Concluding Remark

Thus, the bacteriochlorophyll–protein structure determination has permitted the first visualization of chlorophyll in a component of a photosynthetic unit. To some extent, the bacteriophyll–protein is atypical, but it is reasonable to expect that the general principles of chlorophyll arrangement and chlorophyll–protein association seen for this protein also apply to the organization of chlorophyll in general.

Free-Radical Clocks[1]

David Griller and Keith U. Ingold*

Division of Chemistry, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6

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"Most of the methods for measuring the lapse of time have, I believe, been the contrivance of monks and religious recluses who, finding time hang heavy on their hands, were at some pains to see how they got rid of it."
William Hazlitt, *Sketches and Essays* (1839)

There is no completely general method for measuring the absolute rate constants of radical–molecule reactions.[2] The well-known "rotating sector" method[2,3] is restricted to radical-chain processes which can be initiated photochemically and which are terminated by radical–radical reactions. The chain must be fairly long (not less than five links), and this means that the radical–molecule propagation step(s) must be fairly rapid. Although this technique has proved valuable in kinetic studies of vinyl polymerization[2,4] and of autoxidation,[2,5] there are a great many interesting and important radical–molecule reactions which would be difficult or impossible to make the rate-controlling propagation step in a chain process. Of course, some of these reactions can be studied by flash photolysis, pulse radiolysis, and other special techniques,[2] but many cannot.

All these techniques of physical chemistry are unattractive to the organic chemist who would merely like to know the approximate rate of some new radical-molecule reaction because to use any one would require an inordinate investment of both his time and money. Organic chemists have, therefore, for many years used competing unimolecular radical reactions as qualitative timing devices to investigate the rates of radical–molecule reactions. The relevant information is obtained simply by product analysis.

The norbornenyl–nortricyclyl rearrangement provides a well-known illustration of this approach and has been the subject of numerous investigations.[6,7] The free-radical addition of RX to norbornadiene can be described by Scheme I. The composition of the products, i.e., the [3]/[4] ratio, depends upon whether the equilibrium between norbornenyl (**1**) and nortricyclyl (**2**) has been established. If RX is efficient in chain transfer

Scheme I
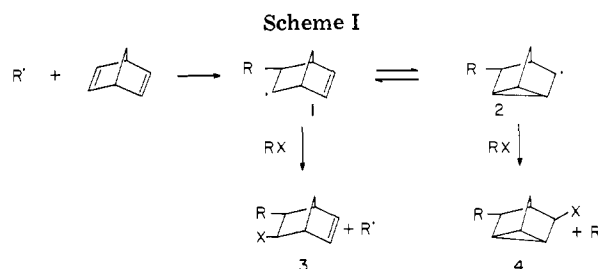
and/or is present in high concentrations, product **3** will be favored, whereas product **4** is normally predominant when **1** and **2** can reach equilibrium. Thus, the radical rearrangement acts as a timing device or *free-radical clock* and provides a method for examining the radical–molecule reaction. Indeed, any unimolecular radical reaction[8] can be used in this way.
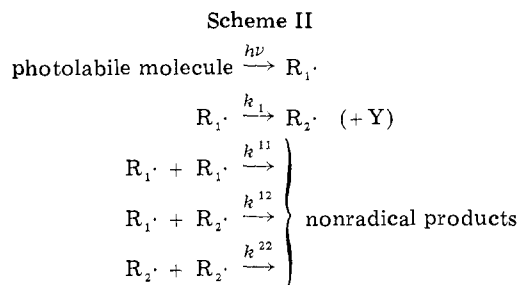
The β scission of *tert*-butoxyl provides an even more simple *clock* which has been in use for over 30 years to measure the relative rates of its hydrogen atom abstractions from organic compounds in solution.[9] In the presence of a hydrogen donor, AH, the following competition will occur.

$$Me_3CO\cdot \xrightarrow{k_\beta} Me\cdot + Me_2CO$$
$$\xrightarrow[AH]{k^{AH}} A\cdot + Me_3COH$$
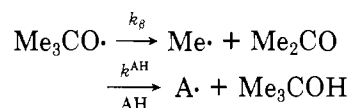
At low conversions, i.e., when the concentration of AH has not changed significantly, the ratio of the rate

(1) Issued as N.R.C.C. No. 18396.
(2) Burnett, G. M.; Melville, H. W. "Techniques of Organic Chemistry"; Friess, S. L., Lewis, E. S., Weissberger, A., Eds.; Interscience: New York, 1963; Vol. VIII, Part II, Chapter 20.
(3) Ingold, K. U. "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, Chapter 2.
(4) Walling, C. "Free Radicals in Solution"; Wiley: New York, 1957.
(5) Howard, J. A. *Adv. Free Radical Chem.* **1972**, *4*, 49.
(6) Davies, D. I.; Cristol, S. J. *Adv. Free Radical Chem.* **1965**, *1*, 155.
(7) Wilt, J. W. In ref 3, p 466.
(8) For an extensive review of unimolecular radical reactions, see: Beckwith, A. L. J.; Ingold, K. U. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, in press.
(9) Raley, J. H.; Rust, F. F.; Vaughan, W. E. *J. Am. Chem. Soc.* **1948**, *70*, 1336.

