Varamine B (2): $C_{21}H_{21}N_3O_2S$; UV (MeOH, free base) λ_{max} 234 nm (ϵ 25900), 274 (21400), 292 (sh), 324 (sh), 382 (3040), 462 (4320), 491 (sh); (pH 2) 223 (20570), 238 (sh), 266 (sh), 282 (sh), 294 (27400), 311 (17300), 362 (sh), 379 (4190), 529 (4720), 552 (4230); IR ($CHCl_3$) ν_{max} 3450, 3280, 3200, 1650, 1617 cm^{-1}; ^1H NMR (TFA salt, CD_3OD), identical with that of 1 except for δ 2.08 (s, 3 H, H-16) and absence of H-17 (see Table I); ^{13}C NMR (TFA salt, CD_3OD), identical with that of 1 except for δ 22.5 (s, C-16), 175.2 (s, C-15), and the absence of C-17 (see Table I); FABMS m/z 380 (MH^+, 100); HRMS found m/z 380.1420 (MH^+), $C_{21}H_{22}N_3O_2S$ requires 380.1433.

Oxidative Demethylation of Varamine A (1). Aqueous ceric ammonium nitrate (0.28 mL, 0.31 M, 87 μmol) was added to a stirred solution of varamine A TFA salt (1, 11.3 mg, 26.3 μmol) in 2:1 acetonitrile/water (5.0 mL) at 25 °C. After 1 min the red solution turned yellow, and TLC indicated the absence of starting material. After 6 min the mixture was diluted with water and extracted twice with ethyl acetate. The combined organic extracts were washed with brine and dried over sodium sulfate, and the solvent was removed to give iminoquinone **3** (9.0 mg, 90%). Chromatography over silica (2% methanol in dichloromethane) and crystallization from methanol gave compound **3** as fine golden needles.

Imino quinone 3: mp 205–207 °C; $C_{21}H_{19}N_3O_2S$; UV (MeOH) λ_{max} 262 nm (ϵ 25000), 299 (15200), 322 (sh), 373 (5300), 447 (3700); IR ($CHCl_3$) ν_{max} 3450, 3000, 1668, 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7.6 Hz), 2.14 (q, 2 H, J = 7.6 Hz), 2.65 (s, 3 H), 3.76 (m, 4 H), 6.30 (b s, 1 H, NH), 7.82 (td, 1 H, J = 8.0, 1.4 Hz), 7.95 (td, 1 H, J = 8.0, 1.4 Hz), 8.29 (dd, 1 H, J = 8.0, 1.4 Hz), 8.45 (d, 1 H, J = 5.6 Hz), 8.52 (dd, 1 H, J = 8.0, 1.4 Hz), 9.15 (d, 1 H, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 9.7 (q), 17.9 (q), 29.6 (t), 29.9 (t), 39.8 (t), 117.4 (s), 119.4 (d), 121.5 (s), 122.9 (d), 129.8 (d), 131.8 (d), 131.9 (d), 137.2 (s), 143.3 (s), 145.6 (s), 146.7 (s), 149.7 (s), 149.9 (d), 151.8 (s), 174.1 (s), 179.6 (s); FABMS m/z 380 ($MH^+ + H_2$, 100), 378 (MH^+, 25).

Acknowledgment. We thank Dr. F. Monniot, Museum National d'Histoire Naturelle, Paris, France, for identification of the tunicate, Mark Zabriskie for recording the 500-MHz ^1H NMR spectrum of 1, Dr. Lee K. Roberts for cytotoxicity testing, the Ministry of Home Affairs, Fiji, and the crew of the Molly Dean and Boss for assistance in the collection. This work was supported by NIH Grants CA 36622 and CA 01179. NMR studies were performed on an IBM AF200 spectrometer purchased with funds from the NSF (PCM 8400801) and partially supported by funds from the University of Utah Cancer Center Core Grant (5P30 CA042014).

Using Electron-Transfer Reactions To Propagate Radical Chain Processes[1]

R. J. Kolt, D. D. M. Wayner, and D. Griller*

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

Received February 1, 1989

The invention of radical-based methods for organic synthesis is an activity that has flourished over the last decade.[2,3] Many of the advances have depended upon a thorough knowledge of the relevant reaction kinetics so that highly reactive radical intermediates could be used in a controlled way. Designing new reactions using kinetic data is highly attractive since it allows the practitioner to select viable schemes with minimal expenditure of labor. While this approach has been highly refined for simple radical reactions, there exists an entire class of processes that are amenable to quantitative design and yet which appear not to have been exploited in a systematic way. These are single-electron-transfer reactions involving organic free radicals and neutral molecules.[4] In principle, the reaction thermodynamics are accessible from redox potentials and the reaction rate constants can be estimated by Marcus theory.[5]

