THE THERMAL REARRANGEMENT OF CIS,CIS-1-FLUORO-2-METHYL-3-VINYLCYLOPROPANE. THE KINETIC EFFECT OF A SINGLE FLUORINE SUBSTITUENT*

SETH ELSHEIMER AND WILLIAM R. DOLBIER, JR.**

Department of Chemistry, University of Florida, Gainesville, FL 32611 (U.S.A.)

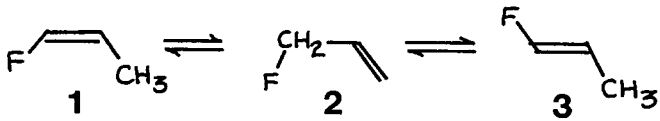
SUMMARY

It was demonstrated through a kinetic study of the thermal rearrangement of cis,cis-1-fluoro-2-methyl-3-vinylcyclopropane to cis-3-fluoro-1,4-hexadiene that a single fluorine substituent lowers that activation barrier for rearrangement by about 2 kcal/mole as compared to 6.4 kcal/mole for geminal difluoro substitution.

INTRODUCTION

Although much has been learned in recent years about the thermodynamic and kinetic effects of gem-difluoro substitution on the thermodynamics and kinetics of hydrocarbon thermal rearrangements[1], particularly with regard to cyclopropane systems, similar information about monofluoro-substituted systems has been scarce.

Equilibration studies of cis and trans-1-fluoro- and 3-fluoropropene have demonstrated that a single fluorine substituent favors the vinylic over the allylic position thermodynamically by ~3 kcal/mole[2]. These results, coupled



ΔH=+3.34 kcal/mole ΔH=-2.68 kcal/mole

* Dedicated to Emeritus Professor W.K.R. Musgrave on the occasion of his 70th birthday.

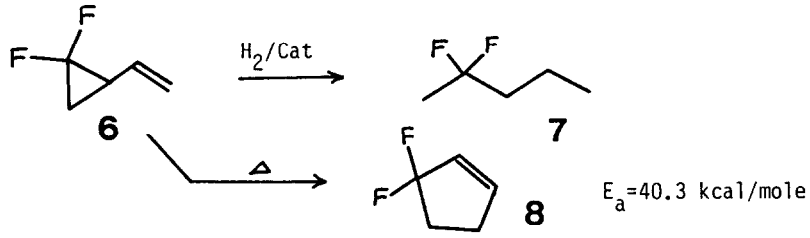
0022-1139/88/$3.50

with those derived from the equilibration of 2-fluoromethylenecyclopropane and fluoromethylenecyclopropane ($\Delta H°=-2.60$ kcal/mole[3], lead one to conclude that

$\Delta H=-2.60\pm0.06$ kcal/mole

substitution of a cyclopropane ring by a single fluorine substituent does not give rise to a significant alteration of the strain of the cyclopropane system.

This is in contrast to the known dramatic effect of geminal difluoro substitution on the apparent strain of cyclopropane systems. Indeed, Roth demonstrated in studies of the heats of hydrogenation of **6** and related systems that geminal difluoro substitution gives rise to an incremental increase in



the heat of formation for **6** relative to hydrogenated acyclic product **7** of ~14 kcal/mole[4].

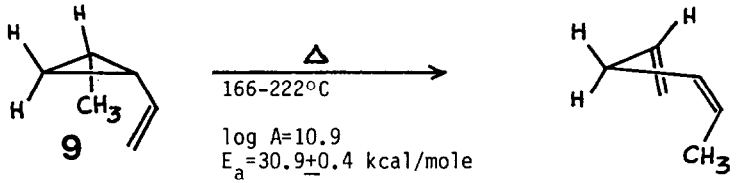
The apparent large incremental destabilization of gem-difluoro-substituted cyclopropanes was reflected by a comparable increase in the ease of cyclopropane homolytic ring cleavage. Thus 2,2-difluorovinylcyclopropane **6** underwent the classic ring expansion process to 3,3-difluorocyclopentene **8** with an activation energy which was ~10 kcal/mole less than that of the hydrocarbon system[5].

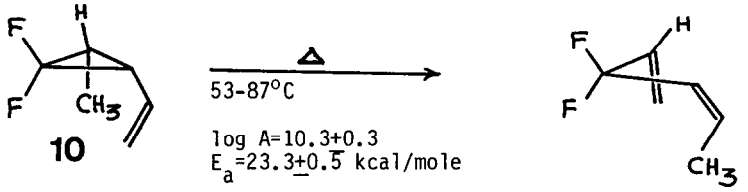
In this report we present the first kinetic data on the effect of a single fluorine substituent on the thermal reactivity of a cyclopropane ring.