Scheme II

$$\text{photolabile molecule} \xrightarrow{h\nu} R_1\cdot$$

$$R_1\cdot \xrightarrow{k_1} R_2\cdot \quad (+Y)$$

$$\left.\begin{array}{l} R_1\cdot + R_1\cdot \xrightarrow{k^{11}} \\ R_1\cdot + R_2\cdot \xrightarrow{k^{12}} \\ R_2\cdot + R_2\cdot \xrightarrow{k^{22}} \end{array}\right\} \text{nonradical products}$$

constants can be determined by analysis for acetone and *tert*-butyl alcohol.

$$\frac{k^{AH}}{k_\beta} = \frac{[Me_3COH]}{[AH][Me_2CO]}$$

If a separate experiment is carried out with a substrate BH at the same temperature and in the same solvent, the relative rates of hydrogen abstraction, k^{AH}/k^{BH}, can be compared since k_β remains constant and can be divided out. Of course, *the absolute values of k^{AH} and k^{BH} could have been determined if the clock had been calibrated*, i.e., if k_β had been measured under the appropriate conditions. The kinetic data would then have come simply from product analysis. This shows that the free-radical clock concept is both simple and powerful.

Rate constants for a large number of unimolecular radical reactions have been measured in the gas phase, generally at elevated temperatures.[10] Most of these reactions are relatively slow at ambient temperatures, and they are therefore unsuitable for use as clock reactions in solution under "typical" organic reaction conditions. If unimolecular clock reactions are to be used to determine *absolute* rate constants for radical–molecule reactions in solution, then, for each class of radical (e.g., primary alkyls), there is a need for clocks, calibrated for solution work, which cover a range of time scales. Only in this way can both fast and slow radical–molecule reactions be examined.

A general procedure using EPR spectroscopy has been developed[11] which allows absolute rate constants, k_1, for unimolecular reactions to be measured in solution over a range of temperature. This yields the Arrhenius parameters, and so the clock reaction can be used in studies carried out at temperatures other than those at which k_1 was measured. Before the EPR procedure was developed, very few k_1 values had been measured for free radicals in solution, and generally such measurements were made at only one temperature. The number of clock reactions calibrated by EPR spectroscopy has grown rapidly in recent years. The purpose of this Account is to illustrate the utility of the approach with a few examples taken from the literature.

Experimental Methods

For calibration of a clock reaction, the radical, $R_1\cdot$, which is to undergo reaction is generated photochemically in an inert solvent directly in the cavity of an EPR spectrometer. The temperature of the sample is adjusted until the spectra of both $R_1\cdot$ and its product, $R_2\cdot$, can be observed simultaneously. Provided there are no

compounds present with which $R_1\cdot$, and $R_2\cdot$ could react, the total reaction system can be described by Scheme II. Under conditions of steady photolysis (where the radical concentrations do not change with time) we can write[12]

$$\frac{d[R_2\cdot]}{dt} = 0 = k_1[R_1\cdot] - 2k^{12}[R_1\cdot][R_2\cdot] - 2k^{22}[R_2\cdot]^2$$

This can be rearranged into the form

$$\frac{1}{[R_2]} = \frac{2k^{12}}{k_1} + \frac{2k^{22}[R_2\cdot]}{k_1[R_1\cdot]}$$

At each temperature the radical concentrations are varied by changing the incident light intensity with wire mesh screens placed between the sample and the lamp. A plot of $1/[R_2\cdot]$ against $[R_2\cdot]/[R_1\cdot]$ gives a straight line of slope $2k^{22}/k_1$ and intercept $2k^{12}/k_1$. This experiment has been carried out in full during studies of the β scission of *tert*-butoxytrialkoxyphosphoranyls,[13,14] $Me_3COP(OR)_3$, and *tert*-butoxycarbonyl,[15] $Me_3CO\dot{C}O$, radicals. However, it is more usual to find that the EPR signals are too weak to make accurate measurements of radical concentrations at anything but full light intensity. This presents no problem if, as is generally the case, the radicals in question are sterically unprotected at the radical center and, in their bimolecular self-reactions, undergo an irreversible coupling and/or β disproportionation. The bimolecular self-reactions for such radicals occur at the diffusion-controlled limit,[2,11] and therefore $k^{11} = k^{12} = k^{22}$. The above equation can, under such conditions, be simplified to

$$\frac{k_1}{2k^{22}} = [R_2\cdot](1 + [R_2\cdot]/[R_1\cdot])$$

and hence $k_1/2k^{22}$ can be obtained by measurement of the $R_1\cdot$ and $R_2\cdot$ concentrations at full light intensity only.[16]

The rate constant, $2k^{22}$, must be determined in a separate experiment by kinetic EPR spectroscopy.[2,11] The radical $R_2\cdot$ should be generated from an independent source and its decay should be monitored in the same solvent and over the same temperature range used to measure $k_1/2k^{22}$. When this is not possible, a

(12) The significance of the 2's in this equation may not be immediately obvious. Rate constants are generally defined in terms of the rate of formation of products, but in this system we are interested in the loss of reactants. In the $R_2\cdot + R_2\cdot$ reaction two $R_2\cdot$ are destroyed and so k^{22} must be multiplied by two. In the $R_1\cdot + R_2\cdot$ reaction only one R_2 is destroyed, but this cross-reaction will be statistically favored by a factor of two and hence k^{12} must also be multiplied by two.

(13) Davies, A. G.; Griller, D.; Roberts, B. P. *Angew. Chem., Int. Ed. Engl.* 1971, *10*, 738; *J. Chem. Soc., Perkin Trans. 2* 1972, 993.

(14) Watts, G. B.; Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* 1972, *94*, 8784.