Table I. Kinetic Chain Lengths, kcl, for the Electron-Transfer Chain Reduction of Isopropyl Bromoacetate by Isopropyl Alcohol[a]

time, min	[I-Br], mM	[I-H], mM	kcl
	$(CH_3)_2CHOH$		
0	200.0	0	58.3
10	74.3	91.6	23.2
20	31.1	147.7	9.2
30	2.6	168.8	3.7
	$(CD_3)CDOD$		
0	200.0	0	14.7
10	173.0	16.0	15.4
20	151.8	30.6	16.0
30	132.1	42.3	16.7
60	96.6	69.3	19.0
90	66.9	91.6	21.6

[a] kcl = R_p/R_i = (-d[I-Br]/dt)/(-d[benzophenone]/dt).

In this work, we have designed some simple radical chain reactions that incorporate an electron-transfer step. The radical, $(CH_3)_2\dot{C}OH$, was chosen as a reactant since it is very readily oxidized.[6-11] In fact, its oxidation potential versus the saturated calomel electrode (SCE) is −0.60 V in acetonitrile,[12,13] −1.11 V in isopropyl alcohol/acetonitrile (3:1, v/v),[12] and −1.3 V in water.[14] The values are below the reduction potentials of several possible substrates. Of these, we selected bromoacetates since, on reduction, they form carbon-centered radicals by loss of bromide ion. Reduction potentials for bromoacetates are ≥−0.88 V versus SCE[15] so that in isopropyl alcohol/acetonitrile mixtures, electron transfer between radical and substrate will be exothermic by at least 0.2 eV (5 kcal mol^{-1}). However, poorly defined values of the reorganization energy (λ_0) preclude calculation of an accurate reaction rate constant using Marcus theory.[5]

The efficacy of the reaction was tested by photolyzing (350 nm, Rayonet reactor at 30 °C) a mixture of benzophenone (0.01 M) and isopropyl bromoacetate, I-Br (0.20 M), in isopropyl alcohol hydrogen bromide formed in the reaction, eq 1–5 (R = CH_3). The rates of product formation were monitored as a function of time by using quan-

(1) Issued as NRCC No. 30210.
(2) Giese, G. In *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986.
(3) Curran, D. P. *Synthesis* **1988**, *417*, 489.
(4) For a comprehensive review of electron-transfer reactions between radicals and ions, see: Russell, G. A. *Adv. Phys. Org. Chem.* **1987**, *23*, 271.
(5) Eberson, L. In *Electron Transfer Reactions in Organic Chemistry*; Springer-Verlag: Berlin, 1987.
(6) (a) McMillan, M.; Norman, R. O. C. *J. Chem. Soc. B.* **1968**, 590. (b) Anderson, H. H.; Dobbs, A. J.; Edge, D. J.; Norman, R. O. C.; West, P. R. *J. Chem. Soc. B* **1971**, 1044.
(7) Shimokawa, T.; Sawai, T. *J. Nucl. Sci. Technol.* **1977**, *14*, 731.
(8) Ayscough, P. B.; Lambert, G. *J. Chem. Soc., Faraday Trans. I* **1978**, 2481.
(9) Wilputte-Steinert, L. *J. Mol. Catal.* **1978**, *4*, 113.
(10) Timpe, H.-J.; Wagner, R.; Dusi, R.; Paleta, O; Dadak, V. *Z. Chem.* **1986**, *26*, 256.
(11) Chaudhary, S. K.; Mitchell, R. H.; West, P. R. *Chemosphere* **1984**, *13*, 1113.
(12) Unpublished results from this laboratory.
(13) For a description of the technique used for measurement, see: Wayner, D. D. M.; McPhee, D. J.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 132.
(14) Lilie, J.; Beck, G.; Henglein, A. *Ber. Bunsenges, Phys. Chem.* **1971**, *75*, 458.
(15) Baizer, M. M.; Chruma, J. L. *J. Org. Chem.* **1972**, *37*, 1951.

