Transition State Polarization Effects and Steric Effects in the Kinetics of Alkoxycarbonyl-Substituted Radical Fragmentations

Martin Newcomb,* John H. Horner, and Calvin J. Emanuel

Department of Chemistry, Wayne State University
Detroit, Michigan 48202

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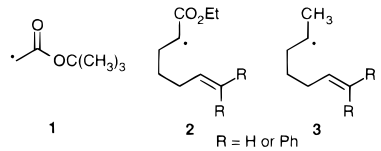
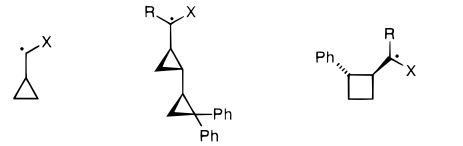
The kinetic effects of substituents on radical reactions have been studied for years and remain a topic of interest. The rates of radical additions to substituted alkenes are influenced both by the enthalpies of the reactions and, importantly, by polarization in the transition states, but there exists a natural tendency to associate kinetic effects solely with enthalpy changes of the reactions or with the stabilities of the radical products as judged by bond dissociation energies. An intuitive approach based on radical stabilities would correctly anticipate the kinetics of reactions that *form* ester-substituted radicals, but it can result in erroneous kinetic predictions about reactions *of* ester-substituted radicals. For example, in a seemingly counterintuitive manner, additions of the (*tert*-butoxycarbonyl)methyl radical (**1**) to simple alkenes[1] are faster than additions of the methyl radical to the same alkenes,[2] and cyclizations of ethoxycarbonyl-substituted radicals **2** are faster than cyclizations of their alkyl radical counterparts **3**.[3]



Fragmentations of alkoxycarbonyl-substituted radicals, the reverse of radical additions to acrylates, represent a class of reactions for which a counterintuitive kinetic effect is clearly predicted. The activation barriers for additions to acrylates of weakly nucleophilic radicals such as methyl, cyclohexyl, and benzyl are 2−4 kcal/mol smaller than those for additions to alkenes,[2,4] but the enthalpies of radical additions to acrylates are only 1.5−2 kcal/mol more exothermic than those for additions to alkenes.[5] It follows that, for the reverse reactions, an ester-substituted radical should fragment with a rate similar to or faster than that of an analogous alkyl radical. Nevertheless, in the only kinetic study of such a fragmentation of which we are aware, Beckwith and Bowry[6] reported that ring opening of the ester-substituted radical **4a** at ambient temperature is about two orders of magnitude *less rapid* than ring opening of the alkyl radicals **4b** and **4c** on the basis of competition kinetic studies of the fragmentation versus nitroxyl radical trapping. We report here direct laser flash photolysis (LFP) kinetic studies of fragmentations of ethoxycarbonyl-substituted radicals. We find that secondary ethoxycarbonyl-substituted radicals fragment as fast or faster than their alkyl radical analogs and that a tertiary ethoxycarbonyl-substituted radical fragments somewhat less rapidly than its alkyl radical counterpart. The results highlight the importance of transition state polarization[7] and the energy demands for deformation of conjugated radical centers.



4a: X = CO_2CMe_3
b: X = CH_3
c: X = H

5a: R = X = H
b: R = Me, X = H
c: R = X = Me
d: R = H, X = CO_2Et
e: R = Me, X = CO_2Et

6a: R = X = H
b: R = Me, X = H
c: R = X = Me
d: R = H, X = CO_2Et

Two families of radicals were studied, cyclopropylcarbinyl radicals **5** and cyclobutylcarbinyl radicals **6**. The cyclopropylcarbinyl radicals **5** incorporate the "reporter group"[8] approach that permits LFP studies of radicals that do not otherwise contain a useful chromophore. Following the initial fragmentations of radicals **5**, very fast ring opening[9] of the second cyclopropane gives diphenylalkyl radicals that are readily detected. Radicals **5** and **6** were produced by 355 nm laser photolyses of the corresponding PTOC[10] ester precursors,[11] and the formation of the diphenylalkyl and benzylic radical products, respectively, was monitored.[13]

