *Organic Syntheses* procedure²¹ and the second through reduction of chalcone with sodium borohydride.^{22,23}

The alcohols did indeed show the rearrangements sought. The pentenol 4, when heated in a base-washed and degassed sealed tube for 30-180 min at 368 °C, gave a mixture of products including a 50-60% yield of 2-pentanone, identified through direct chromatographic and spectroscopic comparisons with authentic material. The diphenyl-substituted system 5, when heated at 302 °C for 10-40 min in a similarly degassed and sealed tube, gave a complex mixture of products which included a 5-8% yield of 3-phenylpropiophenone, identified through chromatographic and spectroscopic comparisons with authentic material.²⁴

Table I. Mass Spectrometric Deuterium Analyses for 2-Pentanone from Thermolysis of 6 and 7^{a,b}

Reaction time, min	Deuterium distribution				
	d ₀	d ₁	d ₂	d ₃	d ₄
30	25	16	19	32	8
62	18	30	28	18	6
180	17	33	30	16	5

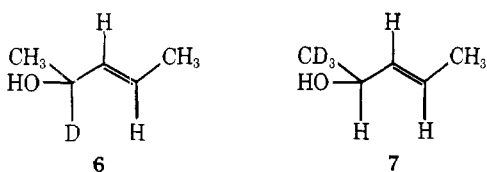
^a 50% d₁, 50% d₃ by NMR and mass spectrometric analysis.^b Temperature 368 °C.**Table II. Mass Spectrometric Deuterium Analyses for 3-Phenylpropiophenone from Thermolysis of 5 and 8^{a,b}**

Reaction time, min	Deuterium distribution							
	d ₀	d ₁	d ₂	d ₃	d ₄	d ₅	d ₆	d ₇
10	45	4	1	0	1	11	37	1
20	44	6	2	0	1	14	30	3
30	51	7	1	0	1	13	25	2
40	49	8	0	1	2	14	23	3

^a 54% d₀, 46% d₆ by mass spectrometric analysis. ^b Temperature 302 °C.

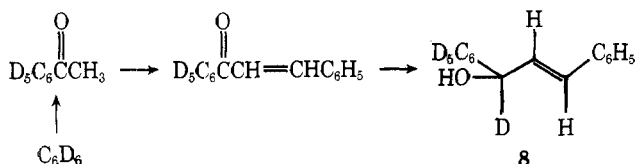
Having established that the rearrangement can be observed under reasonable conditions, the intra- or intermolecularity of the conversions was probed through the use of pairs of deuterium-labeled substrates.

For the aliphatic case, *trans*-2-deuteriopent-3-en-2-ol (6) and *trans*-1,1,1-trideuteriopent-3-en-2-ol (7) were selected



and prepared: the first through reduction of *trans*-pent-3-en-2-one, the second by a Grignard reaction between crotonaldehyde and trideuteriomethylmagnesium iodide.

For the chalcane analogue, the hexadeuterio substrate 8 was



prepared through a sequence beginning with the aluminum trichloride catalyzed reaction of acetyl chloride with perdeuteriobenzene. Aldol condensation with benzaldehyde and reduction with sodium borodeuteride completed the route.

For completely intramolecular [1,3] hydrogen or deuterium migration, the isotopic composition of starting material (6 plus 7, or 5 plus 8) should be preserved in the ketonic products. For intermolecular mechanisms, such a result would be impossible. A free-radical chain process, the most probable intermolecular possibility, should lead to a nearly statistical distribution of labeled products.

In the event, thermal rearrangement of a mixture of 6 with 7 gave labeled 2-pentanone. The mass spectrometrically determined deuterium distributions in starting material and product, summarized in Table I, indicated extensive scrambling of label either prior to, during, or subsequent to the isomerization.

