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Journal of Fluorine Chemistry 126 (2005) 339–343
JOURNAL OF FLUORINE CHEMISTRY
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Competitive kinetic processes in the thermal rearrangement of 1,1-difluoro-2-(dideuteriomethylene)-cyclopropane

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Received 20 October 2004; received in revised form 8 December 2004; accepted 8 December 2004
Available online 11 January 2005

Abstract

The synthesis of 1,1-difluoro-2-(dideuteriomethylene)-cyclopropane is reported along with the kinetics of its competing, reversible, first order rearrangements: (a) the degenerate rearrangement to 1,1-difluoro-3,3-dideuterio-2-methylene-cyclopropane, and (b) its rearrangement to 2,2-dideuterio-1-(difluoromethylene)-cyclopropane. The observed experimental ratio of these two rate constants, 2.3, is consistent with Borden's theoretically predicted ratio of 3.

Keywords: Kinetics; Methylenecyclopropane; Fluorocyclopropanes; Deuterium labeling

1. Introduction

The thermal rearrangement of 1,1-difluoro-2-methylene-cyclopropane has been the subject of much interest and controversy ever since the first publication related to the thermodynamics and kinetics of the thermal equilibrium between isomers **1** and **2** in 1978 (Scheme 1) [1]. In that paper, two key facts were established. First, *gem*-difluoro substituents destabilize a cyclopropane by 1.9 kcal/mol more than they do a double bond, and secondly, the observed kinetic impact of the fluorine substituents on the activation energy of this rearrangement, which involves proximal bond cleavage (~3 kcal/mol), was *much less* than was their effect (~9.5 kcal/mol) on a rearrangement that involved distal bond homolysis, such as the geometric isomerization of 1,1-difluoro-2,3-dimethylcyclopropane [2].

The lack of regioselectivity observed in our later study of the rearrangement of 1,1-difluoro-2-vinyl-cyclopropane, **3** (Scheme 2) [3] demonstrated that there is, in fact, only a small difference in the energy required for homolytic cleavage of the distal and proximal bonds of the usual gem-difluorocyclopropane. Therefore, the observed *smaller* kinetic effect of the fluorine substituents in the methylenecyclopropane system remained an issue of concern. This issue along with others related to the impact of geminal fluorine substituents on the structure and energy of cyclopropane and those intermediates and transition states on its thermal energy surface were initially addressed by Getty et al. [4,5].

By 1999, there remained the most intriguing and difficult to explain aspects of the thermal rearrangements of **1**, which were (a) simply why the fluorines have so little effect on the rearrangement of **1**–**2**, and (b) why the degenerate (interchange of CH_2s) and structural rearrangements occur at such similar rates. The latter result was implied by our kinetic study of the thermal rearrangement of 1,1-difluoro-2-methyl-3-methylene-cyclopropane, **4** (Scheme 3) [6] which showed that the rate of formation of products **5** and **6** (analogous to the "degenerate" process) was only 1.9 times faster than formation of product **7**.

These issues were nicely rationalized in another paper by Borden and coworkers [7], in which it was concluded that "the strong preference of a CF_2 radical center for a pyramidal geometry raised the enthalpies of the transition structures for both the degenerate methylenecyclopropane rearrangement of **1** and for its non-degenerate rearrangement to **2**." This resulted in calculated activation energies

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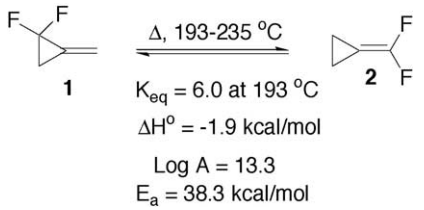
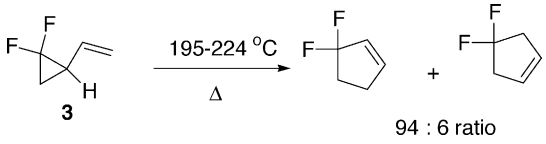
doi:10.1016/j.jfluchem.2004.12.004

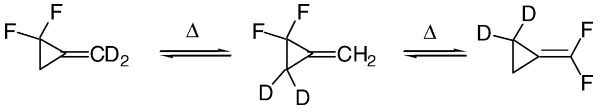


Scheme 1. Synthesis of 1,1-difluoro-2-(dideuteriomethylene)-cyclopropane.



