BLM concentrations was suggested by the reversal of this trend upon aeration of the reaction mixtures.

The demonstration that a synthetic dodecanucleotide can act as a sequence-selective substrate for BLM provides a powerful new tool for the study of this antitumor antibiotic at its putative therapeutic locus and a novel approach for the study of naturally occurring and synthetic DNA interactive agents.

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Photochemistry of [(Acyloxy)methyl]benzylsilanes. Evidence for the Primary Formation of a Benzyl–Silyl Radical Pair and Mechanism of Free Radical 1,2 (C → Si) Acyloxy Migration[1]

Mitsuo Kira, Hitoaki Yoshida, and Hideki Sakurai*

Department of Chemistry, Tohoku University
Sendai 980, Japan

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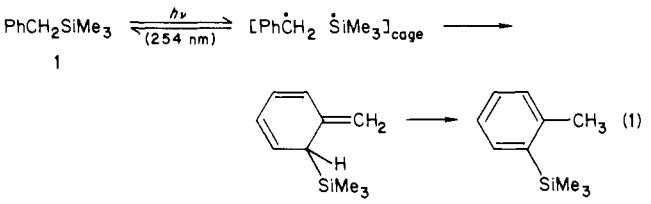
We report herein novel photochemistry of [(acyloxy)methyl]-benzyldimethylsilanes as well as benzyltrimethylsilane.[2] The results provide not only definitive evidence for the formation of a benzyl radical–silyl radical pair in the primary photochemical process but also an important insight into the detailed mechanism for free-radical 1,2 (C → Si) acyloxy migration found recently.[7]

Whereas benzyltrimethylsilane (**1**) has been described as photochemically inert,[3] the detailed study by our hands revealed that **1** actually isomerized to *o*-tolyltrimethylsilane (**2**) but with very low efficiency.[8] The results may suggest that the primary photochemical process is the homolysis of a benzyl carbon–silicon bond affording a benzyl–silyl radical pair in the solvent cage and that **2** is formed through recombination of the pair, while the major pathway of the reaction is the reformation of **1** (eq 1).



(1)

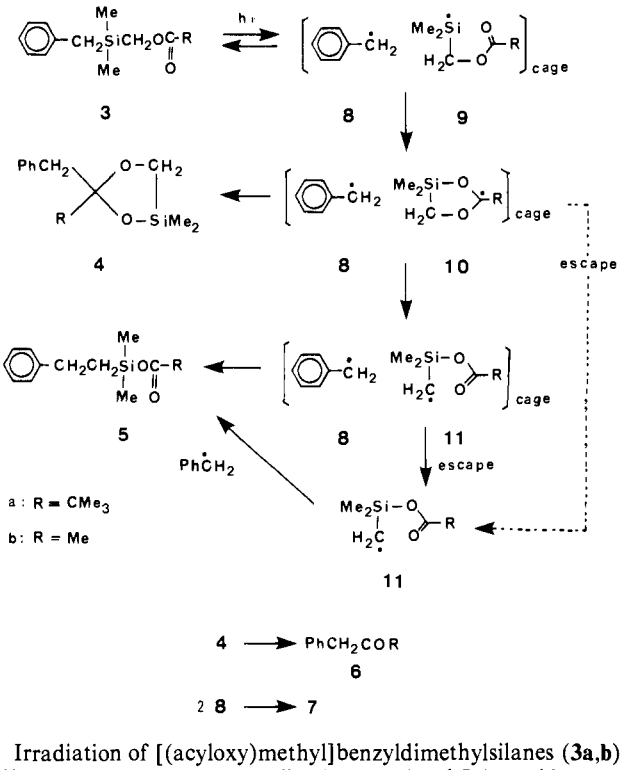
We have designed (acyloxy)methyl-substituted benzylsilanes, which bear an effective intramolecular silyl radical trap, in order to obtain evidence for the formation of the radical pair intermediate in the photoreaction. Intramolecular trapping of a silyl radical by an acyloxy carbonyl group, i.e., free radical 1,2 (C → Si) acyloxy migration,[7] may intercept the radical pair formed initially.