The results from a similar experiment with 5 plus 8 as



Figure 1. Total ion current vs. time from the MS/GC/COM analysis of the thermolysate (305 min at 175 °C) from 5 plus 8. The products are identified as: a, *cis*-1,3-diphenylpropene; b, *trans*-1,3-diphenylpropene; c, *cis*-1,3-diphenylprop-2-en-1-ol; d, *cis*-1,3-diphenylprop-2-en-1-one; e, unknown; f, *trans*-1,3-diphenylprop-2-en-1-ol; g, 3-phenylpropiophenone; h, unknown; and i, *trans*-1,3-diphenylprop-2-en-1-one.

starting alcohol are given in Table II; they indicate a fair degree of intramolecularity. Were the process to involve the 1,3-diphenyl-1-hydroxyallyl radical as a chain-carrying species, an example of one intermolecular possibility, equal proportions of d₀ and d₆ substrates 5 and 8 should lead to equal proportions of d₀, d₁, d₅, and d₆ products. Instead, the distributions of label in starting alcohol are largely retained in the product ketone.

For the purposes of confirming this preliminary result as well as more fully characterizing the thermolysis products, a mass spectrometric/gas chromatographic/computer (MS/GC/COM) study was carried out. Instead of employing neat samples of the labeled chalcals, a highly dilute benzene solution (250 µg/mL) was prepared. Aliquots were placed into base-washed ampules, degassed, sealed, and heated at either 175 or 250 °C. MS/GC/COM analysis of the resulting thermolysate (see Figure 1) revealed a significantly increased yield (40%) of the desired product, 3-phenylpropiophenone, along with the *cis* and *trans* isomers of two previously unidentified products, 1,3-diphenylpropene and 1,3-diphenylprop-2-en-1-one (chalcone).²⁶ A typical gas chromatogram which has been computer generated from the total mass spectrometric ion current is shown in Figure 1. While small amounts of water were formed in the other thermolyses described above, it was not apparent in these gas-phase reactions which were conducted in the presence of a large excess of benzene vapor. The resulting deuterium distributions in the product 3-phenylpropiophenone from two such experiments are presented in Table III. Again, the ketone product is shown to arise from an intramolecular shift of hydrogen. The significant portion of d₅ ketone reflects the loss in isotopic integrity of the starting chalc (5 plus 8), since unreacted starting material was found by mass spectral analysis to have the same concentration of d₅ species. This is most likely the result of a competing free-

Table III. Mass Spectrometric Deuterium Analyses for 3-Phenylpropiofenone from Thermolysis of 5 and 8^a

Reaction temp, °C	Reaction time, min	Deuterium distribution							
		d ₀	d ₁	d ₂	d ₃	d ₄	d ₅	d ₆	d ₇
175	305	47	0	5	4	5	6	32	1
250	71	61	0	2	0	2	15	20	0

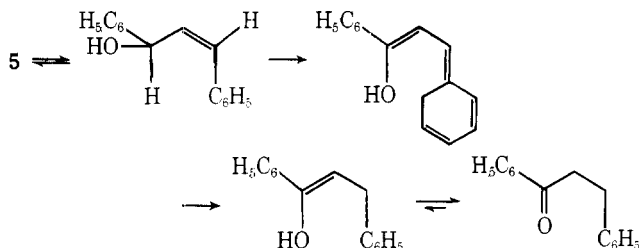
^a 58% d₀, 42% d₆ by mass spectrometric analysis.

radical chain process which has been uncovered previously in the decomposition of the saturated secondary alcohols.²⁵

The deuterium distributions for the alcohol are corrected for [M - 1]⁺ fragmentation and, for this reason, contain relatively larger experimental errors (±8%) than do the distributions reported for the ketone (±4%). All of the data in Tables I-III come from electron impact mass spectra and are fully corroborated by the parallel, but redundant, methane chemical ionization results.

The variations in deuterium distributions for the two experiments reported in Table III are thought to be a result of the significantly different extents of reaction: the low-temperature reaction has been run to a much lower percent conversion.