(15) Griller, D.; Roberts, B. P. *Chem. Commun.* 1971, 1035; *J. Chem. Soc., Perkin Trans. 2* 1972, 747.

(16) This technique can obviously be extended so as to measure rate constants for radical–molecule reactions under pseudo-first-order kinetic conditions. That is, the $R_1\cdot \to R_2\cdot$ rearrangement can be replaced by

$$R_1\cdot + M \xrightarrow{k_1^M} R_2\cdot \ (+Y)$$
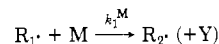
The kinetic treatment is the same except that k_1 must be replaced by $k_1^M[M]$. This procedure and variants of it have been exploited recently by a number of groups.[17]

(17) Hellebrand, J.; Wünsche, P. *Faserforsch. Textiltech.* 1976, *27*, 621. Shiraishi, H.; Ranby, B. *Chem. Scr.* 1977, *12*, 118. Baban, J. A.; Roberts, B. P. *J. Chem. Soc., Chem. Commun.* 1979, 373.

(10) See, for example: Robinson, P. J.; Holbrook, K. A. "Unimolecular Reactions"; Wiley: New York, 1972; Chapter 7.

(11) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* 1980, *13*, 193.

satisfactory procedure is to generate $R_2\cdot$ from $R_1\cdot$ at temperatures sufficiently high that $R_1\cdot$ can no longer be detected. The measured values of $2k^{22}$ can then be extrapolated to the lower temperatures where they are required from a knowledge of the temperature dependence of the solvent's viscosity.[18] Similarly, if $R_1\cdot$ and $R_2\cdot$ are both simple alkyl radicals, $2k^{22}$ can be estimated from measurements of $2k^{11}$ at temperatures below those where $R_1\cdot$ rearranges. For small alkyl radicals $2k^{22}$ can also be calculated from solvent viscosities.[18]

Under typical experimental conditions, free radicals which undergo bimolecular self-reactions at the diffusion-controlled limit can be photogenerated at concentrations of 10^{-6} to 10^{-8} M.[11] To reduce error the $R_1\cdot$ and $R_2\cdot$ concentrations will normally be measured at $[R_1\cdot]/[R_2\cdot]$ ratios from ca. 5:1 to 1:5. Since $2k^{22}$ will generally have a value of ca. 10^9–10^{10} M^{-1} s^{-1}, the experiments are actually carried out at temperatures where k_1 is ca. 10^2–10^4 s^{-1}.

A few additional EPR techniques for calibrating clock reactions are worth noting, though they are all of more limited applicability than the preceding method. For example, radicals which are relatively persistent at low temperatures because their bimolecular self-reactions have been retarded by steric factors may undergo a unimolecular decay at higher temperatures. In such a situation the rate constant for the unimolecular process can generally be obtained simply by monitoring the disappearance of the starting radical. This procedure was first applied to the β scission of *tert*-butoxytrialkoxyphosphoranyls.[14]

$$Me_3CO\dot{P}(OR)_3 \xrightarrow{k_\beta} Me_3\dot{C} + O{=}P(OR)_3$$
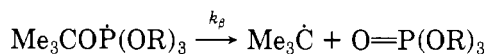
The values of k_β obtained by these direct measurements were in satisfactory agreement with the values obtained by the measurement of the $Me_3CO\dot{P}(OR)_3$ and $Me_3\dot{C}$ concentrations under steady photolysis[13,14] (vide supra), thereby enhancing confidence in both procedures.

Other clock reactions which have been calibrated by direct EPR measurements of unimolecular decay rate constants include the isomerization of certain sterically hindered phenyls[11,19] and the β scission of di-*tert*-butylketiminyl.[20]

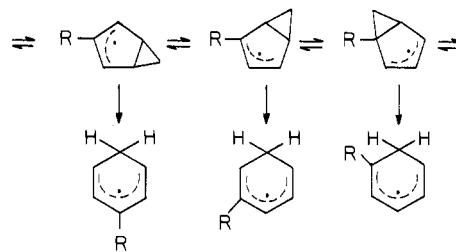$$(Me_3C)_2C{=}N\cdot \rightarrow Me_3C\cdot + Me_3CC{\equiv}N$$

The lifetimes of most radicals can be increased by isolating them in an inert matrix which prevents radical–radical decay processes from occurring. Under such conditions even a very slow unimolecular decay process may be followed by EPR. This procedure was first employed by Sustmann and Lübbe[21] who used an adamantane matrix to study the degenerate 1,4-sigmatropic rearrangement of the methylene bridge in bicyclo[3.1.0]hexenyl and its electrocyclic ring opening to cyclohexadienyl (for which $\Delta G^{\ddagger} = 16.4$ kcal/mol at -50 °C).

The rearrangements of substituted bicyclo[3.1.0]hexenyls have also been studied in the same matrix,[21,22] as has the ring opening of cyclobutylhydroxymethyl.[23] Of course, some question will always remain as to whether rates and Arrhenius factors determined for a radical rearrangement in a matrix can be utilized as a calibrated clock reaction in solution studies, since even as small a radical as *tert*-butyl suffers distortion in adamantane matrixes.[24]

Finally, certain isomerizations which proceed at a rate suitable for study by EPR line broadening[25] could, in principle, serve as clock reactions after labeling the radical either isotopically (e.g., with deuterium) or with a group sufficiently remote from the radical center that it would be unlikely to affect the isomerization rate. The EPR time scale is such that these measured rate constants are about 10^7 s^{-1}. However, since the measurements may have to have been made well above or well below ambient temperatures, the rate constants extrapolated to room temperature can lie in the range 10^5–10^{10} s^{-1}. Many symmetric isomerizations have been studied by line-broadening methods,[9] e.g., rotations of allylic radicals,[26] inversions of vinyl[27] and oxiranyl[28] radicals, etc., but few of these processes have actually been employed in any mechanistic or kinetic studies. Their utility as clock reactions remains largely unexplored.