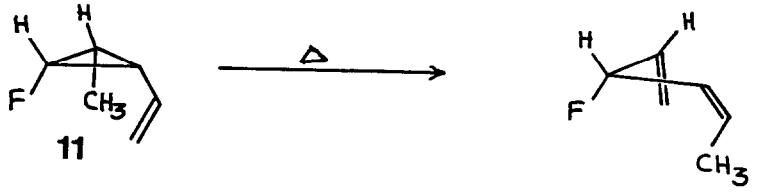
RESULTS AND DISCUSSION

Because of the low activation energy for such rearrangements and because both the parent hydrocarbon system[6] and the gem-difluoro system[7] have already

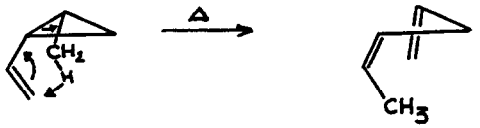
been examined and thus are available for comparison, the thermal homo-1,5-hydrogen shift rearrangement of cis, cis-1-fluoro-2-methyl-3-vinylcyclopropane **11** was chosen to probe the effect of a single fluorine substituent.







The mechanism of this particular rearrangement has been studied in considerable detail, and it is understood as proceeding via a concerted mechanism with a transition state as depicted below[8,9]. The geminal



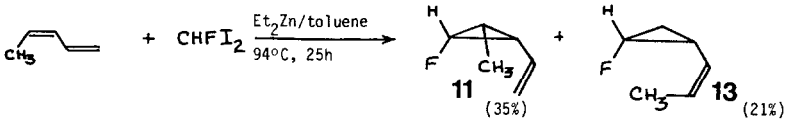
difluoro substituents are seen to give rise to a similar enhancement of reactivity (ΔE_a=-7.9 kcal/mole) as that exhibited in non-concerted cyclopropane ring homolyses (i.e. rearrangement of [5].

It is known that problems are endemic to the study of monofluoro-substituted hydrocarbon systems because of an apparent facile HF elimination

process. We observed this in early studies of the Cope rearrangement of 3-fluoro-1,5-hexadiene wherein 1,3,5-hexatriene was observed to be formed faster than the Cope products E- and Z-1-fluoro-1,5-hexadiene[2]. We were able to overcome the HF elimination problem well enough to recently complete our study of this rearrangement[10], but we've experienced similar problems in virtually all attempts to study monofluoro systems. Therefore this low-activation-energy, concerted rearrangement seemed to provide the greatest chance of an unperturbed probe of the effect of a single fluorine substituent on cyclopropane reactivity.

Synthesis

The desired cis,cis-1-fluoro-2-methyl-3-vinylcyclopropane (**11**) was synthesized by formal addition of monofluorocarbene to Z-1,3-pentadiene.

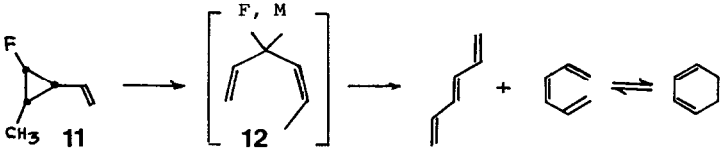


+ 24% bis-adducts (not fully characterized)

In addition to 24% of bis addition of CHF to the diene, the two expected adducts, **11** and cis-2-fluoro-1-(cis-propenyl)cyclopropane **13** were obtained in 35% and 21% yields respectively. Unfortunately, but not unexpectedly, none of the other isomeric potential adducts, with the fluorine substituent in a trans position, were obtained. Additions of CHF to alkenes had been demonstrated earlier to be highly cis-specific as to the disposition of the fluorine substituent[11].

Thermal rearrangement

Gas phase, thermal isomerization of **11** was carried out at six temperatures between 152.8 and 171.4°C in a well-conditioned pyrex vessel immersed in an oil bath. The results of the thermolysis are shown below.



Unfortunately, none of the expected product **12** could be isolated from the reaction, only its expected products derived from HF loss. As we had feared, even the relatively low temperatures required to carry out this rearrangement were too severe to enable isolation of the initially-formed, intact product. The products, cis and trans-1,3,5-hexatriene and 1,3-cyclohexadiene were identified by comparison with authentic materials.