Scheme 2.

for these processes that were, respectively, only 3.1 and 2.0 kcal/mol lower than that predicted for the degenerate rearrangement of the parent, non-fluorine-containing methylenecyclopropane. They predicted a ratio of degenerate versus non-degenerate rate constants of about 3 for the thermal rearrangement of **1**. In the present paper, we present the synthesis of the labeled compound, 1,1-difluoro-2-(dideuteriomethylene)-cyclopropane, **8**, which is required to test this prediction, along with the brief kinetic

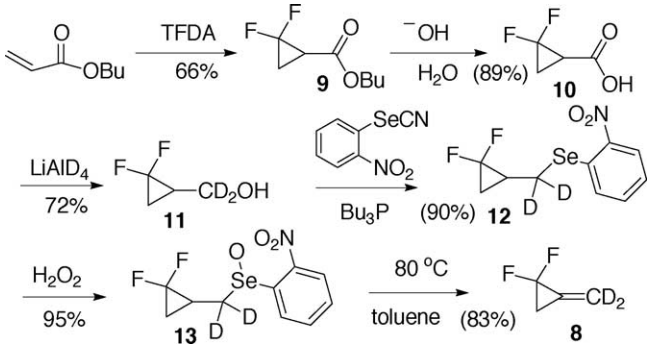


study of the thermal rearrangement of 8 at 180 °C that in fact confirmed the Borden prediction.

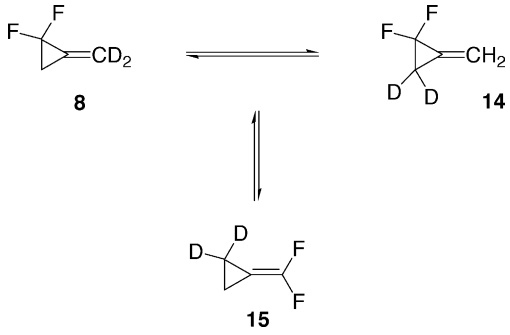
2. Results and discussion

2.1. Synthesis of 1,1-difluoro-2-(dideuteriomethylene)-cyclopropane

The synthesis of **8** is depicted in Scheme 4 below. This synthesis was made feasible by the recent discovery of the trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate (TFDA) difluorocarbene precursor that allowed the high yield addition of difluorocarbene to acrylate esters [8], thus affording us a source of the key 2,2-difluoro-cyclopropanecarboxylic acid butyl ester precursor, **9**.



Scheme 4.



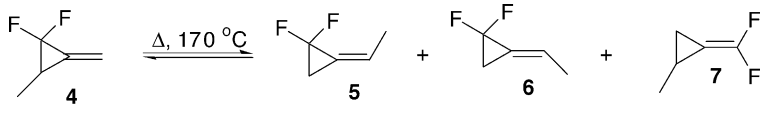
Scheme 5.

2.2. Kinetics

The thermal rearrangement of 1,1-difluoro-2-(dideuteriomethylene)-cyclopropane, **8** (Scheme 5) was carried out in

Table 1
Kinetic data

Kinetic point	Time (s)	Relative amount of each component (%)		
		8	**14**	**15**
1	16,200	75.6	11.9	12.5
2	19,800	72.5	15.5	12.0
3	23,400	67.8	19.3	12.9
4	30,600	56.1	23.4	20.6
5	34,200	58.2	20.6	21.3
6	41,400	50.3	22.7	27.0
7	45,000	49.3	24.3	26.3
8	48,600	46.1	25.0	28.3
9	52,200	45.3	25.6	29.1
10	55,800	42.5	27.2	30.3
11	63,000	40.0	27.1	32.9
12	66,600	35.7	25.6	38.6
13	70,200	34.7	27.9	37.4
14	81,000	31.1	26.4	42.4



Scheme 3.

