grateful to Dr. Verlan van Rheenan of the Upjohn Co. for a generous gift of bisnorcholenaldehyde. Dr. David Pensak of Du Pont graciously cooperated in carrying out the molecular mechanics calculations.

Registry No. A-**1**, 128-08-5; A-**2a**, 66145-20-8; A-**2b**, 34817-42-0; A-**3**, 15481-39-7; A-**4**, 20244-61-5; A-**5**, 18086-96-9; **6**, 17414-02-7; **7a**, 37053-16-0; **7b**, 4922-47-8; **7c**, 52113-72-1; (E)-**7d**, 85894-83-3; (*Z*)-**7d**, 85894-84-4; A-**7**, 7789-45-9; **8**, 67957-91-9; **9**, 85894-85-5; **10a**, 71624-75-4; **10b**, 85894-86-6; **11**, 64740-99-4; **12**, 85894-87-7; **13**, 85894-88-8; **14**, 67150-82-7; **15**, 33689-61-1; **16**, 64741-13-5; **18a**, 60466-70-8; **18b**, 85894-89-9; **19**, 85894-90-2; **20**, 85894-91-3; **22**, 85894-92-4; **23**, 85894-93-5; **24**, 85894-94-6; **25**, 85894-95-7; **26**, 85894-96-8; **27**, 85894-97-9; **28**, 85894-98-0; **29**, 85894-99-1; **30**, 85895-00-7; **31**, 85895-01-8; *cis*-**32**, 85895-02-9; *trans*-**32**, 85895-03-0; **33**, 85895-04-1; **34**, 85895-05-2; **35**, 85895-06-3; (*E*)-**36**, 85895-07-4; (*Z*)-**36**, 85895-08-5; **38**, 85895-09-6; **43**, 85895-10-9; **44**, 85894-85-5; **45**, 71634-05-4; **46**, 85895-11-0; (*E*)-**47**, 85895-12-1; (*Z*)-**47**, 85895-13-2; **48**, 85895-14-3; **49**, 85895-15-4; **50**, 85895-16-5; **51**, 85895-17-6; **52**, 85895-18-7; **53**, 85895-19-8; **54**, 85895-20-1; **55**, 85895-21-2; **56**, 85895-22-3; (*E*)-**57**, 84098-64-6; (±)-**59**, 18681-09-9; **62**, 6090-09-1; **63**, 85895-23-4; **64**, 85895-24-5; (±)-**65**, 4891-79-6; **66**, 3986-89-8; **67**, 85895-25-6; **68**, 85895-28-9; **69**, 85895-29-0; **70**, 85895-30-3; **73**, 85895-32-5; 3-methyl-2-butanone, 563-80-4; thiophenol, 108-98-5; 1,1-bis(phenylthio)cyclohexane, 37457-08-2; cyclohexanone, 108-94-1; 4-*tert*-butyl-1,1-bis(*p*-methoxyphenylthio)cyclohexane, 85895-33-6; 4-*tert*-butylcyclohexanone, 98-53-3; *p*-methoxythiophenol, 696-63-9; **66** C-(22)-alcohol derivative, 40736-33-2; **67** mesylate, 85895-26-7; **67** iodide derivative, 85895-27-8; **70** C(22)-phenylsulfonyl derivative, 85895-31-4; cyclopentanone, 120-92-3; 1,1-bis(phenylthio)cyclopentane, 85895-34-7; cyclooctanone, 502-49-8; 1,1-bis(phenylthio)cyclooctane, 85895-35-8; cyclododecanone, 830-13-7; 1,1-bis(phenylthio)cyclododecane, 85895-36-9; 6-methoxy-2-tetralone, 2472-22-2; diphenyl(1-(phenylthio)ethyl)-phosphine oxide, 66164-48-5; 3-pentanone, 96-22-0; 2-methylcyclohexanone tosylhydrazone, 52826-41-2; diphenyl disulfide, 882-33-7; methyl acrylate, 96-33-3; methyl vinyl ketone, 78-94-4; phenyl vinyl sulfide, 1822-73-7; benzyl bromide, 100-39-0; bis(phenylsulfonyl)methane anion, 25809-66-9; diethyl sodiomalonate, 996-82-7; dimethyl malonate anion, 33673-07-3; methyl acetoacetate anion, 53519-67-8; dimethyl sodiomalonate, 18424-76-5; 1-(phenylthio)-2-bromo-4-isopropenylcyclohexane, 85895-37-0; lithium dimethylcuprate, 15681-48-8; 3,3-dimethyl-2-(phenylthio)-1-butene, 1886-64-2; lithium diphenylcuprate, 23402-69-9; lithium bis(phenylethynyl)cuprate, 62374-50-9; dimethyl (2-oxocyclohexyl)malonate, 63965-89-9; chloramine-T, 127-65-1; ethyl 2-oxocyclopentylcarboxylate sodio derivative, 13697-91-1; methylmagnesium iodide, 917-64-6; 1-methyl-4-(6-methyl-5-(phenylsulfinyl)-1,5-heptadien-2-yl)cyclohexene, 85895-38-1; isopropylmagnesium bromide, 920-39-8; 1,3-propanedithiol, 109-80-8; sodium benzenesulfinate, 873-55-2; 1-cyano-3-methyl-2-(phenylthio)-2-butene, 85895-39-2; tetramethylammonium cyanide, 13435-20-6; (1*S**)(6*S**)-1-methyl[4.4.0]bicyclodecan-4-one, 938-07-8; (1*S**)(6*S**)-4,4-bis(phenylthio)-1-methyl-[4.4.0]bicyclodecane, 85908-84-5; 1-(phenylthio)cyclooctene, 52113-72-1; 2-methoxy-6-(phenylthio)naphthalene, 85895-40-5; 3-(phenylthio)-7-methoxy-1,2-dihydronaphthalene, 64740-99-4; 2-methylcyclohexanone, 583-60-8; 1,1-bis(phenylthio)-2-methylcyclohexane, 85895-41-6; 5-bromo-1-(phenylthio)cyclopent-1-ene, 85895-42-7; 1-bromo-2-(phenylthio)cyclopent-1-ene, 85895-43-8; 3-bromo-1-methyl-2-(phenylthio)-cyclohex-1-ene, 85895-44-9; 6-bromo-4-*tert*-butyl-1-(phenylthio)cyclohex-1-ene, 85895-45-0; 2-bromo-1-(phenylthio)-4-*tert*-butylcyclohex-1-ene, 85895-46-1; 6-bromo-4-*tert*-butyl-1-(4-methoxyphenylthio)cyclohex-1-ene, 85895-47-2; 2-bromo-4-*tert*-butyl-1-(4-methoxyphenylthio)-cyclohex-1-ene, 85895-48-3; [1-(phenylthio)-2-bromoethylidene]cyclohexane, 85895-49-4; 1-(phenylthio)-6-bromo-5-methylcyclohexene, 85895-50-7; 1-(phenylthio)-2-bromo-3-methylcyclohexene, 85895-51-8; methyl 5-bromo-4-(phenylthio)cyclohex-3-enecarboxylate, 85895-52-9; methyl 3-bromo-4-(phenylthio)cyclohex-3-enecarboxylate, 85895-53-0; 1-(phenylthio)-4-acetyl-6-bromocyclohex-1-ene, 85895-54-1; 1-(phenylthio)-4-acetyl-2-bromocyclohex-1-ene, 85895-55-2; 1-(phenylthio)-6-bromo-4-isopropenylcyclohexene, 85895-56-3; 1-(phenylthio)-2-bromo-4-isopropenylcyclohexene, 85895-57-4; (*E*)-1-phenyl-2-(phenylthio)-3-bromoprop-1-ene, 85895-58-5; (*Z*)-1-phenyl-2-(phenylthio)-3-bromoprop-1-ene, 85895-59-6; 1-(phenylthio)-12-bromocyclododec-1-ene, 85895-60-9; 1-(phenylthio)-2-bromocyclododec-1-ene, 85895-61-0; 1-bromo-2-(phenylthio)-3-etyhylpent-2-ene, 85895-62-1; 4-*tert*-butyl-1,1-bis(phenylthio)cyclohexane, 85895-63-2; isoprene, 78-79-5; (*Z*)-**57**, 84098-63-5.