In spite of this difficulty, it was found that the rates for loss of the starting material **11**, relative to an internal standard, followed excellent first-order kinetics at each temperature, as did the rate of formation of the three products. Moreover, an Arrhenius plot of the rate data gave a good

TABLE 1

Rates of Thermal Isomerization of cis,cis-1-Fluoro-2-methyl 3-vinylcyclopropane, **11**.

T, °C	k x 10^4, s^{-1}
152.8	1.21±0.03
157.1	1.74±0.04
160.4	2.30±0.06
165.1	2.98±0.08
168.1	3.61±0.18
171.4	5.06±0.05

straight line, and the frequency factor and energy of activation were calculated by the method of least squares. Thus it was possible for us to ascertain the activation parameters for the assumed concerted, homo-1,5-hydrogen shift process. In a study by Roth in 1983 of various difluoro-vinylcyclopropane rearrangements, similar assumptions due to HF loss, were made in determining activation parameters[4]. The observed rates for the reaction are given in Table 1, while the calculated activation parameters are provided in Table 2 along with those for the parent and gem-difluoro systems. The fact that these activation parameters are consistent with expectations considering our knowledge of the hydrocarbon and gem-difluoro systems, gives us additional confidence that the reaction process measured is actually that depicted.

TABLE 2

Activation Parameters for Homo-1,5-Hydrogen Shifts of cis-2-methylvinylcyclopropanes, **9**, **10** and **11**.

Substrate	E_a[a] kcal/mol	Log A	T_{avg} °C	$\Delta H^{\ddagger}$[a]	$\Delta S^{\ddagger}$[b]	$\Delta G^{\ddagger}$[a] (166.2°C)	k_{rel} at (166.2°C)	Ref.
9 (H,H)	31.2±0.4	11.03±0.2	194.2	29.9	-11.7	35.0	1	6
11 (H,F)	27.6±1.2	10.3±0.6	162.1	26.7	-14.4	33.0	11.2	this work
10 (F,F)	23.3±0.5	10.3±0.3	69.8	22.7	-13.5	28.6	1540	7

[a] kcal/mol; [b] cal/deg

It can be seen from the data in Table 2 that a cis-monofluoro substituent enhances the rate of the homodienyl hydrogen shift process by a factor of only 11.2 relative to the hydrocarbon at 166.2°. The $\Delta\Delta G^{\ddagger}$ for the two processes is only -2 kcal/mole. This can be compared to a rate enhancement of 1540 for the gem-difluoro system relative to the hydrocarbon ($\Delta\Delta G^{\ddagger}$=6.4 kcal/mole). With near-identical pre-exponential factors for the mono and gem-difluoro system one can compare their E_a s directly and there is seen to be a 4 kcal incremental lowering for the gem-difluoro system. What this translates to in the overall comparison of the three systems is the conclusion that the addition of one and then two fluorines to a cyclopropane ring does not lead to additive effects on kinetic reactivity. In terms of lowering of the energy barrier, the second, geminal fluorine substituent has about twice the effect of the first fluorine substituent. Thus the first fluorine enhances the rate 11-fold, while the second an additional 130-fold.

A rationalization for this non-linearity of substituent effect can be found in the following model. Consider the parameters ϕ and θ shown in Fig. 1.

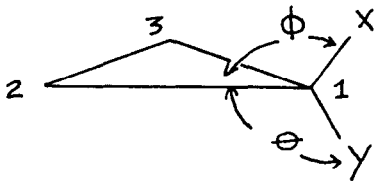


Fig. 1. Substituent Bond Angles Relative to the Cyclopropane Ring Plane.

These are defined as the angle between the cyclopropane ring plane and the C-X or C-Y bond respectively. When X and Y are both F, the bonds to fluorine will

be rich in p-character and the resulting 'rehybridization' around C(1) manifests itself through additional ring strain as the C(2)-C(1)-C(3) valence angle is pressured to open outward.

In the monofluoro case where X=F and Y=H, as before the bond to fluorine is richer in p-character and causes a 'rehybridization' around C(1) resulting in an increase in all the angles not involving the C-F bond. The already strained cylopropane bonds cannot accommodate the loss of p-character as well as the C(1)-H bond can. One would expect a flattening of the C(1)-H bond relative to the cyclopropane ring, i.e., an increase in θ and a decrease in ϕ. The important point here is that the diminution of p-character in the bonds of C(1) to non-fluorine atoms can be partially compensated by something other than ring strain. In the case of the gem-difluoro species (X=Y=F), such compensation is not possible. Therefore one must conclude that while monofluoro substitution of cyclopropane, does impart a degree of reactivity enhancement, it does not reflect the remarkable level of kinetic reactivity which is characteristic of gem-difluoro substitution.