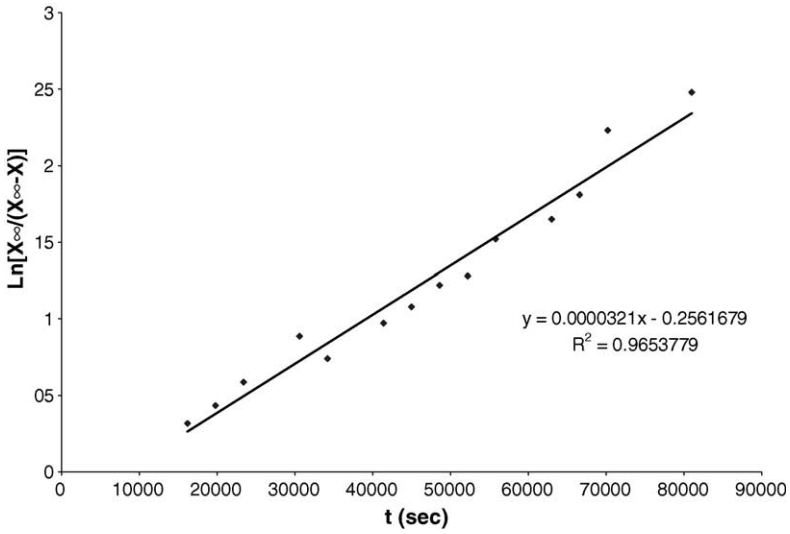


Fig. 1. Plot of kinetic data for the reversible rearrangement of **8**–**14**.

sealed NMR tubes that contained **8** dissolved in hexane. Individual tubes were immersed in an oil bath heated to $180 \pm 2\ ^{\circ}C$, and at designated times the tubes were removed, quickly cooled, and the ^{19}F NMR obtained. The tubes were then reinserted into the oil bath for an additional 30–60 min, after which the analysis procedure was repeated.

The three components in the mixture, **8**, **14** and **15**, were observable as signals appearing at 132.7, 133.0 and 88.0 ppm. The difference in chemical shifts between **8** and **14** is due to the non-extraordinary deuterium isotope effect on the ^{19}F chemical shift. The relative amounts of the three components were obtained by integration of these signals. The data obtained from these samplings are provided in Table 1 in Section 4. The kinetics for the two equilibria were each treated separately and plotted as reversible first order processes. The equation used was $\ln[X_\infty/(X_\infty - X)] = (k_1 + k_{-1})t$, and plots of the data are shown in Figs. 1 and 2. The equilibrium for $\mathbf{8} \leftrightharpoons \mathbf{14}$ is expected [9] to have a $K_{eq} = 1.0$, whereas that of $\mathbf{8} + \mathbf{14} \leftrightharpoons \mathbf{15}$ can be calculated from our earlier reported equilibrium data [1] to have a $K_{eq} = 6.5$.

The slopes of the plots in Figs. 1 and 2 provide the following values for $(k_1 + k_{-1})$: for $\mathbf{8} \leftrightharpoons \mathbf{14}$, 3.2 $(\pm 0.2) \times 10^{-5}\ s^{-1}$, and for $\mathbf{8} + \mathbf{14} \leftrightharpoons \mathbf{15}$, 8.2 $(\pm 0.4) \times 10^{-6}\ s^{-1}$ [10]. Knowing the values for K_{eq} for the two equilibria, values can then be readily calculated for k_1 in

