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Rate Constant for the Ring Opening of the 2,2-Difluorocyclopropylcarbinyl Radical

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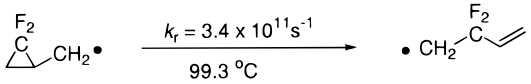
ABSTRACT

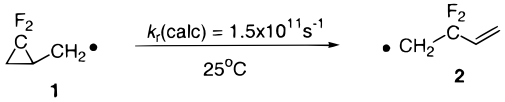


The rate constant for the unimolecular ring opening of the 2,2-difluorocyclopropylcarbinyl radical was determined via its competitive bimolecular trapping by TEMPO. The value of this rate constant (3.4×10^{11} s^{-1} at 99.3 °C) is about 500 times larger than that of the parent, unfluorinated radical and about 5 times smaller than that of the *trans*-2-phenylcyclopropylcarbinyl radical.

The experimental determination of rate constants of unimolecular rearrangements of radicals, so-called "radical clocks", has been an area of significant research interest for the past 20 years.[1] The cyclopropylcarbinyl to allylcarbinyl radical rearrangement[2] has attracted particular attention in recent years because its family of derivatives provides ultrafast mechanistic probes of radical intermediacy and lifetime,[3] with rate constants ranging from 1.2×10^8 s^{-1} for the parent to 3×10^{11} s^{-1} for the 2-phenylcyclopropylcarbinyl radical.[4]

The 2,2-difluorocyclopropylcarbinyl radical, **1**, also undergoes an extraordinarily fast and regiospecific unimolecular ring opening distal to the geminal fluorine substituents to form the 2,2-difluoro-3-butenyl radical, **2** (Scheme 1).

Scheme 1



Although experimental calibration of this process has not been accomplished until now, using computed activation parameters for this rearrangement ($\Delta H^{\ddagger} = 1.6$ kcal/mol; $\Delta S^{\ddagger} = -2$ cal/deg), a rate constant of 1.5×10^{11} s^{-1} for this ring opening at 25 °C has been calculated.[5] Previous attempts to measure this rate constant experimentally, using neat *n*-Bu_3SnH[6] and PhSeH[7] as H-transfer radical traps, led to no observable amount of non-ring-opened products in either case, and therefore such results only provided measures of the *minimum* rate constant ($>10^8$ s^{-1} and $>3 \times 10^{10}$ s^{-1}, respectively).

Nitroxyl radicals, such as 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO),[8] are very efficient radical traps that, because of their large rate constant for trapping ($k_T = 1.2 \times 10^9$ M^{-1} s^{-1} at 25 °C)[8,9] and because of one's ability to detect very low concentrations of their products of radical trapping (by HPLC/ESI−MS), provided us with perhaps our last opportunity to observe an operational bimolecular competition involving the trapping of **1** in competition with its ring opening to **2** (Scheme 2).

On the basis of earlier work by Beckwith dealing with competitive nitroxyl radical trapping,[10] *tert*-butyl perester **5**

(1) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.
(2) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275.
(3) Nonhebel, D. C. *Chem. Soc. Rev.* **1993**, 347−359.
(4) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. J. *J. Am. Chem. Soc.* **1992**, *114*, 10915.
(5) Tian, F.; Bartberger, M. D.; Dolbier, W. R., Jr. *J. Org. Chem.* **1999**, *64*, 540.
(6) Dolbier, W. R., Jr.; Sellers, S. F. *J. Am. Chem. Soc.* **1982**, *104*, 2494.
(7) Tian, F. Ph.D. Dissertation, University of Florida, Gainesville, FL, 1999.
(8) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 1629.
(9) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1988**, *53*, 1632.
(10) Beckwith, A. L. J.; Bowry, V. W. *J. Am. Chem. Soc.* **1994**, *116*, 2710.