EXPERIMENTAL

General

NMR spectra were recorded on a Nicolet NT-300, a Jeol FX-100, or a Varian EM 360L spectrometer. ^{1}H and ^{13}C chemical shifts (δ) are reported as ppm downfield of internal TMS. ^{19}F chemical shifts (ϕ) are reported in ppm upfield of internal $CFCl_3$. All NMR spectra were obtained at ambient temperature in $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer from films of neat liquids between KBr plates. Mass spectra were determined on an AEI-MS 50 spectrometer at 70 eV and are reported as m/q (% rel. base) fragment.

Reaction of Z-1,3-Pentadiene with $CHFI_2$ and Diethylzinc.

The method was based on Nishimura and Furakawa's reported preparation of 7-fluorobicyclo-[4.1.0.]heptane[11]. The reaction was carried out under an atmosphere of dry nitrogen in a 50-mL three-necked flask equipped with a condenser, a rubber septum, and a stirring magnet. Standard syringe techniques were used to place the following reagents into the reaction flask: 20 mL 1.6 M diethylzinc in toluene (32 mmol, Aldrich), 4.0 mL Z-1,3-pentadiene (40 mmol, Fluka), and 2.7 mL $CHFI_2$[12](8.5 g, 30 mmol) Reaction progress was monitored by syringing a small sample of the mixture into a septum-capped NMR tube and examining it by

^{19}F NMR for disappearance of $CHFI_2$ (102, d, J=48 Hz). The sample could then be placed back into the reaction mixture. No reaction was observed to occur at room temperature after 16h. One mL of neat diethylzinc[13] was added by syringe and the mixture was heated in an oil bath at 94° for 25h. The reaction flask was cooled to 0°C and the mixture was slowly quenched with approximately 30 mL of 0.75 M HCl and transferred to a separatory funnel. The organic layer was washed thrice with 0.75 M HCl and thrice with distilled water, then dried over anhydrous $CaCl_2$. Yields were determined on the above solution by ^{19}F NMR integration relative to a preweighed amount of m-bromobenzotrifluoride (Columbia). Samples of the products were isolated by preparative GC (20% Diisodecylphthalate, 10' x 0.25", 73°, 30 mL/min He flow). **11** (35%): ^{1}H NMR δ 4.63 (dt, J=65.5 Hz, J=5.8 Hz, 1H, FC-H), 1.12 (m, 3H, CH_3), 1.48 - 1.60 (m, 1H, allylic), 1.02 - 1.16 (m, 1H, MeC-H), 5.66 (dddd, J=17.2 Hz, J=10.4 Hz, J= 9.3 Hz, J=1 Hz, 1H internal vinyl), 5.24 (dd, J=17.2 Hz, J=2.1 Hz, 1H, terminal vinyl cis to cyclopropyl), 5.15 (dd, J=10.4 Hz, J=2.1 Hz, 1H, terminal vinyl trans to cyclopropyl); ^{19}F NMR: ϕ 237.1 (dt, J=65.6 Hz, J=7 Hz); ^{13}C NMR: 130.6 (d, J=8.5 Hz, internal olefinic), 117.0 (s, terminal olefinic), 74.6 (d, J=221 Hz, CHF), 22.7 (d, J=9.8 Hz, allylic), 15.6 (d, J=11.0 Hz, C-Me), 5.8 (d, J=8.6 Hz, CH_3); IR: 285 (wk), 330 (wk), 710 (wk), 730, 780, 860, 905, 970, 990, 1015, 1045, 1075, 1115 (wk), 1145, 1180, 1230, 1330, 1390, 1460, 1635, 1695, 2880, 2940, 2960, 2990, 3010, 3040, 3085 cm^{-1}; MS: 100 (30.2) M^+, 85 (100) M^+-CH_3, 79 (10.6), 72 (17.3), 65 (18.8) C_5H_5, 59 (37.7) C_2H_2F, 53 (17.4), 51 (11.4), 46 (9.3), 41 (20.7), 39 (46.2) C_3H_3, 27 (20.7) C_2H_3: **13** (21%): ^{1}H NMR δ 4.65 (dtd, J=66 Hz, J=7 Hz, J=4 Hz, FC-H), 4.8 - 5.9 (m, vinylic); ^{19}F NMR ϕ 223.5 (ddddd, J=65.0 Hz, J=23 Hz, J=12.3 Hz, J=5.0 Hz, J=1.1 Hz).