Calibrated Clock Reactions

Full exploitation of the clock reaction concept requires that, for each class of radicals, there should be available a collection of calibrated clock reactions which cover a wide range of time scales. We suggest that such a collection be called an *"horlogerie"* which, in French, denotes a small store where clocks can be obtained.

The Primary Alkyl Horlogerie. The rearrangements of about a dozen primary alkyl radicals have been studied by EPR spectroscopy, and this class of radicals constitutes the most extensive horlogerie of free radi-

(21) Sustmann, R.; Lübbe, F. *J. Am. Chem. Soc.* 1976, *98*, 6037; *Chem. Ber.* 1979, *112*, 42.

(22) Lübbe, R.; Sustmann, R. *Chem. Ber.* 1979, *112*, 57.

(23) Blum, P. M.; Davies, A. G.; Henderson, R. A. *J. Chem. Soc., Chem. Commun.* 1978, 569.

(24) Griller, D.; Ingold, K. U.; Krusic, P. J.; Fischer, H. *J. Am. Chem. Soc.* 1978, *100*, 6750.

(25) For reviews of EPR line broadening by dynamic processes, see: Wertz, J. E.; Bolton, J. R. "Electron Spin Resonance"; McGraw-Hill: New York, 1972; Fischer, H. "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 2, Chapter 19. Ladd, J. A.; Wardale, W. H. "Internal Rotation in Molecules"; Orville-Thomas, W. J., Ed.; Wiley: New York, 1974; Chaper 5. Kochi, J. K. *Adv. Free Radical Chem.* 1975, *5*, 189. Bubnov, N. N.; Solodovnikov, S. P.; Prokof'ev, A. I.; Kabachnik, M. I. *Russ. Chem. Rev.* 1978, *47*, 549.

(26) Sustmann, R.; Trill, H. *J. Am. Chem. Soc.* 1974, *96*, 4343. Krusic, P. J.; Meakin, P.; Smart, B. E. *Ibid.* 1974, *96*, 6211. Smart, B. E.; Krusic, P. J.; Meakin, P.; Bingham, R. C. *Ibid.* 1974, *96*, 7382. Sustmann, R.; Trill, H.; Brandes, D. *Chem. Ber.* 1977, *110*, 245. Sustmann, R.; Trill, H.; Vahrenholt, F.; Brandes, D. *Ibid.* 1977, *110*, 255.

(27) Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* 1963, *39*, 2147. Cochran, E. L.; Adrian, F. J.; Bowers, V. A. *Ibid.* 1964, *40*, 213. Fessenden, R. W. *J. Phys. Chem.* 1967, *71*, 74.

(28) Itzel, H.; Fischer, H. *Helv. Chim. Acta* 1976, *59*, 880.

(18) Schuh, H.; Fischer, H. *Int. J. Chem. Kinet.* 1976, *8*, 341; *Helv. Chim. Acta* 1978, *61*, 2130. Lehni, M.; Schuh, H.; Fischer, H. *Int. J. Chem. Kinet.* 1979, *11*, 705.

(19) (a) Brunton, G.; Griller, D.; Barclay, L. R. C.; Ingold, K. U. *J. Am. Chem. Soc.* 1976, *98*, 6803. (b) Brunton, G.; Gray, J. A.; Griller, D.; Barclay, L. R. C.; Ingold, K. U. *J. Am. Chem. Soc.* 1978, *100*, 4197.

(20) Griller, D.; Mendenhall, G. D.; Van Hoof, W.; Ingold, K. U. *J. Am. Chem. Soc.* 1974, *96*, 6068.

Table I
Kinetic Parameters Obtained by EPR for Primary Alkyl Radical Clocks

no.	reaction	$k^{25\,°C}$, s^{-1}	log (A/s^{-1})	E, kcal/mol	ref
1	(structure)	1.0×10^5	9.5	6.1	29, 30
2	(structure)	3.9×10^3	9.9	8.6	31
3	(structure)	1.3×10^8	12.5	5.9	32
4	(structure)	4.9×10^3	9.1	10.4	33
5	(structure)	$\geqslant 3.2 \times 10^{5}$ [b]	9.1 [c]	$\leqslant 4.9$ [b]	34
6	(structure)	49	12.4	14.6	35
7	(structure)	<0.01 [b]	11.8 [c]	>19 [b]	33
8	(structure)	10 [b]	11.8 [c]	14.7 [b]	36
9	(structure)	59 [b]	11.8 [c]	13.6 [b]	37, 38
10	(structure)	59 [b]	11.8 [c]	13.6 [b]	38
11	(structure)	1.4×10^3	11.8	11.8	38
12	(structure)	7.8×10^2	11.7	12.0	38
13	(structure)	2.9×10^3 [b]	11.8 [c]	11.3 [b]	38

[a] By deuterium labeling.   [b] Calculated from the experimentally measured rate constant (or its limiting value) and the assumed A factor.   [c] Assumed.

cals. The radicals, their rearrangements, and the Arrhenius parameters for these processes are listed in Table I.[29-38] It can be seen that within this horlogerie we have radicals whose room-temperature-rearrangement rate constants cover more than 7 orders of magnitude. This means that a suitable competitor is now available for almost any reaction involving a molecule and a primary alkyl radical.