Supplementary Material Available: Chart of brominating agents, table of bromination conditions, general experimental introduction, and preparations of 1,1-bis(phenylthio)-2-methylcyclohexane, (1*S**,6*S**)-4,4-bis(phenylthio)-1-methyl[4.4.0]bicyclodecane, 4-*tert*-butyl-1,1-bis(phenylthio)cyclohexane, **8**, **9**, **10a**, **10b**, **12**, **50**, **51**, and 2-methoxy-6-benzenethionaphthalene (9 pages). Ordering information is given on any current masthead page.

Stereoelectronic Control of Intramolecular Michael Addition Reactions

Graham W. L. Ellis, C. David Johnson,* and David N. Rogers

Contribution from the School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, United Kingdom. *Received October 18, 1982*

Abstract: Concepts of stereoelectronic control lead to the conclusion that the 5-endo-trig ring closure of (*E*)-2-methyl-3-oxo-5-phenylpent-4-en-2-ol should be disfavored. However, the acid-catalyzed ring closure in trifluoroacetic acid occurs readily, suggesting an alternative mechanism of 5-exo-trig form, proceeding through the protonated species. This explanation involves reversed electronic effects between inter- and intramolecular Michael additions, whereby the ring-closure and ring-opening processes for the above compound can be accelerated by electron-donating substituents in the 5-phenyl ring and decelerated by electron-withdrawing substituents. Detailed kinetic examination of these circumstances, in which the key point established is that the accelerative effect of electron-donating substituents is far greater than could be explained by their influence in increasing the amount of reactive carbonyl-protonated enone, gives insight into the nature of stereoelectronic control in such reactions. Concomitant reaction, trifluoroacetylation of the hydroxyl group of the open-chain compounds, is investigated.

The significance of orbital overlap in controlling the course of organic reactions has long been recognized. Particular landmarks appropriate to cite here are the recognition of antiperiplanar E2 eliminations by Hughes and Ingold,[1] Deslongchamps' theory of stereoelectronic control,[2] and Baldwin's rules for ring closure.[3] Baldwin has shown[4,5] that ring closure of (*E*)-2-methyl-3-oxo-5-phenylpent-4-en-2-ol (**1a**) cannot be effected under basic conditions. However, acidic conditions (refluxing in 1,2-dichloroethane with *p*-toluenesulfonic acid) readily gave 2,2-dimethyl-5-

(1) Ingold, C. K. "Structure and Mechanism in Organic Chemistry"; Bell: London, 1969; pp 689–701.
(2) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463. Perrin, C. L.; Arrhenius, G. M. L. *J. Am. Chem. Soc.* **1982**, *104*, 2839.
(3) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(4) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.
(5) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846. See also: Perkins, M. J.; Wong, P. C.; Barrett, J.; Dhaliwal, G. *J. Org. Chem.* **1981**, *46*, 2196.

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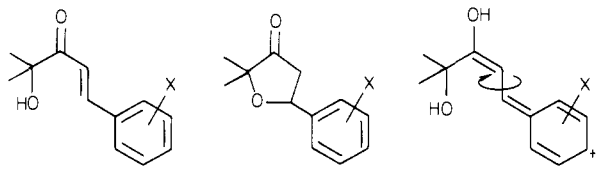
phenyltetrahydro-3-furanone (**2a**). This reaction was interpreted



1a-f **2a-f** **3**

a, X = H; b, X = *p*-OCH_3; c, X = *p*-CH_3; d, X = *m*-CH_3; e, X = *p*-Cl; f, X = *m*-Cl

as involving the intermediacy of the protonated form of **1a**, which from consideration of canonical form **3** would permit rotation about the 4,5 bond and allow 5-exo-trig ring closure. This idea was borne out by preliminary experiments on rates of ring closure of **1a** and **1b** in trifluoroacetic acid,[6] a medium in which ring-open and ring-closed forms existed in equilibrium. We now present a full account of these and further experiments which appear to validate fully Baldwin's original idea and to provide an insight into the detailed mechanism of this reaction.

Experimental Section

Trifluoroacetic acid (TFA) was reagent grade and used as received. Proton NMR spectra were recorded on a Perkin-Elmer R12 60-MHz spectrometer. UV spectra were recorded on a Pye-Unicam SP8-200 UV–vis spectrometer.

(*E*)-**2-Methyl-3-oxo-5-phenylpent-4-en-2-ol** (**1a**) and substituted derivatives **1b–f** were prepared by reaction of 3-hydroxy-3-methyl-2-butanone (25 mmol) with the appropriate benzaldehyde (25 mmol) in an aqueous ethanolic solution of sodium hydroxide and then purified as described previously.[5]

1a: mp 36–39 °C (lit.[5] mp 39–40 °C).