0022-3263/89/1954-4259$01.50/0 Published 1989 by the American Chemical Society

titative GC analysis and authentic samples of reactants and products as calibrants, Table I.

$$R_2CHOH + Ph_2CO \xrightarrow{h\nu} R_2\dot{C}OH + Ph_2\dot{C}OH \quad (1)$$

$$R_2\dot{C}OH + \underset{\text{I-Br}}{BrCH_2C(O)OPr\text{-}i} \rightarrow R_2CO + HBr + \underset{\text{I}^\bullet}{\dot{C}H_2C(O)OPr\text{-}i} \quad (2)$$

$$R_2CHOH + \dot{C}H_2C(O)OPr\text{-}i \rightarrow R_2\dot{C}OH + \underset{\text{I-H}}{CH_3C(O)OPr\text{-}i} \quad (3)$$

$$2\ R_2\dot{C}OH \rightarrow \left.\begin{matrix} \\ \end{matrix}\right\} \text{nonradical products} \quad (4)$$

$$2\ I^\bullet \rightarrow \quad (5)$$

Measurements of benzophenone consumption showed that the rate of initiation, R_i, decreased exponentially with time. Concurrent measurements on the rate of disappearance of I-Br led to the rate of propagation, R_p. The kinetic chain length, i.e., the ratio R_p/R_i, decreased from 58 to 9 during the course of the reaction as the bromoacetate concentration changed from 0.20 to 0.03 M. This indicated that the electron-transfer step was rate controlling and therefore that eq 5 was the termination reaction. If hydrogen transfer had been rate controlling, the kinetic chain length would have increased since the R_p would have been independent of the concentration of I-Br. Kinetic analysis[16] over the course of the reaction using eq 6 and the literature value[8] for $2k_5$ gave $k_{et} = (2.0 \pm 0.4) \times 10^4\ M^{-1}\ s^{-1}$.

$$k_{et} = R_p(2k_5/R_i)^{1/2}/[\text{I-Br}] \quad (6)$$

As control experiments, we monitored the rate of disappearance of benzophenone in the absence of I-Br and found it to be identical with that observed when I-Br was present. This demonstrated that benzophenone was not regenerated during the course of the reaction. Moreover, no reaction took place in the absence of benzophenone, proving that initiation did not occur by direct photolysis of I-Br.

Interestingly, when the solvent was changed to perdeuterioisopropyl alcohol the kinetic chain length increased as the reaction progressed, indicating that deuterium transfer, cf. eq 3 was rate limiting with $R_p(2k_5/R_i)^{1/2} = k_3[(CD_3)_2CDOD] = 550 \pm 50\ s^{-1}$. Hydrogen transfer was also rate limiting when methanol was used as a solvent and a similar kinetic analysis gave $k_3[CH_3OH] = 400 \pm 50\ s^{-1}$ (see eq 3; R = H).

The reactions described above represent a useful way of delivering carbon-centered radicals without the use of tributyltin hydride.[17] Once a carbon-centered radical has been formed, the general practice in synthesis is to use it in inter- or intramolecular additions to multiple bonds.[3] As a preliminary example, we tried addition to an acetylene.

Photolysis of a mixture of non-1-yne (0.1 M), isopropyl bromoacetate (0.5 M), collidine (0.5 M), and benzophenone (0.01 M) in methanol gave I-H (32%; reactions 1–5, R = H), II-H (30%; reactions 1, 2, 7, and 8), and II-Br (38%; reactions 1, 2, 7, and 9) at 14% conversion of isopropyl bromoacetate.[18]

$$I^\bullet + CH_3(CH_2)_6C{\equiv}CH \rightarrow CH_3(CH_2)_6\dot{C}{=}CHCH_2C(O)OPr\text{-}i \quad (7)$$

$$II^\bullet + R_2\dot{C}HOH \rightarrow II\text{-}H + R_2\dot{C}OH \quad (8)$$

$$II^\bullet + I\text{-}Br \rightarrow II\text{-}Br + I^\bullet \quad (9)$$

where R = H

In this preliminary example, a unique product was not formed. However, its moderate success suggests that the approach is viable and that it could usefully be applied in *intra*molecular additions to multiple bonds where regioselectivity is typically much higher than in intermolecular cases. Indeed, we currently believe that there is great potential for the use of redox data in the design of radical chain reactions.

Experimental Section

Reaction mixture were carefully dexoxygenated by using nitrogen purging and were photolyzed (350 nm) in a Rayonet reactor at 30 °C. Samples were characterized by GC (Hewlett-Packard 5890A) and GC/mass spectrometry (Hewlett-Packard 5995) using 10 m × 0.2 mm diameter cross-linked methyl silicon columns and were quantified by GC using authentic samples as calibrants whenever possible and decane as an internal standard. The identity of II-Br was established by using electron impact and chemical ionization mass spectrometry.[18]

Acknowledgment. We thank Dr. L. Kerwin for a grant from the "President's Fund" which made this work possible.

(16) The usual steady-state approximation was made for the radical concentration and led to eq 6. For a related example, see: Howard, J. A. In *Free Radicals*; Kochi, J. K., Ed.; John Wiley & Sons: New York, 1973; Vol. 2, p 4.

(17) Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 299.

(18) II-H and II-Br were present as cis and trans isomers.