Four isomeric diadducts which were not separable by GC were also observed (24%). The chemical shifts and coupling patterns from the ^{19}F NMR spectrum of a mixture of these were consistent with the presence of approximately 11% each of the syn, syn bis-adducts and approximately 1% each of the syn, anti bis-adducts.

Thermolysis of cis, cis-1-Fluoro-2-methyl-3-vinylcyclopropane, **11**.

The thermolysis of **11** was carried out in a well conditioned, spherical, pyrex vessel of approximately 200 mL capacity, submerged in a stirred, thermostated, molten salt bath (eutectic mixture 50/50% by weight of $NaNO_2$ and KNO_3, mp 150°). The temperature was measured using a chromel-alumel

thermocouple in conjunction with Tinsley type 3387E potentiometer. The thermocouple was immersed in a well next to the thermolysis vessel. The temperature was controlled to +0.1°C using Hallikainen (now TOTCO) Instrument Thermotrol proportional controller with a model 1256A platinum resistance probe. The internal standard used was methylcyclohexane and GC analyses were performed using a Hewlett-Packard 5790A series gas chromatograph with gas injection system and flame ionization detector in conjunction with a Hewlett-Packard 3390A integrator. The column was 10' x 0.125", 10% β, β-oxydipropionitrile on chromosorp WHP at 60°C, with 5.5 mL/min N_2 flow. The kinetic runs were sampled at convenient intervals by removing small fractions of the pyrolysis mixture by expansion through a small section of the vacuum line into a gas storage bulb and diluting with argon. This sample bulb was removed and used to make multiple GC injections through a gas sampling valve. Baseline resolution of peaks was observed. Each point in the rate constant plots were the average of at least 3 GC runs. The rate constant plots contained 6 to 9 points and were derived by a linear least squares analysis of the experimental data. A preparative run showed 99% material balance by internal standard after 7.2 half-lives. A sample of the gaseous reaction mixture was taken directly from the thermolysis vessel without condensing and examined by GC/MS. Only C_6H_8 products, starting material, and internal standard could be detected. One preparative run was condensed directly into an NMR tube, which was then sealed at -196°C. The sample was maintained at -50°C or below until NMR analysis was complete. Only elimination products were observed. These were identified by their ^1H and ^{13}C NMR spectra.

ACKNOWLEDGEMENT

The authors acknowledge with thanks the support of this research in part by the National Science Foundation.

REFERENCES

1 W. R. Dolbier, Jr., Acc. Chem. Res., 14 (1981) 195.

2 W. R. Dolbier, Jr., K. S. Medinger, A. Greenberg, J. F. Liebman, Tetrahedron, 38 (1982) 2415.

3 W. R. Dolbier, Jr., C. R. Burkholder, Tetrahedron Lett., 24 (1983) 1217.

4 W. R. Roth, W. Kirmse, W. Hoffman, H.-W. Lennartz, Chem. Ber., 115 (1982) 2508.

5 W. R. Dolbier, Jr., S. F. Sellers, J. Am. Chem. Soc., 104 (1982) 2494.

6 R. J. Ellis, H. M. Frey, J. Chem. Soc., (1964) 5578.

7 W. R. Dolbier, Jr., S. F. Sellers, J. Org. Chem., 47 (1982) 1.

8 J. P. Daub, J. A. Berson, Tetrahedron Lett., 25 (1984) 4463, and references therein.

9 J. J. Gajewski, 'Hydrocarbon Thermal Isomerizations', Academic Press, (1981) 186.

10 W. R. Dolbier, Jr., A. C. Alty, O. Phanstiel, IV, J. Am. Chem. Soc., 109 (1987) 3046.

11 J. Nishimura, J. Furukawa, J. Chem. Soc., Chem. Commun., (1971) 1375.

12 J. Hine, R. Butterworth, P. B. Langford, J. Am. Chem. Soc., 80 (1958) 819.

13 C.R. Noler, in A.H. Blatt, (ed.), Organic Synth. Coll. Vol. II, Wiley, New York, (1943) 184.