With this demonstration of intramolecularity, further work toward defining mechanisms for such conversions seems in order. Such research efforts would need to test not merely for intramolecularity, but whether the hydrogen shift is really [1,3] or a [1,5] followed by [1,7] sequence (as illustrated in the scheme below), and to secure kinetic data as well as quanti-



tative stereochemical information on the isomerization.

Experimental Section

Mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer interfaced to a Texas Instruments 960A computer. Electron impact mass spectra were secured through helium charge exchange (ionization potential = 24 eV) at a source temperature of 70 °C, an electron energy of 100 eV, and a trap current of 400 μ A. Chemical ionization spectra were taken using the same conditions as above along with a methane reagent gas (proton affinity = 126 kcal mol⁻¹) pressure of 1.0 \pm 0.1 mm. The MS/GC/COM work was carried out with the following chromatographic conditions: a 1.5 m \times 2 mm 3% OV-101 on 80/100 Chromosorb WHP glass column operated at 180 °C and a flow rate of 20 mL of methane or helium per minute.

Analytical and preparative GLC separations were carried out on Aerograph A90-P3 and 1520 instruments employing 1.5 m \times 6 mm 20% SE-30 on 60/80 Chromosorb W columns. Analytical TLC was performed on 20 \times 5 cm glass plates coated with a 0.25-mm layer of Brinkmann silica gel GF; preparative TLC was carried out on 20 \times 20 cm glass plates coated with a 1.1-mm layer of Brinkmann silica gel PF-254.

trans-Pent-3-en-2-ol, prepared according to Coburn,²¹ had bp 119–121 °C (lit.²¹ bp 119–121 °C).

trans-2-Deuteriopent-3-en-2-ol (6). To a 100-mL three-neck round-bottom flask with mechanical stirrer, thermometer, and addition funnel was added 0.50 g (17.4 mmol, 4 equiv) of lithium aluminum deuteride (Ventron) and 10 mL of anhydrous ether. At 0 °C 1.45 g (17.3 mmol) of *trans*-pent-3-en-2-one (Pfaltz and Bauer; freshly distilled, bp 124–125 °C) in 35 mL of dry ether was added over 10 min with stirring. The reaction mixture was stirred an additional 35 min at 0 °C, warmed to room temperature for 30 min, and quenched by the addition of 0.5 mL of H₂O, 0.5 mL of 15% NaOH, and finally 1.5 mL of H₂O. The product was isolated by extraction with ether fol-

lowed by washing with H₂O, drying (MgSO₄), filtering, and concentrating by distillation to give 0.967 g (65% yield). The structure of the product was clear from its characteristic infrared and mass spectra, and especially the NMR spectrum where the τ 5.7–6.2 1 H multiplet in 4 was completely absent and the τ 8.85 3 H doublet was now a singlet.

trans-1,1,1-Trideuteriopent-3-en-2-ol (7). Treatment of crotonaldehyde (Matheson, Coleman and Bell; freshly distilled, bp 101–102 °C; 2.20 g, 31.4 mmol) with trideuteriomethylmagnesium iodide from trideuteriomethyl iodide (Stohler Isotopes; 5.00 g, 34.5 mmol) as previously described²¹ gave 2.44 g (80% yield) of 7. The structure of the product was confirmed by its characteristic infrared and mass spectra, and especially the NMR spectrum where the 3 H doublet at τ 8.85 in 4 was completely lacking.

trans-1,3-Diphenylprop-2-en-1-ol (5). Chalcone, prepared by the procedure of Davey and Hearne,²² was reduced with sodium borohydride;²³ the product alcohol had mp 54–56 °C (lit.²³ 55–56 °C).

