

## Experimental Study of the Stereomutation of 1,1-Difluoro-2-ethyl-3-methylcyclopropane Confirms the Predicted Preference for Disrotatory Ring Opening and Closure

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Numerous experiments with substituted cyclopropanes<sup>1</sup> have failed to confirm Hoffmann's 1968 prediction,<sup>2</sup> that cyclopropane should preferentially undergo stereomutation by coupled rotation of two methylene groups in a conrotatory fashion. Elegant experiments on cyclopropanes, containing deuterium as the only substituent, have led to conflicting results.<sup>3–5</sup>

Berson and co-workers found a strong preference for coupled rotation of two methylene groups in their study of the stereomutation of cyclopropane-1,2-d<sub>2</sub>.<sup>3,4</sup> In contrast, Baldwin and co-workers reported nearly equal rate constants for single and double methylene rotations in cyclopropane-1,2,3-d<sub>3</sub>.<sup>5</sup> Recent *ab initio* calculations of the potential surface for stereomutation of cyclopropane and vibrational analyses, performed at the stationary points on this surface, found that the computed isotope effects are incapable of reconciling the results of these two experiments.<sup>6,7</sup>

On the potential energy surfaces that were computed there is only ca. 1 kcal/mol difference between the energies of the transition state for conrotation and the transition states for both single methylene rotation and disrotation.<sup>6–8</sup> Moreover, the calculations found that alkyl substituents significantly reduce the already small preference predicted for conrotatory ring opening and ring closure.<sup>6</sup> These computational findings explain the failure of the experiments on substituted cyclopropanes to detect any significant preference for coupled conrotation.<sup>1</sup>

Transition-state theory, when applied to the potential surfaces computed for stereomutation of unsubstituted cyclopropane,

predicts that disrotatory ring opening should be followed, preferentially, by conrotatory ring closure, because the conrotatory transition state is the lower energy of the two transition states for ring closure. Since disrotatory ring opening, followed by conrotatory ring closure, has the same net effect as passage across the transition state for rotation of a single methylene group,<sup>6,9</sup> transition-state theory predicts nearly equal rate constants for double rotation and net single rotation.<sup>7</sup>

In contrast to transition state theory, very recent reaction dynamics calculations on similar potential energy surfaces for cyclopropane stereomutation predict a 3- to 5-fold preference for double rotation.<sup>10,11</sup> In the dynamical calculations, conservation of angular momentum tends to result in disrotatory ring opening being followed by disrotatory, rather than conrotatory, ring closure.<sup>11</sup> Thus, the dynamical calculations predict that disrotation makes a significant contribution to the coupled rotation that appears to dominate the stereomutation of cyclopropane-1,2-d<sub>2</sub>.<sup>3,4</sup>

Unfortunately, with deuterium as the only substituent, there is no way to distinguish experimentally between the contributions of con- and disrotation to the double rotation found in cyclopropane-1,2-d<sub>2</sub>.<sup>3,4</sup> The results of the reaction dynamics calculations caution against assuming that the observation of coupled rotation in this cyclopropane implies that the mode of coupling is necessarily the conrotation that was predicted by Hoffmann.<sup>2</sup>

*Ab initio* calculations find that the geminal fluorine substituents in 1,1-difluorocyclopropane should make its stereomutation very different from that of cyclopropane.<sup>12a,b</sup> 1,1-Difluorocyclopropane is predicted to show a *large* preference for stereomutation by *disrotation* of C(2) and C(3). This preference is predicted to be *enhanced*, not diminished,<sup>6</sup> by alkyl substituents. Finally, since the *s-trans,s-trans*-(0,0) conformation of 3,3-difluoropentane-2,4-diy is computed to be 3–4 kcal/mol lower in energy than the *s-cis,s-trans*-(0,0) conformation,<sup>12b,c</sup> the relative rates of coupled rotation in *cis*- and *trans*-1,1-difluoro-2,3-dialkylcyclopropanes via these two possible transition states are predicted to be useful for differentiating experimentally between con- and disrotation.

More specifically, an optically active *cis*-1,1-difluoro-2,3-dialkylcyclopropane is predicted to racemize much more rapidly than its *trans* stereoisomer. As shown in Scheme 1, the *cis*-cyclopropane can undergo disrotatory ring opening to the preferred *s-trans,s-trans* transition state for racemization, whereas disrotatory ring opening of the *trans*-cyclopropane gives the higher energy *s-cis,s-trans* conformation of the diradical. On the other hand, if conrotation were preferred, the *trans*-cyclopropane should racemize faster than the *cis* isomer.

In this communication we report experimental confirmation of the prediction<sup>12a–c</sup> that stereomutation of a 1,1-difluorocyclopropane should show a large preference for disrotatory ring opening and closure. We find that racemization of *cis*-1,1-difluoro-2-ethyl-3-methylcyclopropane (**1**) at 274.5 °C is more than 2 orders of magnitude faster than its epimerization to *trans*-1,1-difluoro-2-ethyl-3-methylcyclopropane (**2**).<sup>13</sup> In addition, we find at the same temperature that racemization of **1** is more than forty times faster than racemization of **2**, thus showing that the coupled rotation observed in **1** is, indeed, disrotation.