The very fast ring openings of radicals **5** were studied in THF at low temperatures due to the kinetic limitations imposed by the nanosecond laser and photomultiplier tubes. Arrhenius functions for the ring opening reactions are collected in Table 1, and those for the ester-substituted radicals **5d** and **5e** are shown graphically in Figure 1. The relatively large errors in the Arrhenius functions for **5a** and **5d** resulted from the fact that these radicals reacted so fast that we could only study them over a narrow temperature range (−40 to −10 °C) and not from lack of precision in the individual kinetic values (see Figure 1). Ring openings of the primary, secondary, and tertiary radicals (**5a**−**5c**) at room temperature are about 5−6 times faster than those of the parent systems (cyclopropylcarbinyl, etc.)[14] due to slightly reduced energies of activation for radicals **5** in comparison to those of the parent systems. Minor kinetic effects of the reporter groups were previously noted.[8] The secondary ethoxycarbonyl-substituted radical **5d** fragments faster than the isostructural methyl-substituted radical **5b**, but the tertiary ethoxycarbonyl-substituted radical **5e** fragments less rapidly than the corresponding tertiary alkyl radical **5c**.

The fast fragmentation of the secondary ester-substituted radical **5d** must result from transition state polarization effects because ring openings of the alkyl radicals **5a**−**c** are more

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(8) Newcomb, M.; Tanaka, N.; Bouvier, A.; Tronche, C.; Horner, J. H.; Musa, O. M.; Martinez, F. N. *J. Am. Chem. Soc.* **1996**, *118*, 8505−8506.
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(10) PTOC is an acronym for pyridine-2-thione-*N*-oxycarbonyl. PTOC esters were invented by Barton for synthetic applications, see: Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901−3924.
(11) All precursors for radicals **5** were derived from (1*R**,2*S**,1′*S**)-*N*-methyl-*N*-methoxy-2-(2′,2′-diphenylcyclopropyl)cyclopropanecarboxamide, which was diastereomerically pure and for which an X-ray crystal structure was obtained. The precursors for radicals **6** were prepared from *trans*-2-phenylcyclobutanecarboxylic acid.[12] Details of the syntheses of the radical precursors will be reported. The referees were provided with NMR and mass spectral data for the carboxylic acids that were the immediate precursors of the unstable PTOC esters used in the LFP studies.
(12) Beard, C.; Burger, A. *J. Org. Chem.* **1961**, *26*, 2335−2339.
(13) The experimental design for the LFP studies was conventional. Details will be reported later.
(14) (a) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275−277. (b) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687−5698. (c) Engel, P. S.; He, S.-L.; Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1997**, *62*, 1210−1214.

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Table 1. Arrhenius Parameters and Rate Constants for Fragmentations of Radicals **5** and **6** in THF[a]

radical[b]	log *A*	E_a (kcal/mol)	$10^{-6}k_0$[c] (s^{-1})
5a (H, H)	12.9 ± 0.3	5.75 ± 0.34	200
5b (Me,H)	12.72 ± 0.12	6.10 ± 0.15	70
5c (Me, Me)	13.10 ± 0.16	6.86 ± 0.19	40
5d (H, CO_2Et)	13.6 ± 0.5	6.7 ± 0.6	170
5e (Me, CO_2Et)	12.88 ± 0.11	7.46 ± 0.13	8
6a (H, H)	13.1 ± 0.3	8.0 ± 0.4	4.9
6b (Me, H)	12.1 ± 0.6	6.8 ± 0.9	4.5
6c (Me, Me)	11.9 ± 0.5	6.6 ± 0.7	4.1
6d (H, CO_2Et)	(12.5)[d]	(7.8)[d]	(2)[d]

[a] Listed uncertainties are at 2σ. [b] The R and X groups at the radical center are given in parentheses. [c] Rate constants at 0 °C calculated from the Arrhenius functions. [d] Arrhenius parameters for **6d** were estimated from the observed rate constants at 19.1 and 10.7 °C and an assumed log $A = 12.5$.

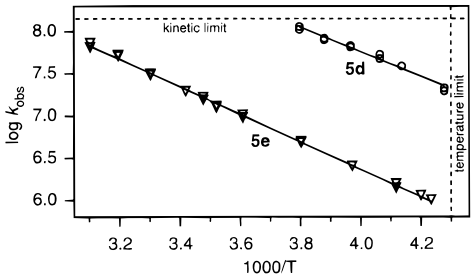

Figure 1. Kinetics of fragmentations of ethoxycarbonyl-substituted radicals **5d** and **5e**. The solid lines are for the Arrhenius functions in Table 1. The upper kinetic limit of the nanosecond laser unit and the lower temperature limit of the system are shown as dashed lines.