1b: 24% yield, yellow oil; bp 94 °C (0.15 torr). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.53; H, 7.32.

1c: 38% yield, colorless needles; mp 48–50 °C. Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.29; H, 7.96.

1d: 79% yield, yellow oil; bp 103 °C (0.25 torr). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.43; H, 8.08.

1e: 93% yield, pale yellow prisms; mp 60–63 °C. Anal. Calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.78; Cl, 15.78. Found: C, 64.07; H, 5.76; Cl, 15.87.

1f: 35% yield, colorless needles; mp 48.5 °C. Anal. Calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.78; Cl, 15.79. Found: C, 64.18; H, 5.89; Cl, 15.68.

2,2-Dimethyl-5-phenyltetrahydro-3-furanone (**2a**) and substituted derivatives **2b,c,e,f** were prepared by refluxing **1a–c,e,f** (5 mmol) with *p*-toluenesulfonic acid (2 mmol) in dichloroethane for 24 h, as described previously.[5] Crude yields were good (65–80%), but proton NMR and TLC revealed small amounts of impurities which we could not remove by distillation. These were therefore removed by repeated chromatography (column and thick layer) on silica with 3:1 hexane–ethyl acetate, and the resultant light yellow oils, obtained in very low yield (~15%), were characterized by proton NMR and chemical analysis. In the case of **2f**, these impurities persisted.

2a proton NMR and IR agreed with the literature,[5] but we could not induce crystallization.

2b: Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.05; H, 7.45.

2c: Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.84; H, 8.01.

2e: Anal. Calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.78; Cl, 15.78. Found: C, 64.19; H, 5.72; Cl, 15.74. Obtained on one occasion as a white solid, mp 51–52 °C.

IR (cm^{-1}, CH_2Br_2): compounds **1**, 3460 (broad), 1680, 970. Compounds **2**, 1760.

NMR: See Table I.

UV: The spectra of 2,2-dimethyl-3-oxo-5-phenylpent-4-ene and phenyl-substituted derivatives *p*-OMe, *p*-Me, p-Cl, and *p*-NO_2 were taken in TFA, and also in varying concentrations of aqueous sulfuric acid from 30 to 95%. Over this range the equilibrium changed from predominant free base to conjugate acid form. Comparison with the spectra in TFA showed in all cases free base predominated in this acidic solvent. This correlates with the fact that pure TFA has an effective H_0 value of −3.0,[7] while our measurements indicated that the H_0 values for half-protonation of the above compounds were −4.8 (*p*-OMe), −5.5 (*p*-Me), −5.9 (unsubstituted), −6.5 (*p*-Cl), and −7.1 (*p*-NO_2). We deduce that the similar structures **1a–f** and their ring-closed forms **2** should all exist predominantly in the free base form in TFA.

Table I. ^1H NMR of Compounds 1 and 2[a]

	arom	H_A	H_B	J_{AB}	Me(s)	X(s)	OH(s)
1a	7.50 (m)	7.93	7.11	15.7	1.42		4.30
1b	7.58, 6.92 (dd, 9.3)	7.82	6.95	15.3	1.45	3.78	4.15
1c	7.56, 7.23 (dd, 8.3)	7.89	7.01	15.3	1.47	2.40	3.65
1d	7.30 (m)	7.83	7.04	15.3	1.47	2.35	4.15
1e	7.64 (m)	7.81	7.01	15.7	1.46		3.87
1f	7.53 (m)	7.80	7.14	16.0	1.46		4.01

	arom	H_X	H_A	H_B	J_{AX}	J_{BX}	J_{AB}	Me(s)	X(s)
2a	7.36 (s)	5.16	2.86	2.40	6.7	10	19.3	1.37, 1.29	
2b	7.60, 6.95 (dd, 9.0)	5.11	2.81	2.39	6.7	10	19.3	1.32, 1.25	3.72
2c	7.26 (m)	5.16	2.87	2.46	6.7	10	18.0	1.37, 1.29	2.33
2e	7.37 (s)	5.19	2.89	2.42	6.7	10	18.0	1.39, 1.32	
2f	7.37 (m)	5.17	2.89	2.41	6.7	10	18.7	1.38, 1.29	

[a] δ units; coupling constants in Hz; solvent $CDCl_3$; all peaks integrated correctly for the appropriate number of hydrogen atoms.

Table II. Treatment of Data for the Ring Closure of 1b in TFA at 34.5 °C[e]

time, min	integral A,[a,b] mm	integral B,[c,d] mm
1.42	74.63	4.31
4.75	71.06	9.06
8.08	66.19	18.81
11.12	71.88	24.88
14.75	51.44	24.75
18.83	52.13	29.50
22.17	52.19	33.75
26.58	48.06	39.44
32.00	41.56	40.81
37.33	43.19	45.94
43.75	43.44	50.69
75.92	37.63	64.00
87.25	31.63	56.63
143.25	31.44	63.06
150.42	29.06	58.25
362.92	28.69	59.94
434.83	25.67	53.58

[a] For methyl singlet of 1b. [b] $A_{corr} = A(A + B)_0/(A + B)$. [c] For methyl singlet of 2b. [d] $B_{corr} = B(A + B)_0/(A + B)$. [e] A plot of A_{corr} vs. time gave, from a short extrapolation by eye, A^0_{corr}(time zero) = 78.94. A^E_{corr}(equilibrium) = 25.48. A plot of ln ($B^t_{corr} - B^E_{corr}$) vs. time is linear (correlation coefficient 0.998), and $k_{obsd} = (5.61 \pm 0.11) \times 10^{-4}$ s^{-1}, whence from eq **1** and 2 and $K = B^E_{corr}/A^E_{corr} K = 2.10$, $k_f = 3.80 \times 10^{-4}$ s^{-1}, $k_r = 1.81 \times 10^{-4}$ s^{-1}.

Kinetics. Rates and positions of equilibria were obtained by monitoring the methyl peaks at suitable time intervals. A weighed amount of ring-open (**1**) or ring-closed compound (**2**) was dissolved in TFA in the NMR tube. The molar excess of TFA over compound was kept constant at about 20 to 1. The tube was stoppered and shaken and timing started. Spectra were taken at appropriate intervals and the methyl peaks integrated eight times in both directions. The temperature was in all cases 34.5 ± 1.0 °C.