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(4) Experimental results on the stereomutation of cyclopropane-d<sub>2</sub>, very similar to those of Berson and co-workers,<sup>3</sup> have been reported (Cianciosi, S. J.; Raganathan, N.; Freedman, T. R.; Nafie, L. A.; Baldwin, J. E. *J. Am. Chem. Soc.* **1990**, 112, 8204). More recently, however, a statistical analysis has led Baldwin to conclude that one of the rate constants, measured by him and co-workers, contains too large an uncertainty to warrant any definitive conclusion being drawn about the ratio of double to single methylene rotations in the stereomutation of cyclopropane-d<sub>2</sub>. See: Baldwin, J. E. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1995; Vol. 2, Chapter 9.

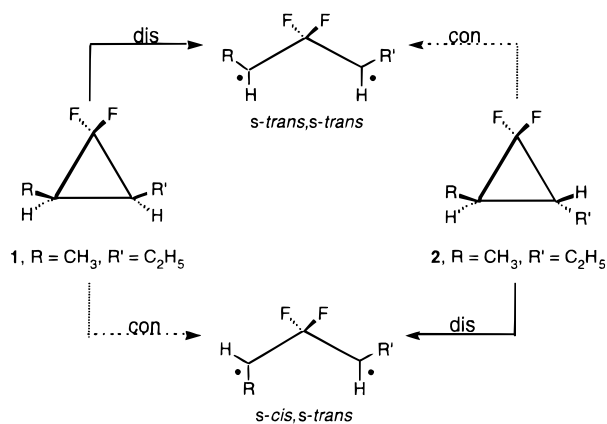
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(8) Reference 6 contains a complete list of calculations performed prior to 1992.

## Scheme 1



The kinetic studies of optically active **1** and **2**<sup>14</sup> were carried out in toluene solution.<sup>15</sup> Analyses were performed by GLC on a chiral polysiloxane cyclodextrin capillary column,<sup>16</sup> which gave four well-resolved peaks for racemic mixtures of **1** and **2**. Rate constants for racemization of optically active *cis*-cyclopropane (**1**) were obtained at five temperatures in the range 201.1–240.7 °C. An Arrhenius plot of the racemization data provided the following activation parameters:  $\log A = 13.3 \pm 0.9$  and  $E_a = 41.3 \pm 2.0$  kcal/mol. The energy of activation for racemization of **1** is  $8.4 \pm 2.1$  kcal/mol lower than that reported for epimerization of *cis*-1,1-difluoro-2,3-dimethylcyclopropane.<sup>17,18</sup>

The epimerization of **1** was examined at 274.5 °C: ( $k_{ct} + k_{ic}$ ) =  $(8.73 \pm 0.17) \times 10^{-6}$  s<sup>-1</sup>;  $K_{eq} = k_{ic}/k_{ct} = 0.41$ . The resulting values of  $k_{ct} = (6.20 \pm 0.12) \times 10^{-6}$  s<sup>-1</sup> and  $k_{ic} = (2.53 \pm 0.05) \times 10^{-6}$  s<sup>-1</sup> in toluene are in good agreement with the rate constants for epimerization of *cis*- and *trans*-1,1-difluoro-2,3-dimethylcyclopropanes in the gas phase at the same temperature.<sup>17,19</sup>

The activation parameters for the racemization of **1** can be used to extrapolate  $k_{rac}^1 = 7.03 \times 10^{-4}$  s<sup>-1</sup> at 274.5 °C. The factor by which coupled rotation in **1** is favored over the sum of all the processes that result in net single rotation<sup>20</sup> is, therefore,  $k_{rac}^1/k_{ct} = 107$  at 274.5 °C.

(13) Our experimental results on the stereomutations of fluorocarbons **1** and **2** contrast with the nearly equal rates of one- and two-center rotations found in the pyrolyses of the corresponding optically active hydrocarbons. Carter, W. L.; Bergman, R. G. *J. Am. Chem. Soc.* **1968**, *90*, 7344. Bergman, R. G.; Carter, W. L. *J. Am. Chem. Soc.* **1969**, *91*, 7411.

(14) Experimental procedures for the syntheses of **1** and **2** are available as Supporting Information.

(15) The enantiomeric excesses of the optically active cyclopropanes **1** and **2** which were used in the racemization studies were 30.2 and 66.1%, respectively, with the reactions being followed for approximately one half-life. The racemization rates were obtained by a plot of the experimental data according to the following kinetic expression:  $\ln(e_0/e) = 2k_{rac}t$ , the derivation of which can be found in the Supporting Information.

(16) Review: Schurig, V.; Nowotny, H.-P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 939. We are indebted to Professor Schurig for providing us with the column that was used in this study.

(17) Dolbier, W. R., Jr.; Enoch, H. O. *J. Am. Chem. Soc.* **1977**, *99*, 4532.