The primary alkyl radical clocks listed in Table I have, with one exception, been used only occasionally in quantitative kinetic studies of radical–molecule reactions. This can be attributed to the fact that many of these clocks have been calibrated only recently. The exception is the cyclization of 5-hexenyl to cyclopentylmethyl (reaction 1) which has been widely used as a mechanistic probe and kinetic standard. This is probably because the rearrangement rate constant at ambient temperatures was first estimated back in 1968[39]

and the Arrhenius parameters were determined by the steady-state EPR method as early as 1974.[29]

Examples illustrative of its use in mechanistic studies include examinations of the formation[40] and oxidation[41] of Grignard reagents, the reduction of alkyl halides with sodium napthalenide and similar reagents,[42] the reactions of enones,[43] the Wittig rearrangement,[44] the reductive-elimination reactions of dialkylmercury compounds,[45] the reductive demercuration of alkylmercury halides,[46] and the reduction of alkyl halides with zinc and acid.[47] While a knowledge of the rate constant for the 5-hexenyl cyclization was of considerable importance in all above-mentioned work, rate constants for the radical–molecule reactions of interest were not evaluated. However, the fact that this clock has been calibrated has been used in other studies in which rate constants have been evaluated for the reactions of primary alkyls with cupric acetate,[48] with chromium(II)

(29) Lal, D.; Griller, D.; Husband, S.; Ingold, K. U. *J. Am. Chem. Soc.* 1974, *96*, 6355.
(30) Schmid, P.; Griller, D.; Ingold, K. U. *Int. J. Chem. Kinet.* 1979, *11*, 333.
(31) Griller, D.; Schmid, P.; Ingold, K. U. *Can. J. Chem.* 1979, *57*, 831.
(32) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* 1976, *98*, 7024.
(33) Effio, A.; Griller, D.; Ingold, K. U.; Beckwith, A. L. J.; Serelis, A. K. *J. Am. Chem. Soc.* 1980, *102*, 1734.
(34) Effio, A.; Griller, D.; Ingold, K. U.; Warkentin, J. Unpublished results.
(35) Warkentin, J.; Ingold, K. U. *Can. J. Chem.* 1980, *58*, 348.
(36) Brunton, G.; McBay, H. C.; Ingold, K. U. *J. Am. Chem. Soc.* 1977, *99*, 4447.
(37) Hamilton, E. J., Jr.; Fischer, H. *Helv. Chim. Acta* 1973, *56*, 795.
(38) Maillard, B.; Ingold, K. U. *J. Am. Chem. Soc.* 1976, *98*, 1224, 4692.

(39) Carlsson, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* 1968, *90*, 7047.
(40) Bodewitz, H. W. H. J.; Blomberg, C.; Bickelhaupt, F. *Tetrahedron* 1975, *31*, 1053.
(41) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* 1970, *92*, 6609.
(42) Garst, J. F.; Barbas, J. T. *J. Am. Chem. Soc.* 1974, *96*, 3239. Garst, J. F.; Roberts, R. D.; Pacifici, J. A. *Ibid.* 1977, *99*, 3528. Sease, J. W.; Reed, R. C. *Tetrahedron Lett.* 1975, 393.
(43) House, H. O.; Weeks, P. D. *J. Am. Chem. Soc.* 1975, *97*, 2778.
(44) Garst, J. F.; Smith, C. D. *J. Am. Chem. Soc.* 1976, *98*, 1526.
(45) Nugent, W. A.; Kochi, J. K. *J. Am. Chem. Soc.* 1976, *98*, 5405; *J. Organomet. Chem.* 1977, *124*, 327.
(46) Quirk, R. P.; Lea, R. E. *Tetrahedron Lett.* 1974, 1925; *J. Am. Chem. Soc.* 1976, *98*, 5973.
(47) Brace, N. O.; Van Elswyck, J. E. *J. Org. Chem.* 1976, *41*, 766.
(48) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* 1972, *94*, 843.

salts,[49] with sodium naphthalenide,[50] with alkali benzophenone ketyls,[51] with protonated heteroaromatic bases,[52] with a vanadium hydride,[53] with 1,4-benzoquinone,[54] with *tert*-butyl hydroperoxide,[55] and with a variety of nitroso and nitrone spin traps.[56] The two last mentioned reactions provide particularly good illustrations of the 5-hexenyl clock in action:

Hydrogen Atom Abstraction from Hydroperoxides. It is well established[57] that the rates of free-radical bromination of alkanes and alkyl halides in solution are influenced by reaction of the chain-carrying alkyl radical with the HBr produced as the reaction progresses. That is, in these reactions, the H-atom abstraction step is reversible.

$$Br\cdot + RH \rightleftharpoons HBr + R\cdot$$
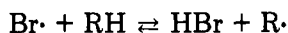
The question arose as to whether the H abstraction in autoxidation was also reversible under normal conditions since the thermochemistry of this reaction is similar to that of $Br\cdot + RH$ reactions.