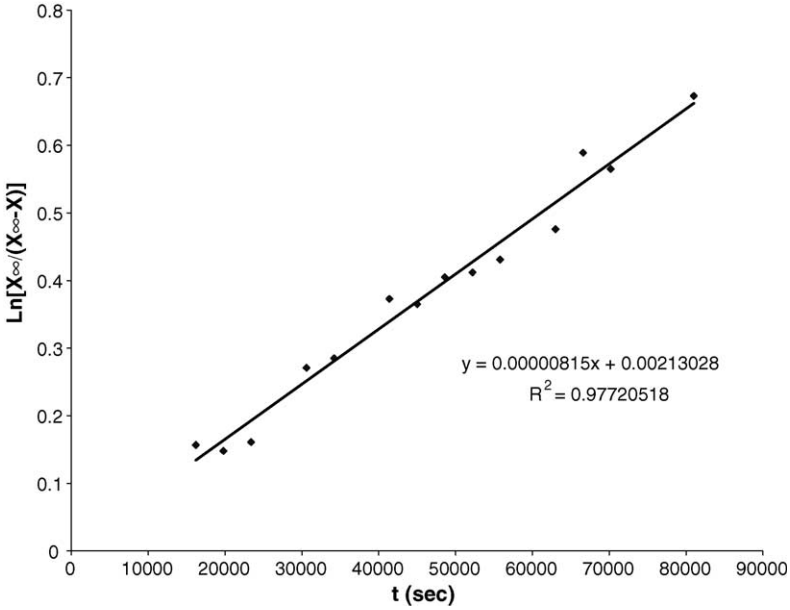


Fig. 2. Plot of kinetic data for the rearrangement of **8** and **14**–**15**.

each case. Those values are 1.6 ($\pm$0.2) $\times$ 10^{-5} s^{-1}, and 7.1 ($\pm$0.4) $\times$ 10^{-6} s^{-1}, respectively [10]. A measure of the reliability of the current kinetic data can be obtained by comparing the *latter* rate constant with that calculated from our earlier *gas phase* kinetic study with the undeuterated compound [1]. That calculated value for k_1 is 5.9 $\times$ 10^{-6} s^{-1} which is quite consistent with the obtained solution value.

3. Conclusion

The two rate constants give a ratio of 2.3, which can be compared with the predicted value of 3 published by Borden. This effective confirmation by our current experiments of the predicted ratio of rate constants for the two competing processes serves to provide excellent credibility to the kinetic model of the methylenecyclopropane energy surface that was described by Borden in the 1999 paper [7]. Thus, the final kinetic issue related to the effect of fluorine substituents on the thermal rearrangement of 1,1-difluoro-2-methylene-cyclopropane has seemingly been answered.

4. Experimental

4.1. General

^{1}H, and ^{13}C NMR spectra were determined at 300 MHz (^{1}H), 75 MHz (^{13}C) using $CDCl_3$ as solvent, unless otherwise mentioned, and tetramethylsilane as an internal standard; ^{19}F NMR spectra were measured on a Varian XL at 282 MHz, referenced to external $CFCl_3$ in $CDCl_3$. Tetrahydrofuran (THF) was distilled under nitrogen immediately before use from sodium/benzophenone. All other reagents and solvents were obtained from commercial sources and were used without additional purification.

4.2. 2,2-Difluorocyclopropanecarboxylic acid butyl ester, **9** [11]

A three-necked flask is charged with 100 mL of dry toluene, 0.20 g of sodium fluoride (0.06 eq.) and 10.0 g of *n*-butyl acrylate (0.078 mol). The solution is heated to reflux and slow N_2 bubbling is initiated with stirring for 1 h. Trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate (32.0 g, 0.128 mol, 1.6 eq.) is then added dropwise. The reaction mixture is refluxed for 8 h, and then cooled down to RT. Toluene is removed by simple distillation at atmospheric pressure, and the residue distilled at reduced pressure to obtain product, **9** (9.1 g, 66%) as a colorless liquid: bp 95–97 °C at 50 mm; ^{1}H NMR, δ 0.78–0.88 (m, 3H), 1.18–1.32 (m, 2H), 1.44–1.66 (m, 3H), 1.84–1.96 (m, 1H), 2.23–2.35 (m, 1H), 3.98–4.03 (m, 1H); ^{13}C NMR, δ 13.4 (m), 16.2 (m), 18.9, 25.5 (m), 30.4, 65.2, 110.6 (dd, J = 283.0 and 288.1 Hz), 166.5; ^{19}F NMR, δ −125.5 (dd, J = 152.6 and 12.2 Hz, 1H), −141.3 (dd, J = 152.6 and 12.2 Hz, 1F).