(18) Calculations which include dynamic electron correlation predict that the transition state for disrotatory ring opening and closure of *cis*-1,1-difluoro-2,3-dimethylcyclopropane is 6.6 kcal/mol lower in energy than the transition state for monorotation, 6.3 kcal/mol lower than the transition states for conrotation in both the *cis* and *trans* isomers, and 4.3 kcal/mol lower in energy than the transition state for disrotation in the *trans* isomer.<sup>12c</sup>

(19) The gas-phase rate constants for epimerization of *cis*- and *trans*-1,1-difluoro-2,3-dimethylcyclopropane at 274.5 °C, calculated from the 1977 Arrhenius data, are the following:  $k_{ct} = 7.4 \times 10^{-6}$  s<sup>-1</sup> and  $k_{ic} = 3.8 \times 10^{-6}$  s<sup>-1</sup>.<sup>17</sup>

(20) These processes are (a) monorotation of C-2 or C-3 upon breaking of the bond between these two carbons, (b) ring opening by one mode of coupled rotation and ring closure by the opposite mode,<sup>6,9</sup> and (c) rotation of C-2 or C-3 upon cleavage of the bond between C-1 and either of these carbons.

The rate constant for racemization of *trans*-cyclopropane (**2**) was measured at 274.5 °C:  $k_{rac}^2 = (1.66 \pm 0.02) \times 10^{-5}$  s<sup>-1</sup>. When combined with the value for  $k_{ic}$  obtained above, one obtains the ratio  $k_{rac}^2/k_{ic} = 6.6$ . Thus, even though disrotatory ring opening of *trans*-cyclopropane **2** must pass over the disfavored *s-cis,s-trans* transition state, coupled rotation in **2** at 274.5 °C is a factor of ca. 7 faster than the sum of all the processes that result in net single rotation.<sup>20</sup>

The ratio of the rate constants of racemization and epimerization is 16.2 times larger for **1** than for **2**, indicating that the transition state for racemization of **1** is substantially lower in energy than that for racemization of **2**. The free energies of activation ( $\Delta G^\ddagger$ ) for racemization of **1** and **2** at 274.5 °C can be calculated from their rate constants to be 40.7 and 44.8 kcal/mol, respectively, whereas  $\Delta G^\circ$  (**1** → **2**) can be calculated from the  $K_{eq}$  (0.41) to be -1.0 kcal/mol. Thus the difference between the free energies of formation of the transition states for racemization of **1** and **2** is 3.1 kcal/mol. This free energy difference is about the same size as the calculated energy difference between the transition states for coupled disrotation in *cis*- and *trans*-1,1-difluoro-2,3-dimethylcyclopropane.<sup>18</sup>

In summary, racemization of both **1** and **2** has been found to be much faster than any process that leads to epimerization.<sup>20,21</sup> Coupled rotation is preferred to single rotation by a factor of 107 for **1** and 6.6 for **2** at 274.5°. The finding that the ratio of racemization to epimerization is more than sixteen times larger for **1** than for **2** indicates that the transition state for racemization of the *cis* isomer is ca. 3 kcal/mol lower in energy than that for racemization of the *trans* isomer, thus demonstrating that the mode of coupled rotation that is preferred in **1** and **2** is disrotation, not conrotation.

**1** is the first cyclopropane in which a *very* large preference for coupled rotation has been found and for which the mode of coupling has been identified. The experimental results reported here amply confirm the theoretical predictions<sup>12a-c</sup> that disrotation is strongly favored over both conrotation and monorotation in the stereomutation of 1,1-difluorocyclopropane and that this preference survives the presence of alkyl groups at C-2 and C-3.<sup>22</sup>

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**Supporting Information Available:** Experimental procedures for the syntheses of optically active **1** and **2**, spectral and analytical data for these cyclopropanes and for the intermediates (**4**–**14**) in the preparation of **1** and **2** from **3**, and procedures for and kinetic data from the pyrolyses of **1** and **2** (30 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(21) It has recently been found [Roth, W. R.; Wasser, T.; Boenke, M. *Liebigs Ann./Recueil* **1997**, 1323] that the energies of activation for racemization and epimerization of optically active *trans*-1,1-difluoro-2,3-diphenylcyclopropane are identical within experimental error and that a diradical intermediate can be trapped by oxygen. It was also claimed that disrotatory closure of the diradical is preferred.

(22) Another theoretical prediction<sup>12</sup>—that geminal fluorines at C-2 stabilize the lowest singlet state of both trimethylene and cyclopentane-1,3-diyl electronically, relative to the triplet state, and thermodynamically, toward ring closure—has also received strong support from the results of recent experiments [Adam, W.; Borden, W. T.; Burda, C.; Foster, H.; Heidenfelder, T.; Heubes, M.; Hrovat, D. A.; F. Kita, F.; Lewis, S. B.; Scheutzw, D.; Wirz, J. *J. Am. Chem. Soc.* **1998**, *120*, 593].