Pentadeuteriophenyl Methyl Ketone. To a 100-mL three-neck round-bottom flask was added 5.60 g (59.5 mmol) of perdeuteriobenzene (Stohler Isotopes), 9.40 g (71 mmol) of AlCl₃, and 25 mL of CS₂. With cooling 5.60 g (72 mmol) of acetyl chloride was added by means of an addition funnel. A condenser was fitted to the flask and the reaction mixture was heated at reflux for 2 h. After quenching the reaction by the addition of 5 mL of D₂O, the aqueous phase was extracted with CS₂ (3 \times 10 mL) and ether (3 \times 10 mL). The combined organic phases were washed with 5% NaOH (3 \times 10 mL) and H₂O (3 \times 10 mL), dried (MgSO₄), filtered, and concentrated by distillation to give 6.10 g (82% yield) of acetophenone-*d*₅, whose NMR spectrum confirmed that the benzene ring was >97% deuterated.

trans-1-Pentadeuteriophenyl-3-phenylprop-2-en-1-ol (Chalcone-*d*₅). Chalcone-*d*₅ was prepared through the aldol condensation of acetophenone-*d*₅ with benzaldehyde as described previously.²²

trans-1-Deuterio-1-pentadeuteriophenyl-3-phenylprop-2-en-1-ol (8). Chalcone-*d*₆ (8) was obtained by sodium borodeuteride reduction of chalcone-*d*₅.²³

3-Phenylpropiofenone, prepared by the method of Miyano and Sako,²⁴ had mp 69–72 °C (lit.²⁴ mp 70.5–71 °C).

Thermolyses. Neat samples of allylic alcohols in 18 cm \times 8 mm ammonia-washed and oven-dried Pyrex ampules were thoroughly degassed through four freeze-pump-thaw cycles on a vacuum line and were sealed at 10⁻⁴ to 10⁻⁵ mm. Thermolyses were done by immersing the tubes in a potassium nitrate/sodium nitrite salt bath stirred with a Lightnin stirrer and maintained at constant temperature with two (450- and 125-W) heaters.

For the MS/GC/COM studies in the chalcone series, a dilute solution of *d*₀ and *d*₆ *trans*-1,3-diphenylprop-3-en-2-ol was made up in freshly distilled benzene (250 μ g/mL of benzene). Pyrolyses were performed in ampules as above, but in the oven of a Varian A90-P3 gas chromatograph.

Products. 2-Pentanone was isolated from the thermolysis mixture by preparative GLC on the SE-30 column (vide supra) maintained at 125 °C. GLC-collected product was identical with authentic material (Eastman) both chromatographically and spectroscopically. 3-Phenylpropiofenone was isolated from the thermolysis mixture by preparative TLC on silica gel PF-254 (vide supra) eluting with 10:1 pentane/ether. The TLC-collected product was identical with authentic material²⁴ both chromatographically and spectroscopically. For the reactions employing deuterium-labeled substrates, 2-pentanone and 3-phenylpropiofenone were isolated and purified by preparative GLC or TLC, respectively, and analyzed mass spectrometrically.

In the MS/GC/COM study, products were delivered to the source of the mass spectrometer through the interfaced gas chromatograph (vide supra) using either helium (electron impact mode) or methane (chemical ionization mode) as the carrier gas.

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Registry No.—4, 3899-34-1; 5, 62668-02-4; 6, 64364-81-4; 7, 64364-82-5; 8, 64364-83-6; crotonaldehyde, 4170-30-3; 2-pentanone,

107-87-9; 3-phenylpropiophenone, 1083-30-3; *cis*-1,3-diphenylpropene, 1138-83-6; *trans*-1,3-diphenylpropene, 3412-44-0; *cis*-1,3-diphenylprop-2-en-1-ol, 62839-70-7; *cis*-1,3-diphenylprop-2-en-1-one, 614-46-0; *trans*-1,3-diphenylprop-2-en-1-one, 614-47-1; *trans*-pent-3-en-2-one, 3102-33-8.

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- (26) Identified through chromatographic and mass spectrometric comparisons with authentic samples.