4.3. 2,2-Difluorocyclopropanecarboxylic acid, **10** [12]

2,2-Difluorocyclopropanecarboxylic acid butyl ester, **9** (3.56 g, 20.0 mmol), was added to a solution of NaOH (3.2 g, 80 mmol) in H_2O (50 mL). The reaction mixture was refluxed overnight. After removing all the solvents under vacuum, the white residue obtained was dissolved in some water. Then concentrated hydrochloric acid was added slowly until the pH was below 7. The mixture was then extracted with diethyl ether (30 mL $\times$ 5), and the organic layer dried with $MgSO_4$. After removing the solvent, 2,2-difluorocyclopropanecarboxylic acid, **10**, was obtained (2.17 g, 89%) as light yellow prisms: mp 60–62 °C (Lit. 61–62 °C); [12] ^{1}H NMR δ 1.67–1.82 (m, 1H), 1.94–2.08 (m, 1H), 2.31–2.44 (m, 1H), 11.75 (br s, 1H); ^{13}C NMR, δ 17.1 (m), 25.4 (dd, J = 13.1 and 12.1 Hz), 110.6 (dd, J = 283.5 and 289.1 Hz), 173.7; ^{19}F NMR, δ −125.7 (dm, J = 152.6 Hz, 1F), −140.7 (dm, J = 152.6 Hz, 1F).

4.4. Dideuterio-(2,2-difluorocyclopropyl)-methanol, **11**

Under N_2 atmosphere, to a solution of $LiAlD_4$ (18.0 mL, 1 M, 18.0 mmol) in ether, a solution of 2,2-difluorocyclopropanecarboxylic acid, **10** (2.44 g, 20.0 mmol) in fresh distilled ether (35 mL) was added slowly while cooling the flask with an ice-water bath. Then the reaction mixture was allowed to be warmed to RT and to react overnight. After the reaction was quenched slowly with water (40 mL), the mixture was poured into a saturated solution of sodium potassium tartrate (100 mL). The solution was extracted three times with ether, and the combined ether layers then washed with brine and dried with $MgSO_4$. After removing the ether, dideuterio-(2,2-difluorocyclopropyl)-methanol, **11**, was obtained (1.58 g, 72%) as a colorless oil: ^{1}H NMR, δ 0.98–1.14 (m, 1H), 1.30–1.44 (m, 1H), 1.71–1.84 (m, 1H); ^{13}C NMR, δ 14.1 (t, J = 11.1 Hz), 23.8 (t, J = 11.1 Hz), 58.6 (m), 113.8 (t, J = 282.5 Hz); ^{19}F NMR, δ −129.1 (dm, J = 164.8 Hz, 1F), −145.7 (dm, J = 164.8 Hz, 1F).

4.5. Dideuterio-(*o*-nitrophenylselenyl)methyl-2,2-difluorocyclopropane, **12**

Under N_2 atmosphere, to a solution of dideutero-(2,2-difluorocyclopropyl)-methanol, **11** (0.76 g, 6.9 mmol) and 2-nitrophenyl selenocyanate (1.92 g, 8.46 mmol) in dry THF (16 mL), was added Bu_3P (2.1 mL, 8.46 mmol) at RT. After the reaction mixture was stirred for 4 h at RT, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (hexanes/AcOEt: 14:1) to give dideutero-(*o*-nitrophenylselenyl)methyl-2,2-difluorcyclopropane, **12** (1.83 g, 90%) as a yellow solid: mp 43–45 °C; ^{1}H NMR, δ 1.11–1.22 (m, 1H), 1.53–1.66 (m, 1H), 1.82–1.95 (m, 1H), 7.31–7.38 (m, 1H), 7.47–7.58 (m, 2H), 8.29 (dd, J = 8.2 and 1.3 Hz, 1H); ^{13}C NMR, δ 17.6 (t, J = 11.1 Hz), 20.7 (t, J = 11.1 Hz), 22.0 (m), 113.8 (t,