Table I. Product Distributions of the Photolysis of [(Acyloxy)methyl]benzyldimethylsilanes (**3**)[a]

3	conversion, %	products and yields, %[b,c] 4	5	6	7
a, R = *t*-Bu[d]	67	21 (0)	24 (0)	0 (21)	16 (16)
b, R = CH_3	88	11 (0)	13 (0)	4 (14)	13 (14)

[a] Irradiation was performed on a 0.1 M solution of **3** in benzene in a quartz tube with a 10-W low-pressure mercury arc lamp at ambient temperature for 4 h. [b] Yields were determined by GLC. [c] Yields after hydrolysis of the reaction mixtures were shown in parentheses. [d] *t*-$BuCO_2SiMe_3$ was also obtained in ca. 5% yield.

Scheme I



Irradiation of [(acyloxy)methyl]benzyldimethylsilanes (**3a,b**) afforded mainly the corresponding isomers **4** and **5**, benzyl ketones **6**, and bibenzyl (**7**). The reaction conditions, products,[9] and the yields are shown in Table I. The formation of these products may well be explained as shown in Scheme I involving the initial homolysis of the benzyl carbon–silicon bond followed by the 1,2 (C → Si) acyloxy migration of the [(acyloxy)methyl]dimethylsilyl radical **9**.

Detection of a dioxasilolane (**4a,b**) is particularly interesting since the results indicate involvment of the dioxasilolanyl radical **10** as an important intermediate of free radical 1,2 (C → Si) acyloxy migration. In contrast, the corresponding (C → C) acyloxy migration reportedly does not involve such a cyclic intermediate.[10]

In order to determine whether **4** and **5** were cage or escape products, a 51:49 mixture of **3a** and **3b**, where the former was labeled with deuterium at the para position (89% deuterium

(1) Chemistry of Organosilicon Compounds. 204.

(2) Whereas a number of photoreactions including cleavage of benzylic carbon–silicon bonds have been reported,[3–6] these cannot necessarily be regarded as intrinsic photochemistry of benzylsilane chromophore.

(3) Valkovich, P. B.; Ito, T. J.; Weber, W. P. *J. Org. Chem.* **1974**, *39*, 3543.

(4) (a) Nakadaira, Y.; Otsuka, T.; Sakurai, H. *Tetrahedron Lett.* **1981**, *22*, 2417, 2421. (b) Rich, J. D.; Dranhnak, T. J.; West, R. *J. Organomet. Chem.* **1981**, *212*, C1.

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(6) Sakurai, H.; Nakadaira, Y.; Sakaba, H. *Organometallics* **1983**, *2*, 1484.

(7) Wilt, J. W.; Keller, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 1395.

(8) In a typical experiment, irradiation of **1** in dry benzene (ca. 0.1 M) with a 10-W low-pressure mercury arc lamp for 9 h afforded **2** in 2% yield with recovered **1** (91%).

(9) All the products except for **4b** were isolated by preparative GLC and identified with mass and ^1H NMR spectroscopy. **4a**: ^1H NMR (200 MHz, $CDCl_3$) δ −0.63 (s, 3), 0.17 (s, 3), 0.97 (s, 9), 2.83 (d, 1, J = 13.2 Hz), 3.00 (d, 1, J = 13.2 Hz), 3.08 (d, 1, J = 12.8 Hz), 3.25 (d, 1, J = 12.8 Hz), 7.0–7.4 (m, 5); mass spectrum (70 eV), *m/e* (relative intensity) 264 (0.5, M^+), 249 (3.2, $M^+ - 15$), 173 (90), 91 (34), 57 (100). Whereas **4b** could not be isolated by routine methods, the proposed structure was supported by the analogous mass spectral pattern with **4a** as well as the facile hydrolysis to **6b**.

(10) (a) Beckwith, A. L.; Thomas, C. B. *J. Chem. Soc., Perkin Trans 2* **1973**, 861. (b) Perkins, M. J.; Roberts, B. P. *Ibid.* **1975**, *77*. (c) Barclay, L. R. C.; Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1982**, *104*, 4399. (d) Barclay, L. R. C.; Lusztyk, J.; Ingold, K. U. *Ibid.* **1984**, *106*, 1793. (e) Beckwith, A. L.; Ingold, K. U. In "Rearrangements in Ground and Excited States"; Mayo, P. de, Ed.; Academic Press: New York, 1980; Vol. 1, p 161, and references cited in.