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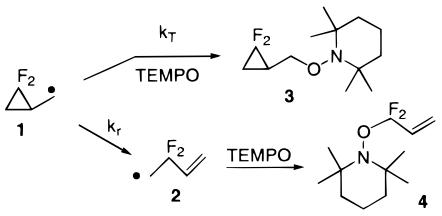
Scheme 2

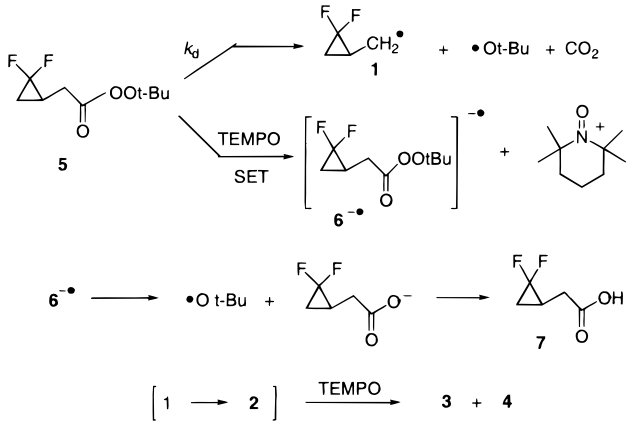


$$[\mathbf{3}]/[\mathbf{4}] = [\text{TEMPO}]\,(k_T/k_r)) \qquad \text{eq (1)}$$

appeared to be the precursor of choice for this competition study of **1** → **2**. Perester **5**[11] was synthesized readily from 3-butenyl benzoate via a novel difluorocyclopropanation procedure[12] followed by standard hydrolytic, oxidative, and functionalization methodologies. When heated to 99.3 °C in cyclohexane, in the *absence* of TEMPO, **5** underwent smooth, first-order decomposition to give a product mixture that, by ^{19}F analysis, consisted only of ring-opened products.[13] The mechanism of the thermal decomposition of peresters (RCO_3-*t*Bu), in cases where R is a primary alkyl group, is likely a two-step process involving reversible O−O bond homolysis, followed by loss of CO_2 by the $RCO_2^{\bullet}$ radical to form $R^{\bullet}$.[14,15] The fact that the rate constant for decomposition of perester **5** ($k_d = 2.1\ (\pm\ 0.2) \times 10^{-5}\ s^{-1}$) is only 5.5 times larger than that of *tert*-butyl peracetate[16] is consistent with the 2,2-difluorocyclopropylcarbinyl radical not being a significantly stabilized radical, relative to a simple primary system.

A 0.01 M solution of **5** in cyclohexane, containing a large excess (0.6 M) of TEMPO, was observed to decompose with enhanced rate,[17] and two products could be detected by ^{19}F NMR, the ring-opened, TEMPO-trapped product **4** and the ring-closed carboxylic acid **7** (ratios of **7**:**4** = 2.3 and 3.5 for 0.6 and 1.0 M TEMPO, respectively) (Scheme 3).

Scheme 3



Carboxylic acid product **7** appears to have been formed via the previously reported polar mechanism involving electron transfer from TEMPO,[18] a bimolecular, TEMPO-induced process that competes favorably with the desired unimolecular homolytic decomposition process of **5**.

Although the intervention of this polar process lowers the yield for the desired homolytic process, it should not affect the diagnostic efficacy of the kinetically controlled ratio of trapped products **3** and **4**, which would derive strictly from the homolytic process. Indeed, careful HPLC/ESI−MS analysis of the aforementioned product mixture indicated the presence of two products (ratio, ∼100:1) that had a molecular weight consistent with their deriving from TEMPO trapping of the radical species **1** and **2**. To unambiguously identify the minor (presumably non-ring-opened) product, **3** along with presumed major product **4** were synthesized by alternative routes, the products were fully characterized,[11] and mixtures of the two authentic materials were subjected to HPLC/ESI−MS analysis. Their retention times were coincident with and their mass spectra were identical in all ways with those of the two products from the TEMPO trapping experiments of **5**. Therefore, it appears that a successful competitive trapping of **1** prior to its ring opening to **2** has occurred.

To relate the experimental total ion count integration of **3** and **4** to their relative concentrations, it was necessary to determine their relative sensitivities to the analytical method. A relative response coefficient for **3** versus **4** of 0.71 ± 0.10 was obtained using pure samples of **2** and **3** under analytical conditions that approximated those used in the competition study.[19] The actual competition study was carried out by decomposing perester **5** (0.012 M in cyclohexane) at 99.3 °C in the presence of varying concentrations of TEMPO (0.5−1.1 M) and observing the ratio of products **3** and **4** (as measured by HPLC/ESI−MS) as a function of TEMPO concentration.[20] The obtained ratios of **3**:**4**, after correction by the response coefficient, ranged from 0.0069 at 0.5 M TEMPO to 0.0139 at 1.1 M TEMPO. A plot of these ratios versus [TEMPO] yielded a slope of $1.2 \pm 0.2 \times 10^{-2}$ ($r^2 = 0.945$), which according to eq 1 (Scheme 2) is equal to the ratio of k_T/k_r.