Table 2. Solvent Effects on the Kinetics of Radical Fragmentations[a]

radical[b]	THF	CH_3CN	temp (°C)[c]
5a (H, H)	43	43	−33.3
5b (Me, H)	15	16	−31.2
5d (H, CO_2Et)	38	52	−31.6
5e (Me, CO_2Et)	19	24	19.5
6b (Me, H)	7.1	7.5	16.0
6d (H, CO_2Et)	5	8	19.1

[a] The values listed are $10^{-6}k_{obs}$ in units of s^{-1}. [b] The R and X groups at the radical center are given in parentheses. [c] Average temperatures for the two solvents differed by <0.3 °C.

exothermic processes. Transition state polarization in this reaction was further indicated by the observation that the ring opening of **5d** exhibited a kinetic solvent effect not found for the alkyl radicals **5a** and **5b** (Table 2).

The reduced rate of ring opening of the tertiary ester-substituted radical **5e** resulted from an increased energy of activation for fragmentation in comparison to those for other radicals **5**. The kinetics of the reaction displayed a minor solvent effect (Table 2), indicating that the transition state is polarized, and on the basis of this solvent effect and the fact that **5d** fragments rapidly, we believe it is highly unlikely that the reduced rate of ring opening of **5e** is due to the inherent stability of the radical. We speculate that the origin of the kinetic retardation is steric and that it is related to an enforced planarity of the radical center in **5e**. Figure 2 shows a possible transition structure for ring opening of a tertiary cyclopropylcarbinyl radical based on the computed transition state for ring opening of the parent cyclopropylcarbinyl radical;[15] an eclipsing interaction of one group at the radical center with the cyclopropyl ring is apparent. In the case of the tertiary alkyl radical such as **5c**, the radical center might pyramidalize and reduce steric compression, but a similar pyramidalization of radical **5e** would be accompanied by an energy penalty due to loss of resonance stabilization.[16] We suggest, then, that the enforced planarity at the radical center in **5e** results in increased steric compression as the radical rotates into an optimal alignment for fragmentation.

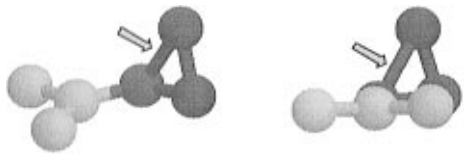

Figure 2. Two views of a possible transition structure for ring opening of the dimethylcyclopropylmethyl radical. The breaking bond of the cyclopropyl ring is indicated with an arrow. The structure was created from the QCISD/6-31G* optimized transition state for ring opening of the cyclopropylcarbinyl radical reported in ref 15, which served as a template, by replacement of the hydrogens at the radical center with methyl groups.

The kinetics of ring openings of cyclobutylcarbinyl radicals have not been studied extensively. Fragmentations of the *trans*-2-phenylcyclobutylcarbinyl radicals **6** displayed kinetic behavior similar to that observed for radicals **5** (Table 1). Studies of the secondary ester-substituted radical **6d** were limited due to the extreme instability of the radical precursor, and Arrhenius parameters for ring opening of this radical in THF were estimated from the kinetic data we could obtain and the log *A* values measured for the other members of this family. The ethoxycarbonyl-substituted radical **6d** fragmented[16] slightly less rapidly than the methyl-substituted counterpart **6b** in THF, but the rate constants for the two were about the same in acetonitrile (Table 2). A noteworthy point regarding the fragmentations of radicals **6** is that the product benzylic radicals are considered to be weakly nucleophilic, but the kinetics for the series of radicals **6** and the observed solvent effect for **6d** (Table 2) clearly suggest polar transition state effects in the ring opening of the ester-substituted radical.

The fast rates of fragmentations of ester-substituted radicals have ramifications for both synthetic and mechanistic work. In regard to syntheses with radicals, one should be aware of the possibility that equilibration of an acrylate adduct via fragmentation could occur with consequences regarding the stereoselectivity of a reaction. In mechanistic studies, fast ring openings of cyclopropylcarbinyl radicals have been employed in the design of probes for tests for radical intermediates in a number of reactions. In applications of alkyl cyclopropylacetate probes for putative alkoxycarbonyl-substituted radical intermediates,[18] one should assume that the ring opening rate constants are comparable to those of cyclopropylcarbinyl radical analogs, a collection of radicals for which a considerable amount of kinetic information is available.

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