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content),[11] was irradiated in benzene for 5 h; the conversions of **3a,b** were found by GLC analysis to be 87% and 76%, respectively. The deuterium contents of the products were detemined as shown in eq 2.[11] Expectedly, the observed d_0:d_1:d_2 ratio in bibenzyl (7)

$$\begin{aligned}\textbf{3b} + \textbf{3a}\ (d_0,\ 11\%;\ d_1,\ 89\%) \xrightarrow{h\nu(254\ \text{nm})} \textbf{4a}\ (d_0,\ 11\%;\ d_1,\ 89\%) \\ + \textbf{4b}\ (d_0,\ 96\%;\ d_1,\ 4\%) + \textbf{5a}\ (d_0,\ 37\%;\ d_1,\ 63\%) + \\ \textbf{5b}\ (d_0,\ 63\%;\ d_1,\ 37\%) + \textbf{7}\ (d_0,\ 22\%;\ d_1,\ 46\%;\ d_2,32\%)\end{aligned} \quad (2)$$

is compared with a calculated ratio based on the random encounter of the generated benzyl radicals,[12] d_0:d_1:d_2 = 30:50:20. Whereas cross products were produced in significant amounts in **5a** and **5b**, no scrambling of deuterium was observed in **4a** and **4b** as well as in recovered **3a** and **3b** within experimental errors.

Therefore, it can be concluded that the formation **4** occurred only in the solvent cage, while **5** arises as both cage and escaped products. These results imply that **10** is formed in the cage as a transient species during the acyloxy migration.

Further insight into the mechanism of the free radical acyloxy migration was given by ESR. Thus, the superimposed ESR spectra of two radical species, **9b** and **11b**, were observed between −134 and −80 °C,[13] when a mixture of (acetoxymethyl)dimethylsilane, di-*tert*-butyl peroxide, and cyclopropane was photolyzed in an ESR cavity. The relative signal intensity of **11b** to **9b** increased with increasing temperature. It is worthy of noting that the rearrangement from **9b** to **11b** is observed even at very low temperatures compared with the corresponding acyloxy migration from carbon to carbon, which are usually studied at around 80 °C.[10] The activation energy for the rearrangement from **9b** to **11b** is suggested to be much lower than that for the 1,2 (C → C) acyloxy migration.[14,15]

No signal due to **10b** was detected by ESR in the temperature range studied probably because of its short lifetime. The success of detecting **10** as **4** in the present case may be a result of the concurrent generation of an effective radical trap such as **8** in the vicinity of **10**.[17] Further works are in progress.

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(11) The deuterium contents in starting materials and products were all determined by mass spectral analysis.

(12) The small discrepancy between the observed and calculated ratios may be caused by the difference of the cage efficiency between **3a** and **3b**. Assuming that the ratio between benzyl and benzyl-d_1 radicals escaping from the solvent cage is reflected in the d_0:d_1:d_2 ratio observed in **7**, **5a** and **5b** generated in the cage are estimated as 24% and 33% of the total, respectively.

(13) The hyperfine splitting constants (hfs) of these radicals were determined as follows at −134 °C. **9b**: 3.25 (2 H), 6.50 G (6 H). **11b**: 21.3 (2 H), 0.69 G (6 H). The triplet hfs of **9b** increased with increasing temperature (da/dT = 7.4 mG/K), while the other hfs were independent of temperatures. Magnitudes and temperature dependence of the hfs suggest that the acetoxy group eclipses the singly occupied orbital in the preferred rotational conformation of **9b**. This is actually a favorable conformation for the acyloxy migration.

(14) The rate of 1,2 (C → Si) acetoxy migration of **9b** is estimated as to be roughly 10–10^3 s^{-1} at −100 °C under reasonable assumptions. By use of a typical A factor for the radical rearrangement (log A = 11–13),[10c] the activation energy Ea is calculated to be 7–9 kcal/mol, which is ca. 10 kcal/mol lower than that for the 1,2 (C → C) acyloxy rearrangement.[10] The very low Ea may be mainly attributed to larger bond energy of Si–O than C–O.