Tetramethylsilane was initially used as internal reference for integration. This did not react with TFA over the longest time intervals used, but in such cases slow evaporation occurred, and therefore the Me_4Si was omitted and the combined integrals of the methyl peaks were taken for internal reference. Table II gives details of a typical run, for compound **1b**. Linear rate plots were obtained for at least 3 half-lives. The observed rate constant and equilibrium constant, k_{obsd} and K, respectively, may be used to calculate the forward and reverse rate constants k_f and k_r from the equations

$$k_{obsd} = k_f + k_r \quad (1)$$

$$K = k_f/k_r \quad (2)$$

(6) Ellis, G. W. L.; Johnson, C. D.; Rogers, D. N. *J. Chem. Soc., Chem. Commun.* **1982**, 36.

(7) Hyman, H. H.; Garber, R. W. *J. Am. Chem. Soc.* **1959**, *81*, 1847.

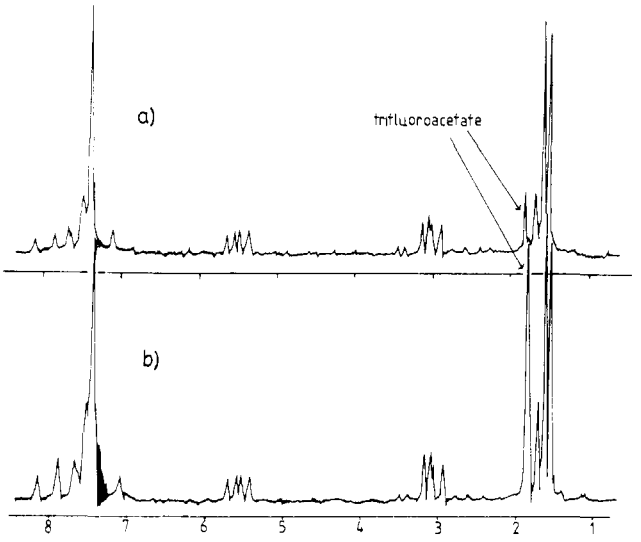
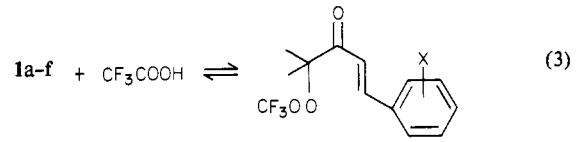


Figure 1. NMR spectrum of reaction approaching equilibrium: (a) starting with ring-closed compound **2e**; (b) starting with ring-opened compound **1e**.

Checks were carried out by determining K, k_f, and k_r, starting with the ring-closed compounds.

For the slower reactions of both ring-closed and ring-open compounds it was found that an additional peak appeared at δ 1.70, with no other spectral change whatsoever. The fact that the peak is a singlet and increases more rapidly when approaching equilibrium from the ring-open than the ring-closed side (see Figure 1) suggests that this arises from a reaction of the ring-open compound. The only explanation is the formation of the trifluoroacetate



(3)

This type of reaction has previously been fully investigated.[8,9] We examined the behavior of 3-hydroxy-3-methyl-2-butanone with TFA, a model system which should replicate the reaction of **1a–f** with TFA, but without the possibility of ring closure. Kinetic analysis by NMR as above with the use of integration of the methyl peaks showed the trifluoroacetate to lie in equilibrium with the hydroxy compound, the latter being predominant ($K = 0.33$, $k_f = 1.68 \times 10^{-6}$ s^{-1}, $k_r = 5.12 \times 10^{-6}$ s^{-1}). These values compare with $K = 0.26 \times 10^{-3}$ and 2.70×10^{-3} s^{-1} for trifluoroacetylation of isopropyl and *tert*-butyl alcohols, respectively, in TFA,[9] reactions which go to completion. We conclude therefore that 3-hydroxy-3-methyl-2-butanone esterifies by an $A_{Ac}2$ mechanism, the electron-withdrawing influence of the carbonyl group lowering the rate, cf. isopropyl alcohol, eliminating the possibility of an $A_{Al}1$ mechanism by which *tert*-butyl alcohol reacts[8] and destabilizing the trifluoroacetate producing an equilibrium in favor of the hydroxy form. The existence of this competing reaction obviously complicates evaluation of rate data. However, for all compounds except **1f** the formation of the trifluoroacetate was sufficiently slow compared with the ring closure to enable kinetic evaluation as exemplified in Table I. For the 3-chloro-derivatives **1f** and **2f** the rate of esterification is very similar to that of ring closure and opening. Full analysis of such a scheme is fairly complex,[10] and we are submitting full details of our calculations elsewhere.[11] Good estimates of rate constants could however be found by plotting the standardized integrals of the methyl peaks for all three components and drawing tangents to the curves at time zero, as shown in Figure 2, and these accorded with the values obtained by complete kinetic analysis.[11]

Results

Values obtained for K, k_f, and k_r are given in Table III. Duplicate runs agreed quite well for the faster ring-closure rates

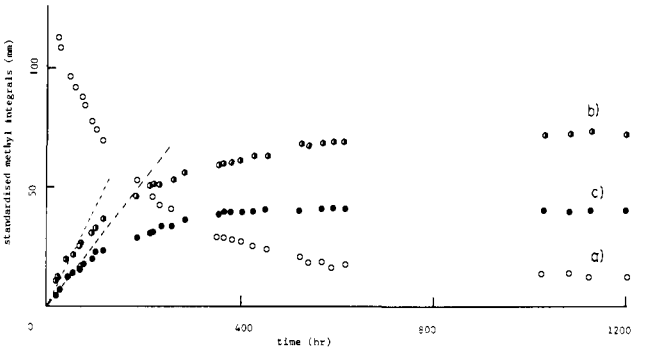


Figure 2. Change of methyl integrals with time for ring closure, ring opening, and trifluoroacetylation of **1f**: (a) **1f**; (b) **2f**; (c) trifluoroacetate of **1f**.