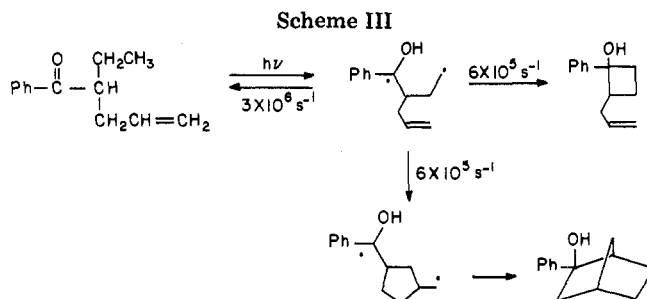$$R'OO\cdot + RH \underset{?}{\rightleftharpoons} R'OOH + R\cdot$$
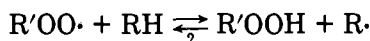
Such reversibility could interfere with relative and absolute reactivities.[58] Experiments in which 5-hexenyl was generated in the presence of *tert*-butyl hydroperoxide at 50 °C showed that the rate constant for abstraction of the peroxidic hydrogen was some 5 orders of magnitude smaller than the rate constant for the reaction of alkyls with molecular oxygen.[55]
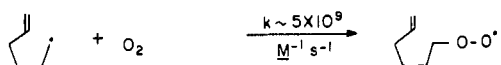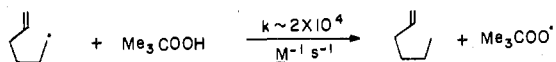

Reversibility of hydrogen abstraction is therefore unimportant under the autoxidation conditions usually employed.

Rate of Trapping by "Spin Traps". In the EPR spectroscopic technique of "spin trapping"[60] a transient radical, R·, is "visualized" by allowing it to add to a spin trap, T, and so form a persistent spin adduct, RT·. This technique has been employed qualitatively to detect and identify free radicals for several years, but its quantitative use in mechanistic studies has been hampered by a lack of knowledge of the rates at which

(49) Kochi, J. K.; Powers, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 137.

(50) Garst, J. F.; Barton, F. E., II. *J. Am. Chem. Soc.* **1974**, *96*, 523.

(51) Garst, J. F.; Smith, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 1520.

(52) Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *J. Am. Chem. Soc.* **1977**, *99*, 7960.

(53) Kinney, R. J.; Jones, W. D.; Bergman, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 7902.

(54) Citterio, A. *Tetrahedron Lett.* **1978**, 2701; Citterio, A.; Arnoldi, A.; Minisci, F. *J. Org. Chem.* **1979**, *44*, 2674.

(55) Howard, J. A.; Tong, S. B. *Can. J. Chem.* **1979**, *57*, 2755.

(56) Schmid, P.; Ingold, K. U. *J. Am. Chem. Soc.* **1978**, *100*, 2493. Maeda, Y.; Schmid, P.; Griller, D.; Ingold, K. U. *J. Chem. Soc., Chem. Commun.* **1978**, 525.

(57) Tanner, D. D.; Pace, T.; Ochiai, T. *Can. J. Chem.* **1975**, *53*, 2202; *J. Am. Chem. Soc.* **1975**, *97*, 4303, 6162. Tanner, D. D.; Kosugi, Y.; Arhart, R.; Wada, N.; Pace, T.; Ruo, T. *Ibid.* **1976**, *98*, 6275.

(58) This aspect is particularly important for reactivities determined in the presence of large concentrations of hydroperoxide (the hydroperoxide method[5,59]).

(59) Howard, J. A.; Schwalm, W. J.; Ingold, K. U. *Adv. Chem. Ser.* **1968**, *No. 75*, 6. Korcek, S.; Chenier, J. H. B.; Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1972**, *50*, 2285.

(60) Perkins, M. J. *Spec. Publ. Chem. Soc.* **1970**, *No. 24*, 97. Janzen, E. G. *Acc. Chem. Res.* **1971**, *4*, 31.

Scheme III

radicals of different classes react with the most commonly employed spin traps. For primary alkyls the 5-hexenyl cyclization appeared likely to provide an ideal clock if it were not for the fact that because both the open and cyclized radicals are primary alkyls the spectrum of their spin adducts would be indistinguishable.[56] This difficulty was overcome by labeling 5-hexenyl with ^{13}C in the 1-position. The spin adduct of the uncyclized radical then showed an additional EPR hyperfine splitting due to the neighboring ^{13}C, while the adduct of the cyclized radical did not because the ^{13}C was too remote from the radical center.[56]
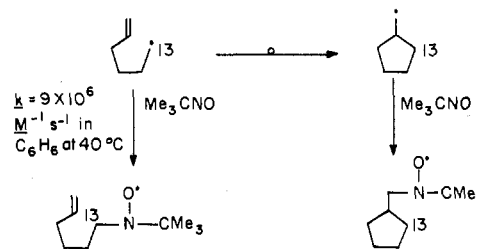
Perhaps the most intriguing application to date of the 5-hexenyl clock has been its use to estimate the lifetime of a triplet-derived 1,4-diradical.[61] This ingenious experiment, which yielded ca. 1% of 2-phenyl-2-norbornanol, is outlined in Scheme III.