J = 283.6 Hz), 125.8, 126.5, 128.8, 132.7, 133.8, 146.7; ^{19}F NMR, δ −128.0 (dm, J = 152.6 Hz, 1F), −144.0 (dm, J = 152.6 Hz, 1F); anal. calculated for $C_{10}H_7D_2F_2NO_2Se$: C, 40.84; H, 3.09; N, 4.76; found: C, 41.13; H, 3.01; N, 4.60.

4.6. Dideuterio-(*o*-nitrophenylselenoxy)methyl-2, 2-difluorocyclopropane, ***13***

Dideuterio-(*o*-nitrophenylselenyl)methyl-2,2-difluorocyclopropane, **12** (220 mg, 0.77 mmol) was treated with 30% H_2O_2 (0.6 mL, 5.3 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred overnight (monitoring by TLC), and the solvent was then removed under vacuum. To the residue was added CH_2Cl_2 and the solution washed with saturated $Na_2S_2O_3$ solution and water. The organic layer was dried with $MgSO_4$, and removed under vacuum. The product selenoxide, **13** (227 mg, 95%) was obtained as a yellow solid, diastereomeric mixture (ratio = 1.7:1): major isomer, ^{1}H NMR, δ 0.82–0.94 (m, 1H), 1.28–1.42 (m, 1H), 1.90–2.05 (m, 1H), 7.66–7.74 (m, 1H), 7.90–7.97 (m, 1H), 8.24–8.36 (m, 2H); ^{19}F NMR, δ −129.7 (dm, J = 152.6 Hz, 1F), −141.4 (dm, J = 152.6 Hz, 1F). Minor isomer, ^{1}H NMR, δ 1.02–1.14 (m, 1H), 1.46–1.59 (m, 1H), 1.90–2.05 (m, 1H), 7.66–7.74 (m, 1H), 7.90–7.97 (m, 1H), 8.24–8.36 (m, 2H); ^{19}F NMR, δ −129.4 (dm, J = 152.6 Hz, 1F), −142.4 (dm, J = 152.6 Hz, 1F).

4.7. 1,1-Difluoro-2-(dideuteriomethylene)-cyclopropane, ***8***

All glassware was oven-dried beforehand. A one-necked, 25 mL, round bottomed flask was equipped with a magnetic bar, a trap at −78 °C attaching to a bubbler. The flask was charged with selenoxide, **13** (420 mg, 1.3 mmol) in dry toluene (10 mL) while the temperature was maintained at 80 °C for 6 h (monitoring by TLC). Product **8** (100 mg, 83%) was collected as colorless liquid: ^{1}H NMR, δ 1.92–1.97 (m, 2H); ^{19}F NMR, δ −132.2 (m, 2F).

4.8. Kinetic procedure

Approximately 50 mg of 1,1-difluoro-2-(dideuteriomethylene)-cyclopropane, **8**, was added to an NMR tube that contained 1 mL of hexane. The tube was then cooled in a dry ice/acetone bath and sealed by a flame. The sealed tube containing **8** was immersed in an oil bath heated to 180 ± 2 °C, and at designated times removed, quickly cooled, and the ^{19}F NMR spectrum of the mixture obtained. The tube was then reinserted into the oil bath for an additional 30–60 min, after which the analysis procedure was repeated.

Each of the three components in the mixture, **8**, **14** and **15**, were observable as signals appearing at 132.7, 133.0 and 88.0 ppm, and their relative amounts obtained by integration of these signals. The times of sampling and the ratios of **8**, **14**, and **15** are given below in Table 1.

Acknowledgment

Support of summer researcher, Emilie Gautriaud, by an NSF-REU grant to the Chemistry Department is acknowledged with thanks, as is NSF support of the research program of WRD.

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