Table III. Values of k_f, k_r, and K

substrate	K	$10^6 k_f$/ s^{-1}	$10^6 k_r$/ s^{-1}	av K[d]	av $10^6 k_f$/ s^{-1} [d]	av $10^6 k_r$/ s^{-1} [d]
1b[a]	2.14	369	172	2.06	367	178
	2.10	380	181			
2b	1.95	274	141			
	2.04	446	219			
1c	2.19	14.7	6.71	2.39	20.0	8.32
	2.52	21.4	8.49			
2c	2.57	24.1	9.27			
	2.57	19.8	8.71			
1d	3.49	10.3	4.13	3.47	9.12	3.22
	3.45	7.93	2.30			
1a[a,b]	4.53	7.97	1.76	4.50	6.53	1.45
	4.53	6.72	1.52			
2a	4.53	4.91	1.08			
1e	4.56	2.63	0.577	4.65	2.49	0.537
	4.52	3.13	0.692			
2e	4.80	2.42	0.504			
	4.70	1.77	0.376			
1f[c]	4.82	0.834	0.173			

[a] Previous[6] preliminary results obtained were: 1b, $K = 2.0$, $10^6 k_f/s^{-1} = 260$, $10^6 k_r/s^{-1} = 130$; 1a, $K = 3.5$, $10^6 k_f/s^{-1} = 4.3$. [b] A run using Me_4Si as standard gave $K = 4.60$, $10^6 k_f/s^{-1} = 6.35$, $10^6 k_r/s^{-1} = 1.38$. [c] See Figure 2. [d] No significant variation was found between the logs of these averages and the averages of the logs of K_f, k_f, and k_r taken individually.

but were more scattered for the slower runs, where half-lives of many days were involved. Results obtained starting with the ring-closed compounds also showed less good agreement, particularly for the slower rates, and correspondence was also poorer with the equivalent values obtained from the open-chain compounds. This must be partially due to trifluoroacetate formation becoming significant. Another very important factor is that the equilibrium lies well in favor of the ring-closed compounds, increasingly so for those bearing electron-withdrawing groups; one therefore observes only small changes in NMR signals when following the reaction from the ring-closed side. Another potential source of errors was overlap of methyl peaks which made accurate integration difficult. This again affected slow runs the most, because degree of resolution could vary from day to day. The NMR technique was however a very convenient way to follow these kinetics, indeed probably the only way considering the additional complexities arising from incursion of trifluoroacetate formation. We have no reasons to believe that the scatter of results was anything other than random, and the results certainly seem sufficiently accurate to use with reasonable confidence in the following discussion.

As Figure 3 shows, plots of log K, log k_f, and log k_r are very significantly better against σ^+ than σ. The relevant ρ values are set out in the legend to this figure. We emphasize the magnitude of these for the kinetic processes, since, as we now discuss, it is this that provides evidence of significant aryl involvement, and therefore of C_4–C_5 rotation in **3**.

(8) Kavanagh, P.; Knipe, A. C.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1979**, 905.
(9) Johnston, B. H.; Knipe, A. C.; Watts, W. E. *Tetrahedron Lett.* **1979**, 4225. Gillen, C. J.; Knipe, A. C.; Watts, W. E. *Ibid.* **1981**, *22*, 597.
(10) Frost, A. A.; Pearson, R. G. "Kinetics and Mechanism"; 2nd ed.; Wiley: New York, 1961; pp 173–177.
(11) To be submitted to *J. Chem. Educ.*

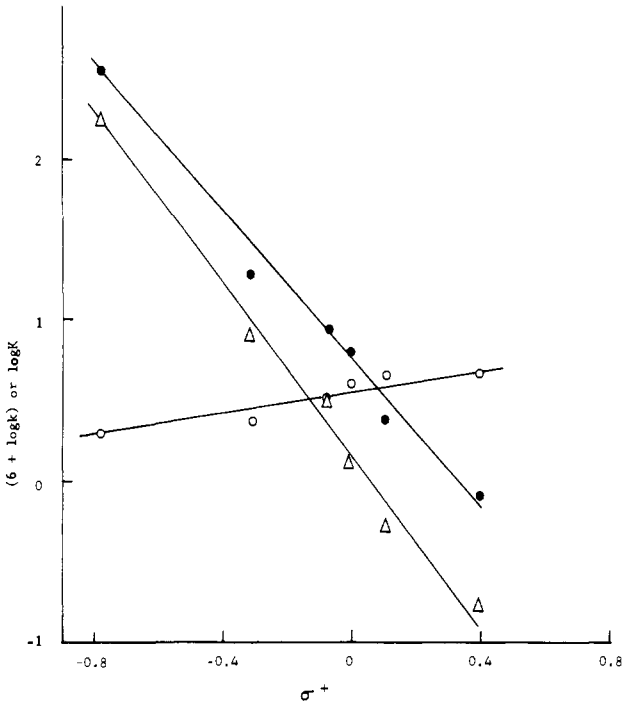


Figure 3. LFER's from Table III: (○) log K vs. σ^+, $\rho = 0.37 \pm 0.07$, cc = 0.928 (with σ, $\rho = 0.58 \pm 0.15$, correlation coefficient cc = 0.884); (●) log k_f vs. σ^+, $\rho = -2.23 \pm 0.12$, cc = 0.994 (with σ, $\rho = 3.42 \pm 0.74$, cc = 0.916); (▲) log k_r vs. σ^+, $\rho = -2.60 \pm 0.14$, cc = 0.994 (with σ, $\rho = -4.02 \pm 0.80$, cc = 0.928).

Discussion

Electron withdrawal from the β-carbon of a double bond, activated toward nucleophiles by a powerful electron sink attached to the α-position, should accelerate the rate of the nucleophilic attack at that β-carbon. Rate studies are surprisingly few for such Michael additions, but the results that do exist[12] show clearly that this prediction is borne out. Substituent effects on the rate will be in the same sense as those on the equilibrium between double-bond compound and adduct, providing K is defined as [adduct]/[double-bond compound].

A particularly useful study of rates of acid-catalyzed Michael addition of water to β-oxy-α, β-unsaturated ketones has been provided.[12a] This shows that for such an intermolecular situation, the electronic requirements of the initial protonation equilibrium just about compensate for the opposing requirements for nucleophilic attack, in marked contrast to the effects discussed here, for the intramolecular reaction.

From Table III and Figure 3, it can be seen that for the analogous intramolecular equilibria **1** ⇌ **2**, electron withdrawal from a β-substituent indeed pushes the equilibrium over to the right ($\rho = +0.4$), since the open form is stabilized by through conjugation between carbonyl and electron-donating substituents. Substituent effects on the rate of ring closure however are such that electron donation accelerates reaction. We take this to be indicative of a kinetic stereoelectronic effect, as postulated by Baldwin.[3,5] Our measurements enable us to diagnose each step of the reaction, as shown in Scheme I.