It is interesting to compare the rates of some of the reactions listed in Table I. The cyclization of 5-hexenyl (reaction 1) is about 5 times faster than that of 5-hexynyl ($k^{25°C} \sim 2 \times 10^4$ s^{-1})[62] which is 5 times faster than that of 4-cyanobutyl (reaction 2). This order and the relatively small change in rate are consistent with the estimated thermochemistry for the model reactions: H· + C_2H_4, −38.6 kcal/mol; H· + C_2H_2, −37.3 kcal/mol; and H· + CH_3CN, −36.7 kcal/mol.[31] There is, in contrast, a very large difference in the rates of the "neophyl-like" rearrangements of the radicals derived from 1,2-di-*tert*-butylethylene (reaction 5) and di-*tert*-butylacetylene (reaction 6). This can be explained by the fact that in these 1,2-group shifts the transition state (or intermediate) has a three-center cyclic structure and there is considerably more strain energy (ca. 14 kcal/mol) in the alkylidenecyclopropane, B, than in the alkylcyclopropane, A.[35]

A   B

The 3-butenyl rearrangement (an identity reaction) proceeds via an intermediate cyclopropylmethyl radical

(61) Wagner, P. J.; Liu, K.-C. *J. Am. Chem. Soc.* **1974**, *96*, 5952.

(62) Not measured by EPR. See footnote 7 of ref 31.

Table II
Kinetic Parameters Obtained by EPR for Other Radical Clocks

reaction	$k^{25°C}$, s^{-1}	log (A/s^{-1})	E, kcal/mol	ref
[structure → structure]	1.3×10^5	9.8	6.4	67
[structure → structure]	9.8×10^3	15	15	28[a]
[structure → structure]	b	b	8.0	68
[structure → structure]	6.5×10^4	11.2	8.7	69
[structure → structure]	1.6×10^4	9.7	7.5	69[a]
[structure → structure]	1.3×10^3	9.0	8.0	69[a]
[structure → structure + CO_2]	3.3×10^4	13.4	12.1	15[c]
[structure → structure + CO]	1.2×10^5	11.9	9.3	70
[structure → structure + CO]	5.2×10^{7} [d]	13[e]	7.2[d]	36
[structure → structure]	1.3[f]	g	g	19[a]
[structure → structure]	1.2×10^5	12.8	10.5	71
[structure → structure + structure]	71	14.4	17.1	20
$+OP(OEt)_3 \rightarrow {>}{-} + O{=}P(OEt)_3$	6.3×10^4	10.3	7.5	13, 14,[a] 72
$+OP({-}⟨O⟩)_3 \rightarrow {>}{-} + O{=}P({-}⟨O⟩)_3$	6.6×10^2	11.7	12.1	73

[a] Additional kinetic data are reported for some analogous reactions. [b] Not measured. [c] See also: Perkins, M. J.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2*, 1974, 297. [d] Calculated from the experimentally measured rate constant and assumed A factor. [e] Assumed. [f] At -26 °C. [g] Does not follow normal Arrhenius behavior because of quantum-mechanical tunneling.

(reaction 4). The latter undergoes a very rapid ring opening (reaction 3). Comparisons of reactions 4 (+3) with 5 and 7 with 9 shows that there is a very large rate enhancement in the 1,3 shift of an unsaturated group for $RCMe_2\dot{C}H_2$ radicals relative to $RCH_2\dot{C}H_2$ radicals. This can be attributed to the *gem*-dialkyl (Thorpe–Ingold) effect.[63] That is, ring closure reactions yielding three-membered rings proceed more rapidly when methyl groups are introduced into the reactant. This effect is usually ascribed to compression of the internal angle of the ring and expansion of the external angle as steric strain between the alkyl groups is relieved. However, it must be added that current thermochemical methods[64] do not predict any such effect.[35,65] Whether the problem lies in the thermochemistry itself or in its application to an assumed transition state remains to be determined.

The neophyl rearrangement (reaction 9), though relatively slow, has the distinction of being the first free-radical rearrangement to be recognized.[66] Some analogues of this rearrangement (reactions 11–13) occur more rapidly and others (reactions 7, 8) more slowly. The benzoylmethyl rearrangement (reaction 8) remains the only clock reaction in which there is a 1,2 shift of an unsaturated group from carbonyl carbon to alkyl carbon.

The Other Horlogeries. Although the primary alkyl horlogerie is well stocked, the inventories in other horlogeries, particularly those of heteroatom-centered radicals, are very disappointing. This can be seen from Table II[67–73] which lists the majority of the remaining clock reactions which have been calibrated (many

(63) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; pp 197–202.

(64) Benson, S. W. "Thermochemical Kinetics", 2nd ed.; Wiley: New York, 1976.

(65) That is, $\Delta H_f^°[RCMe_2\dot{C}H_2] - \Delta H_f^°[\cdot \overline{RCMe_2CH_2}] = \Delta H_f^°[RCH_2\dot{C}H_2] - \Delta H_f^°[\cdot \overline{RCH_2CH_2}]$, R = $H_2C{=}CH$, $HC{\equiv}C$, C_6H_5.[35]

(66) Urry, W. H.; Kharasch, M. S. *J. Am. Chem. Soc.* 1944, *66*, 1438.

(67) Maeda, Y.; Ingold, K. U. *J. Am. Chem. Soc.* 1979, *101*, 4975.

(68) Steenken, S.; Schuchmann, H. P.; von Sonntag, C. *J. Phys. Chem.* 1975, *79*, 763.

(69) Perkins, M. J.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* 1975, 77.

(70) Schuh, H.; Hamilton, E. J.; Paul, H.; Fischer, H. *Helv. Chim. Acta* 1974, *57*, 2011.

(71) Maeda, Y.; Ingold, K. U. *J. Am. Chem. Soc.* 1980, *102*, 328.

(72) See also: Baban, J. A.; Cooksey, C. J.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* 1979, 781.