The α Effect in α -Chlorofluoro Ketones

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Contribution No. 2505 from the Central Research and Development Department,
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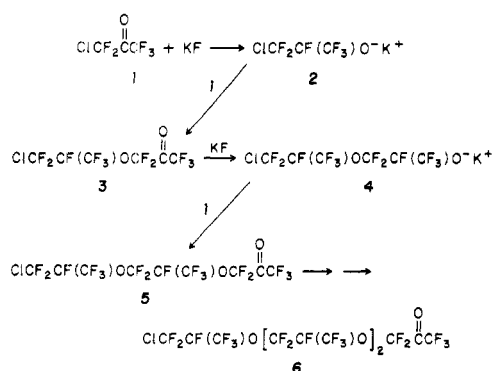
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α -Chloropolyfluoro ketones are subject to displacement of chloride ion under mild conditions by relatively weak bases, notably fluoroalkoxide salts. The latter reagents react with α -chlorofluoro ketones to form fluorinated keto ethers; since these keto ethers add fluoride ion to give new, reactive fluoroalkoxides, a series of low oligomers is produced in each case. The new fluorinated keto ethers are shown to resemble hexafluoroacetone in their response to free radicals as well as to fluoride ion.

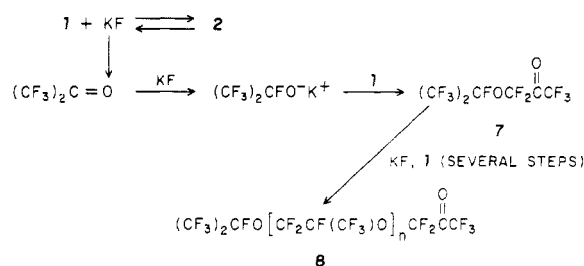
Anionic attack on saturated carbon with displacement of a substituent X^- is rarely encountered in highly fluorinated systems. If reaction with the fluorinated substrate does occur, the incoming base most frequently attacks a nonfluorine substituent with displacement of fluorocarbanion.¹ The known cases of intermolecular nucleophilic attack at sp^3 carbon in fluorinated compounds seem to be limited to those in which a carbonyl group is α to the leaving group X , and the nucleophile has usually been fluoride ion.² The results described below further define the conditions under which such reactions occur and demonstrate a wider scope for the reaction by the use of some other types of nucleophile.

Fluoroalkoxides. Chloropentafluoroacetone (1) in dimethylformamide reacts easily with 1 equiv of potassium fluoride to give the soluble adduct 2 which only slowly undergoes further change at 25 °C. In the presence of excess 1, however, displacement of chloride ion by chlorohexafluoroisopropoxide ion 2 occurs to form the new ketone 3 (Scheme I). The reaction proceeds slowly at 25 °C and more rapidly at

Scheme I



Scheme II



temperatures up to 80 °C. Moreover, ketone 3 has a relatively unhindered carbonyl group and competes successfully with 1 for fluoride ion to form the fairly stable adduct fluoroalkoxide 4. The latter also displaces chloride ion from 1 to form the higher fluoro ketone 5. Ketone 5 and its higher analogues similarly form reactive alkoxides by addition of fluoride ion with the net result that a series of fluorinated keto polyethers is formed in diminishing yield as molecular weight increases. After the first displacement, each subsequent displacement will be seen to have the effect of introducing a unit of hexafluoropropene epoxide.³

Yields obtained with a 1:2 KF/1 mol ratio in dimethylformamide have been 30% for 3 and 14% for 5 with about 12% conversion to by-product hexafluoroacetone. In addition, a related series of by-products is formed in amounts that increase with increase in proportion of KF. These by-products contain no chlorine and result from formation of hexafluoroacetone and its subsequent reaction as indicated in Scheme II. Coreaction of both 1 and hexafluoroacetone with KF gave preparative yields of these by-products, and ketones 7 and 8 ($n = 1, 2$) were isolated.⁴

A reaction of 1 with KF carried out in triglyme proceeded very slowly at 40–80 °C, so the temperature was raised to 95