We have shown that in TFA free base forms **1** and **2** predominate over conjugate acids **3'** and **6**, respectively (see Experimental Section, where H_0(half-protonation) values, ~pK_as, are given). The involvement of canonical **3** in the resonance hybrid of the conjugate acids suggests that the C_4–C_5 bond contains some

(12) (a) Fedor, L. R.; De, N. C.; Gurwara, S. K. *J. Am. Chem. Soc.* **1973**, *95*, 2905, see especially the discussion on p 2909. (b) Deles, J. *Rocz. Chem.* **1961**, *35*, 861. Kamlet, M. J.; Glover, D. J. *J. Am. Chem. Soc.* **1956**, *78*, 4556. Pritchard, R. B.; Lough, C. E.; Reesor, J. B.; Holmes, H. L.; Currie, D. J. *Can. J. Chem.* **1976**, *45*, 775. Crowell, T. I.; Helsley, G. C.; Lutz, R. E.; Scott, W. L. *J. Am. Chem. Soc.* **1963**, *85*, 443. Agami, C.; Levisalles, J.; Puchot, C. *J. Org. Chem.* **1982**, *47*, 3561.

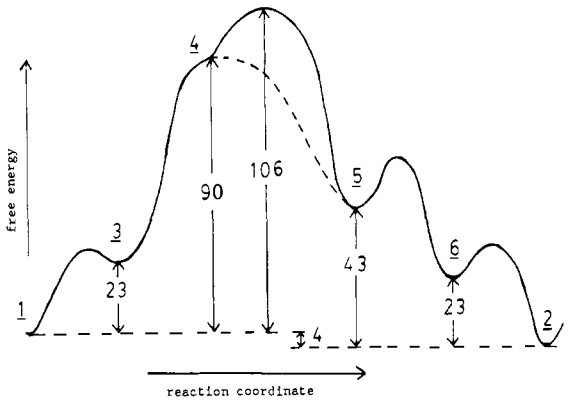
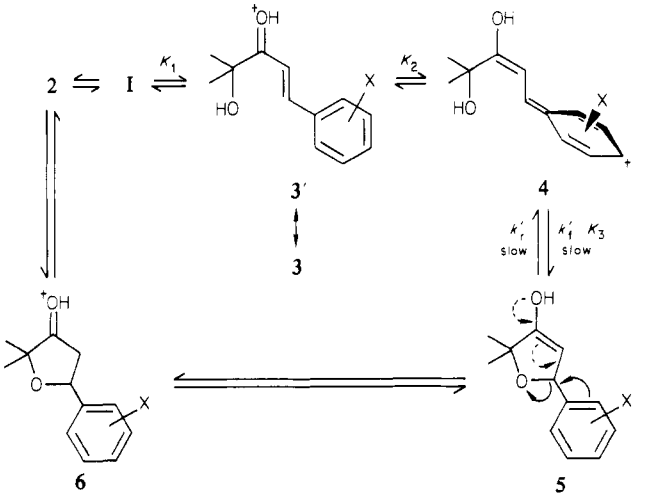


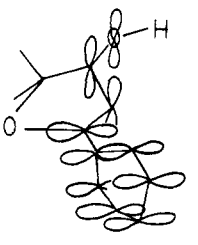
Figure 4. Reaction profile for **1a** ⇌ **2a**. The free energies given are kJ mol^{-1}.

Scheme I



single-bond character, facilitating rotation around it.[4] This allows overlap between one of the lone pair orbitals on the hydroxyl oxygen and the C_5 p orbital. It is this rotation that distinguishes the intramolecular Michael addition from intermolecular cases, and gives rise to the reversed substituent effect.

By the law of microscopic reversibility, the backward reaction contains the stereoelectronic effect in reverse, and it is often a useful ploy when examining the applicability of Baldwin's rules to look at this reverse reaction, ring opening. As the breaking C–O bond in **5** is orthogonal to the π-orbitals of the enol system, the overlap implied by the dotted arrows cannot occur, and therefore ring opening can only proceed by involvement of the aryl group (full curly arrows in **5**), which thus has to twist to permit maximum orbital overlap as shown in **7**.



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The reacting rotamer **4** is an unstable species (see Figure 4), having a structure closely similar to that of the carbenium ion generated in the acid-catalyzed hydration of styrenes, since in **4** the positive charge can no longer be delocalized onto the enol system. The stabilization of structure **4** by electron-donor substituents X explains the accelerative effect of such groups. We may estimate a ρ value for this K_1K_2 equilibrium (**1** ⇌ **4**) as follows. Styrene hydration in aqueous sulfuric acid follows the

H_C^+ kinetic acidity function with a slope of about unity.[13] As H_C^+ is related to the H_C acidity function by a factor of 0.65,[13] we can assume that the transition state for the rate-limiting step of styrene hydration has 65% full carbenium ion character. Therefore the ρ value for K_1K_2 vs. σ^+ should be around $-3.5/0.65 = -5.4$, where the numerator is the ρ value for styrene hydration rates. This does neglect the conjugative stabilization of **1**, which is absent in styrenes. However, even if one took equilibrium **2** $\rightleftharpoons$ **4** as a closer model, ρ changes to only −5.8, and here **2** has less conjugation than in styrenes. The medium is TFA, but there are good indications that carbenium ion forming reactions have very similar ρ values in the two acidic systems.[14]

The ring-closure reaction (**4** → **5**), which we take to be the slow step (see subsequent discussion), will be accelerated by electron-withdrawing groups, destabilizing carbenium ion **4** and making it more susceptibile to nucleophilic attack.

Since

$$k_f = K_1K_2k_f' \quad (4)$$

$$\rho(k_f) = \rho(K_1K_2) + \rho(k_f') \quad (5)$$

and so

$$\rho(k_f') = 5.4 - 2.2 = 3.2$$

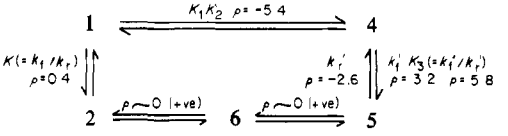
It is possible that step **5** $\rightleftharpoons$ **6** of the keto–enol tautomerism (**5** $\rightleftharpoons$ **2**) could be rate limiting, but we regard this as unlikely. Kresge, in a very extensive series of papers,[15] has shown that C protonation of vinyl ethers, and therefore presumably of enols, is a rapid reaction, even in very dilute acid. Thus if this was indeed the rate-determining step, the observed rate constants should be several orders of magnitude greater, although it must be noted that this is offset by the fact that equilibrium **1** $\rightleftharpoons$ **2** lies in favor of **1**, and **5** is thus a minority species. However, the keto–enol tautomerism would also have to be the rate-limiting step of the backward reaction. Thus the large value of −2.6 for $\rho(k_r)$ would be impossible to justify. Even for substituted acetophenones, where the reaction site is joined directly to the phenyl ring, acid-catalyzed enolization rates are correlated by ρ values of between only −0.48 and −0.16.[16]

The ρ value for this keto–enol tautomerism will thus be very small. For both steps the reaction site is shielded from the substituted phenyl ring by a saturated carbon atom, and in the case of the common intermediate **6**, which bears a charge, by two saturated units. Moreover, the sign of ρ for reaction **5** $\rightleftharpoons$ **6** is opposite to that for **6** $\rightleftharpoons$ **2**, so what small substituent effects there are will tend to cancel.