Beckwith's determined activation parameters[9] for k_T [log $k_T = 9.7 - 0.9\theta$] allow one to calculate the rate constant k_T

(11) Products are fully characterized by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy and by HRMS and/or elemental analysis.

(12) Tian, F.; Kruger, V.; Bautista, O.; Duan, J.-X.; Li, A.-R.; Dolbier, W. R., Jr.; Chen, Q.-Y. *Org. Lett.* **2000**, *2*, 563−4.

(13) Ring-opened and non-ring-opened products are readily distinguished by their distinctive ^{19}F NMR signals: the former always appears as a single fluorine signal, whereas the latter always appears as an AB pattern (two fluorine signals).

(14) Koenig, T.; Huntington, J.; Cruthoff *J. Am. Chem. Soc.* **1970**, *92*, 5413.

(15) Neuman, R. C.; Behar, J. V. *J. Am. Chem. Soc.* **1969**, *91*, 6024.

(16) Bartlett, P. D.; Hiatt, R. R. *J. Am. Chem. Soc.* **1958**, *68*, 1398.

(17) The overall rates of decomposition of **5** were found to be dependent on [TEMPO], with pseudo-first-order $k_{obs} = 4.0$ and $4.9 \times 10^{-5}\ s^{-1}$ for [TEMPO] = 0.6 and 1.0 M, respectively.

(18) Moad, G.; Rizzardo, E.; Solomon, D. H. *Tetrahedron Lett.* **1981**, *22*, 1165.

(19) Obtained by comparing ratios of experimental integrations of total ion current for the respective products from the kinetic experiments with the ratios for samples containing the two products in authentic ratios between 1:1 to 1:300, where the concentrations (total ion current) of the larger component, **4**, always approximated those in the kinetic study.

(20) To minimize chromatographic ambiguities by largely quenching the *t*-BuO• radicals, 5 vol % of 1,4-cyclohexadiene was added to the mixture.

at 99.3 °C to be 1.5×10^9 M^{-1} s^{-1}, which yields the value of 1.3×10^{11} s^{-1} for rate constant k_r.[21] This value of k_r is consistent with that (3.4×10^{11} s^{-1} at 99.3 °C) calculated from the earlier-mentioned computed activation parameters for the rearrangement of **1** to **2**, which were derived using conventional transition state theory at the UB3LYP/6-311+G(2df,2p)//UB3LYP/6-31G(d) level of theory.[5] Rate constant k_r should exhibit little temperature dependence, and assuming the preexponential factor of the computed parameters, a value of 6×10^{10} s^{-1} can be considered valid for k_r at room temperature.

Thus, a careful kinetic study involving competitive bimolecular trapping of the 2,2-difluorocyclopropylcarbinyl radical by TEMPO in competition with its unimolecular rearrangement to the 2,2-difluoro-3-butenyl radical has resulted in the first determination of the rate constant for this rearrangement, the value of which is about 500 times larger than that of cyclopropylcarbinyl itself and 5 times smaller than that of the 2-phenylcyclopropylcarbinyl radical. Considering its modest steric demand, this radical clock should prove a useful addition to the growing list of ultrafast radical clocks that can be used to probe the mechanisms of reactions that potentially involve radical intermediates. As noted in our earlier communication, this probe is also capable of clearly distinguishing between radical and carbocation intermediates because of their distinctive ring-opening regiochemistries.[22] Moreover neither radical nor carbocation formation receives significant kinetic preference as a result of the presence of this probe. Therefore, the 2,2-difluorocyclopropylcarbinyl system, now calibrated, should be an ideal mechanistic probe of radical or carbocation intermediacy.

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Supporting Information Available: Full details regarding the synthesis and characterization of products **3**−**5**, procedures for kinetic experiments, and tables of kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) This value has a 2σ error of 0.2 that does not take into account the error in Beckwith's data (not provided).

(22) Tian, F.; Battiste, M. A.; Dolbier, W. R., Jr. *Org. Lett.* **1999**, *1*, 193−196.