(15) Recent ab initio MO calculations[16] for the migration showed that the barrier to the path leading to a dioxolanyl radical intermediate is much higher than the barrier for the direct migration via the polar cyclic transition state.[10c,d] The intermediacy of **10** during 1,2 (C → Si) acyloxy migration may suggest the substantial decrease of the barrier to the formation of the dioxolanyl radical by substitution of a silyl group.

(16) Saebo, S.; Beckwith, A. L. J.; Radom, L. *J. Am. Chem. Soc.* **1984**, *106*, 5119.

(17) In the strict sense of words as one referee has pointed out, we cannot exclude the possibility of other pathways to **4** and **5** without intervening **10**, because **10** was not detected. However, it is very difficult to postulate the proper mechanism other than the scheme shown to account for the formation of **4**. In connection to this point, we have observed an ESR spectrum of the $\cdot C(CH_3)SCH_2SiMe_2S$ radical produced from $HSiMe_2CH_2SC(S)CH_3$ by hydrogen abstraction. Details will be published in a forthcoming paper.

Catalysis by Human Leukocyte Elastase. 5.[1] Structural Features of the Virtual Transition State for Acylation

Ross L. Stein

Pulmonary Pharmacology Section
Department of Biomedical Research
Stuart Pharmaceuticals
a Division of ICI Americas Inc.
Wilmington, Delaware 19897

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Recent publications from this laboratory[1,2] suggest that HLE[3] is acylated according to the mechanism of eq 1 involving the

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E{:}S \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} (E{:}S)' \xrightarrow{k_b} E\text{-acyl} \quad (1)$$

$$K_s = k_{-1}/k_1 \quad (2)$$

$$k_2 = \frac{k_a k_b}{k_{-a} + k_b} \quad (3)$$

$$k_E = k_2/K_s = \frac{k_1 k_a k_b}{k_{-1}(k_{-a} + k_b)} \quad (4)$$

intermediacy of a complex, (E:S)', formed from the Michaelis-complex through some physical process that is relatively insensitive to substrate structure and isotopic composition of the solvent. The rate-limiting step and transition-state properties of acylation depend on the relative magnitudes of k_{-a} and k_b (see eq 4). If k_{-a} and k_b are similar, the transition state of k_E will be "virtual"[4,5] and reflect properties of the transition states for both the physical step and the chemical steps of acylation.

It has also been suggested[6,7] that serine protease catalyzed reactions following the mechanism of eq 1 will generate proton inventories[8] of k_E that obey the relationship[9]

$$k_{E,n}/k_{E,n=0} = Z^n\left[C_1 + \frac{C_2}{(1 - n + n\phi_T)^2}\right]^{-1} \quad (5)$$

where Z is a composite, transition-state fractionation factor reflecting the generalized solvent reorganization that occurs during substrate binding, ϕ is one of two identical transition-state fractionation factors corresponding to the two exchangeable hydrogenic sites of the charge-relay system, and C_1 and C_2 are the transition-state contributions made by the physical and chemical steps, respectively. These transition-state contributions are expressed as

$$C_1 = k_E/k_a' \quad (6)$$

$$C_2 = k_E/k_b' \quad (7)$$

where $k_a' = k_a/K_s$, $k_b' = k_b/(K_sK_a)$, and $K_a = k_{-a}/k_a$.[4,5] Z is similar in magnitude to solvent isotope effects on dissociation constants for complexes of serine proteases with their substrates or inhibitors and thus will frequently be greater than one.[7] This, combined with the fact that ϕ_T values are invariably less than one[2,8] (typically, $0.53 < \phi_T < 0.63$), allows us to predict that proton inventories of k_E will have a characteristic "bowed-upward" shape.[8]

(1) For part 4, see: Stein, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 5767–5775.
(2) Stein, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 5111–5116.
(3) Abbreviations: HLE, human leukocyte elastase; MeOSuc, *N*-methoxysuccinyl; pNA, *p*-nitroanilide; ONP, *p*-nitrophenyl ester.
(4) Schowen, R. L. In "Transition States of Biochemical Processes"; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978.
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(9) A derivation of eq 5 is provided in the supplementary material to this article.

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