For the ring-opening reaction therefore the ρ value for correlation of logarithms of the observed rate constants k_r will pertain solely to the slow step **5** → **4**. Thus in Scheme I, $\rho(k_r') = \rho(k_r) = -2.6$, so that ρ for the correlation of K_3 becomes $3.2 + 2.6 = 5.8$. This has the opposite sign but a similar size to the ρ value for the equilibrium **1** $\rightleftharpoons$ **4** of −5.4 which is an expected result, for both equilibria the size of the substituent effect should be governed by the positively charged intermediate **4** common to both.

A representation of the reaction profile is given in Figure 4 (full line). An intriguing possibility is that rotamer **4** is the highest energy species encountered in the sequence, and this represents a transition state with increasing stabilization as soon as C–O bond formation commences (dotted line in Figure 4). In this case, the transition-state model would have been defined with far greater exactitude than is customary. However, it is very unlikely that **4** indeed fills this role, because if it did we would expect the ρ value for correlation of log k_f to be about −5.4 rather than −2.3,

Scheme II



since it would lack the positive component derived from attack of the nucleophile on the carbenium ion center, step **4** → **5**.

A clearer way to reject **4** as the transition state is to note that $\rho(k_f') \sim {}^1/_2\rho(K_3)$, suggesting that the C–O bond is "half"-formed at the transition state. It is not legitimate however to treat **4** as an intermediate, because it is a conformation of maximum energy, with respect to C_4–C_5 rotation, as shown in Figure 4.

The free energy values shown in the reaction profile (Figure 4) are very approximate and indicate orders of magnitude only. They have been calculated from the rates and equilibria given in Table III, together with the following data and assumptions: that rates and equilibria in neat TFA will parallel those in aqueous sulfuric acid of H_0 −3 (see previous discussion); that the pK_as of **3'**, **6**, and protonated acetophenone and acetone are the same (−4 at 35 °C);[17] that the keto/enol tautomerism ratio would be the same for **1** $\rightleftharpoons$ **4**, **2** $\rightleftharpoons$ **5**, acetophenone, and acetone at about 10^{-8};[18] and that the rate for protonation of styrene in acid media of H_0 −3 would be 3×10^{-3} s^{-1} at 35 °C,[13] and that this can be used to evaluate the relative stabilities of styrene and the carbenium ion produced by proton addition to the side chain.

Summary and Conclusion

Scheme II summarizes the ρ values we have obtained for each step of the overall reaction path, arising from a reversed substituent effect on the observed rate constants for the forward reaction. This vindicates Baldwin's original view of the reaction,[4,5] in that the analysis requires that carbenium ion **4** should be fully twisted about the C_4–C_5 bond so that the two sets of π orbitals are orthogonal to each other and complete overlap between one of the lone pair orbitals on oxygen and the p orbital on C_5 is possible. The situation therefore appears to represent a further critical test of the theory of stereoelectronic control.[2]

Menger has suggested that in certain nucleophilic attacks at carbon the angle of approach is not critical.[19] Such reactions are said to have a large "reaction window". A number of reactions are known, particularly involving nucleophilic attack on imino groups, where Baldwin's rules apparently break down[20] and reaction windows are large. In the intramolecular Michael addition studied here, however, it seems apparent that even if a definite reagent trajectory is not required, the reaction window is rather

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(14) (a) Clementi, S.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans 2* **1973**, 1077. These workers give $\rho(\text{TFA}) = 1.13\rho(H_2SO_4)$, but the latter reaction is at 100 °C and the former at 70 °C. An increase in temperature is known to decrease ρ values.[14b] (b) Johnson, C. D. "The Hammett Equation"; Cambridge University Press: New York, 1973; p 147.

(15) Kresge, A. J.; Chwang, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 1249 and references collected therein.

(16) Toullec, J. *Adv. Phys. Org.* Chem. **1982**, *18*, 1.

(17) Gilbert, T. J.; Johnson, C. D. *J. Am. Chem. Soc.* **1974**, *96*, 5846. Levy, G. C.; Cargioli, J. D.; Racela, W. *Ibid.* **1970**, *92*, 6238. Levy, A.; Modena, G.; Scorrano, G. *Ibid.* **1974**, *96*, 6585.

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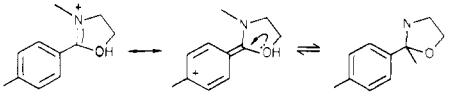
(19) Menger, F. M.; Glass, L. E. *J. Am. Chem. Soc.* **1980**, *102*, 5405. Menger, F. M.; Williams, D. Y. *Tetrahedron Lett.* **1982**, *23*, 3879.

(20) McClelland, R. A.; Somani, R. *J. Org. Chem.* **1981**, *46*, 4345. McClelland's report of facile ring opening of an *N*-alkyloxazolidine may readily be explained in terms of a canonical form enabling alternative 5-exo-trig reaction, viz:



but other examples he quotes are not so easy to explain, see particularly: Lambert, J. B.; Majchrzak, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3588. In this latter case, trifluoroacetylation in the solvent TFA may be a complicating factor in the results on the oxazolidine and perhydrooxazine systems, not foreseen by the authors, but nevertheless the overall conclusions appear correct (personal communication). Such 5-endo-trig ring openings and closures of oxazolidine systems also occur rapidly in basic or neutral media: Paukstelis, J. V.; Hammaker, R. M. *Tetrahedron Lett.* **1968**, 3557. Paukstelis, J. V.; Lambing, L. L. *Ibid.* 1970, 299. Filer, C. W.; Granchelli, F. E.; Soloway, A. H.; Neumeyer, J. L. *J. Org. Chem.* **1978**, *43*, 672. Pelletier, S. W.; Mody, N. V. *J. Am. Chem. Soc.* **1979**, *101*, 492. Grigg, R.; Kemp, J.; Malone, J.; Tangthongkum, A. *J. Chem. Soc., Chem. Commun.* **1980**, 648.

narrow: we hope that the resultant reversed substituent effect may be an observation of use in other mechanistic investigations of stereoelectronic control.