(73) Griller, D.; Ingold, K. U.; Patterson, L. K.; Scaiano, J. C.; Small, R. D., Jr. *J. Am. Chem. Soc.* 1979, *101*, 3780.

somewhat roughly) by EPR together with their kinetic parameters. Some important classes of radicals are represented by only a single clock, but many more are completely unrepresented. Few readers will be lucky enough to find in this table a clock reaction of use to them in their current research. We hope, therefore, that this Account will stimulate additional EPR kinetic studies on unimolecular radical reactions and that many horlogeries will become well stocked during the coming decade.

Catalysis of Chemical Reactions by Electrodes

JEAN MICHEL SAVEANT

Laboratoire d'Electrochimie de l'université de Paris VII, 75221 Paris Cedex 05, France

An early example of catalysis of an organic reaction by an electrode was given by the observation that the nucleophilic substitution reaction of 4-bromobenzophenone (ArX) with thiophenolate (Nu⁻) can be triggered electrochemically, the electrode potential being set in a region corresponding to reduction of the substrate (Scheme I). Evidence for such a reaction mechanism was provided by cyclic voltammetry but also by preparative-scale experiments in which the yield of substitution product was 80% and the number of faradays passed through the electrolytic cell per mole of starting material was 0.2. The latter figure clearly pointed to the catalytic character of the electrochemical process.
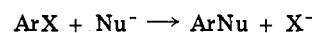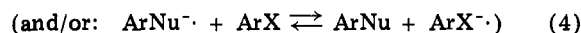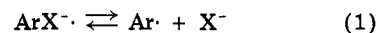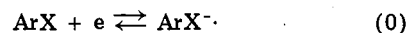
This reaction can be viewed as an example of a general class of processes in which a chemical reaction that would proceed slowly under normal thermal conditions is accelerated by the presence of an electrode set up at a suitable potential. Such electrochemical inducements are based upon the greater reactivity of a lower or higher oxidation state than of the starting system.

Scheme II represents inducement of reaction by a reduction–oxidation cycle but is immediately transposable to an oxidation–reduction process. The reaction at the −1 oxidation state need not necessarily be a single-step reaction. In Scheme I it is indeed a two-stage reaction: cleavage of the anion radical (eq 1) and then nucleophilic attack of the resulting neutral radical (eq 2).
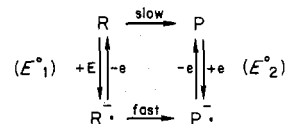
More generally, one can view the processes going on at each electrode of any electrochemical cell as adding up to a balanced overall chemical reaction. If the standard free energy, $\Delta G°$, of this reaction is positive, electrolysis will involve the conversion of electrical energy into chemical energy leading thus to an actual *electrosynthesis*. The amount of electrical energy required to carry out the synthesis will generally be larger than $\Delta G°$ owing to the necessity of overcoming activation barriers in both electrode reactions.

In the reverse situation where $\Delta G° < 0$, the generation of electricity is in principle possible. The activation barriers may, however, be so high that no electricity can

Jean-Michel Savéant was born in Brittany in 1933. He attended the École Normale Supérieure where he received the Doctorat-es-Sciences degree and taught until 1971 when he moved to his present position as Professor of Chemistry at the University of Paris VII. His current research interests involve the study of reactivity and mechanisms in organic and bioinorganic electrochemistry. He has contributed to the development of electrochemical methods, especially cyclic voltammetry.

Scheme I

$$ArX + e \rightleftarrows ArX^{-\cdot} \qquad (0)$$

$$ArX^{-\cdot} \rightleftarrows Ar\cdot + X^{-} \qquad (1)$$

$$Ar\cdot + Nu^{-} \longrightarrow ArNu^{-\cdot} \qquad (2)$$

$$ArNu^{-\cdot} - e \rightleftarrows ArNu \qquad (3)$$

(and/or: $\quad ArNu^{-\cdot} + ArX \rightleftarrows ArNu + ArX^{-\cdot}$)   (4)

$$ArX + Nu^{-} \longrightarrow ArNu + X^{-}$$

Scheme II

$$R \xrightarrow{\text{slow}} P$$

$$(E°_1) \; +E \Big\updownarrow -e \qquad -e \Big\updownarrow +e \; (E°_2)$$

$$R^{-\cdot} \xrightarrow{\text{fast}} P^{-\cdot}$$

R, reactant; P, product

be obtained. An *electrochemical activation* of the reaction can then be obtained by providing a finite, stoichiometric, amount of electricity which serves to overcome the activation barriers.

An actual *electrocatalytic* situation is met when, $\Delta G°$ still being negative, the number of faradays required to drive the reaction to completion tends toward zero.

With reference to Scheme II, two opposite situations can be encountered differing in the sequencing of the characteristic potentials. These are pictured in Figure 1 in the framework of a cyclic voltammetric analysis of the problem.

In the first case (Figure 1a) the reduction potential of the reactant (wave R) is positive with respect to the reduction potential of the product (wave P). Under such conditions, electrochemical inducement of the reaction will be obtained by setting the electrode potential just after the first wave. The process is then clearly electrocatalytic since at this potential, P⁻· is reoxidized into P. The catalytic efficiency will depend upon the competition offered by side reactions. An estimation of its magnitude within the time scale of cyclic voltammetry can be obtained from the heights of the R and P waves: an infinitely efficient process would correspond to complete disappearance of the R wave and full development of the P wave while a completely inefficient process would lead to the reverse situation.

In the reverse case, where the reduction potential of the reactant is negative to the standard potential of the (product)/(product)⁻· couple (Figure 1b), electrolysis at