Acknowledgment. One of us (G.W.L.E.) thanks the British Science Research Council for a grant. The arguments in this paper were modified following suggestions by a referee, to whom we extend our thanks.

Registry No. **1a**, 63677-96-3; **1b**, 81791-30-2; **1c**, 85736-11-4; **1d**, 85736-12-5; **1e**, 85736-13-6; **1f**, 85736-14-7; **2a**, 63678-00-2; **2b**, 81791-31-3; **2c**, 85736-15-8; **2e**, 85736-16-9.

Rate Constants for the Reactions of Free Radicals with Oxygen in Solution[1]

B. Maillard,[2] K. U. Ingold, and J. C. Scaiano*

Contribution from the Division of Chemistry, National Research Council, Ottawa, Ontario, Canada K1A 0R6. *Received February 2, 1983*

Abstract: The kinetics of the reactions of several free radicals with oxygen have been examined in solution at 300 K using laser flash photolysis techniques. The reactions of resonance-stabilized radicals are only slightly slower than those of nonstabilized radicals: for example, for *tert*-butyl (in cyclohexane), 4.93×10^9; benzyl, 2.36×10^9 (in cyclohexane); cyclohexadienyl (in benzene), 1.64×10^9 M^{-1} s^{-1}. The reaction of *n*-$Bu_3Sn^{\cdot}$ radicals is unusually fast (7.5×10^9 M^{-1} s^{-}), a fact that has been tentatively attributed to a relaxation of spin selection rules due to heavy atom effects.

Liquid-phase autoxidations play an important role in the synthesis of oxygenated organic compounds and in the oxidative degradation of materials as varied as plastics, lubricating oils, and living organisms.[3] Although these processes all involve the reaction of free radicals with atmospheric oxygen, there have been rather few determinations of the rate constants for these reactions. To a large extent, this lack of accurate kinetic data reflects the fact that under most conditions the reaction of free radicals with oxygen is not the rate-determining step in the propagation of the autoxidation chain. That is, of the two propagating steps:

$$R\cdot + O_2 \xrightarrow{k_{Ox}} ROO\cdot \quad (1)$$

$$ROO\cdot + RH \rightarrow ROOH + R\cdot \quad (2)$$

it is reaction 2 that is generally rate controlling. A great many rate constants have therefore been determined for this reaction.[4,5]

The few published rate constants for reaction 1 for carbon-centered radicals range from as low as 4×10^6 M^{-1} s^{-1} all the way up to 5×10^9 M^{-1} s^{-1} in fluid solution at ambient temperatures.[6-17] While some of the differences in k_{Ox} values may reflect genuine differences in reactivity due to differences in radical structure, in many cases the differences must reflect either experimental error or inaccurate assumptions regarding reactions occurring in competition with radical scavenging by oxygen. The most notable of the "slow" $R\cdot + O_2$ reactions in solution are those for which $R\cdot$ is benzyl or a benzylic type of radical.[6-9] Reported[6-9] rate constants are in the range $2.5–6.8 \times 10^7$ M^{-1} s^{-1} (though a higher value has been found in the gas phase).[18] A slow reaction between O_2 and the benzyl radical might be attributed to the resonance stabilization of this radical. However, other resonance-stabilized radicals of the allylic and pentadienylic type have been reported to react with O_2 more rapidly,[14] while stabilized hydroxyalkyl radicals have k_{Ox} values $\geq 10^9$ M^{-1} s^{-1}.[13,19]

The possibility that the benzyl radical has an anomalously low reactivity toward oxygen has led us to measure the rate constant

(1) Issued as NRCC No. 21119.
(2) NRCC Visiting Scientist from the University of Bordeaux I, 1982.
(3) For reviews of autoxidation see: "Autoxidation and Antioxidants"; Lundberg, W. O., Ed.; Interscience: New York, 1961; Vols. I and II. Scott, G. "Atmospheric Oxidation and Antioxidants"; Elsevier: Amsterdam, 1965. Mayo, F. R. *Acc. Chem. Res.* **1968**, *1*, 193–201. Ingold, K. U. *Ibid.* **1969**, *2*, 1–9. Reich, L.; Stivala, S. S. "Autoxidation of Hydrocarbons and Polyolefins"; Marcel Dekker: New York, 1969. Betts, J. *Q. Rev., Chem. Soc.* **1971**, *25*, 265–288. Howard, J. A. "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. II, Chapter 12. "Autoxidation in Food and Biological Systems"; Simic, M. G., Karel, M., Eds.; Plenum: New York, 1980. Tappel, A. L. *Free Radicals Biol.* **1980**, *4*, 1–47.
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(6) Values of k_{Ox} (M^{-1} s^{-1} units) at ambient temperature for carbon-centered radicals have been reported as follows: 6.8×10^7, α-tetralyl;[7] 4×10^7, polystyryl/poly(peroxystyryl);[8] 2.5×10^7, benzyl;[9] 3.9×10^6, cyclopentyl (at 233 K);[10] 4.3×10^7, cyclohexyl;[10] $(3.4 \pm 0.6) \times 10^9$, cyclohexyl; $(4.9 \pm 0.6) \times 10^9$, cyclopentyl;[12] 4.8×10^9, hydroxymethyl;[13] $1.6–4.6 \times 10^9$, various hydroxyalkyls;[13] 2×10^8, arachidonyl;[14] 3×10^8, linolenyl and linoleyl;[14] 1.0×10^9, oleyl;[14] 1×10^9, 2-hydroxyvinyl;[15] 3.3×10^9, trichloromethyl;[16] 5×10^9, mixture of $C_6H_5C(OH)CF_3 + C_{10}H_{21}$·.[17] Values reported for k_1 for carbon-centered radicals in the gas phase at ambient temperature show somewhat less variation: e.g., 6.0×10^8, benzyl;[18] 1.2×10^9, hydroxymethyl;[19] 1.4×10^9, *tert*-butyl.[20]
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