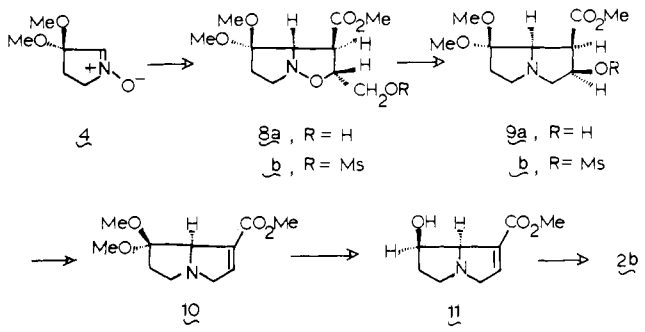
Scheme I



eclipsing interactions (i.e., to a more favorable dihedral angle relationship) in proceeding from **6** to **4** (cf. **4a**).[10]

Although it was envisaged that steric factors might retard the addition of **4** to methyl γ-hydroxycrotonate, in fact this reaction proceeds smoothly in chloroform at 45 °C to provide isoxazolidine **8a** in 86% yield[11] (Scheme I).

The regiochemical assignment is consistent with those previously observed for various crotonate–nitrone cycloadditions[1a,12] and is reinforced by the spectral similarity of **8a** to the isoxazolidine[1a] derived from 1-pyrroline 1-oxide and the same dipolarophile. Isoxazolidine **8a** exhibits the expected three singlets (NMR) at δ 3.20, 3.68, and 3.76 ppm, attributed to the three methyl groups. Conversion of **8a** into the corresponding mesylate **8b** ($MeSO_2Cl$, Et_3N, CH_2Cl_2) in 99% yield is accompanied by the loss of hydroxyl stretching absorption (~3 μ) with persistence of carbonyl absorption (5.77 μ) in the IR spectrum. Moreover, an additional methyl resonance appears at δ 3.10 ppm (NMR). While the NMR spectra of **8a** and **8b** suggest the presence of a diastereomeric mixture of adducts, this factor in no way complicates our synthetic objectives since the chirality at both C-2 and C-3 is subsequently annihilated.

The hydrogenolysis of the nitrogen–oxygen bond at **8b** (Pd/C, H_2, MeOH) leads to the formation **9a** (84%) by the concomitant displacement of the mesylate by the newly liberated secondary amine function. The pyrrolizidine **9a**, IR ($CHCl_3$) 2.84 (OH) and 5.78 μ (C=O), incorporates three three-proton singlets at δ 3.19, 3.22, and 3.71 ppm in the NMR spectrum. The mass spectrum exhibits a molecular ion at *m/e* 245.

Conversion of the β-hydroxy ester **9a** into the corresponding mesylate **9b** was followed by triethylamine-mediated elimination to give the α,β-unsaturated ester **10** (98%). The carbonyl absorption of **10** appears at 5.80 μ (IR), while its NMR spectrum contains the vinyl signal at δ 6.64 ppm (br s, 1) and three methoxyl signals at δ 3.75 (s, 3, CO_2Me), 3.20 (s, 3, OMe), and 3.36 ppm (s, 3, OMe). The ketone (81% yield) derived from **10** by hydrolysis (37% hydrochloric acid, DME) shows pronounced thermal lability even at 0 °C and was therefore rapidly reduced to the corresponding alcohol ester **11**, mp 122–123 °C, with sodium borohydride in methanol. This alcohol exhibits spectral properties identical with those recorded by Culvenor,[13] who obtained **11** from natural *d*-retronecine.

The hydroxy ester **11** was converted into *dl*-retronecine by reduction with alane in THF.[14] The *dl*-retronecine (mp 130 °C, lit.[9] mp 130–131 °C) so obtained possessed IR and NMR spectral properties identical with those of an authentic sample of *dl*-retronecine.

In an effort to provide the efficient synthesis delineated above with even further economy, we attempted to generate the α-keto nitrone **1** from the ketal **4**. Indeed, exposure of **4** to 1% hydrochloric acid at 0 °C for 1 h resulted in the generation of the nitrone as indicated by an absence of the methoxyl singlets, and the presence of the nitrone proton at C-2, δ 7.15 ppm (s, 1), in the NMR spectrum; however, the solution containing this α-keto nitrone darkened rapidly. Clearly, the ketal nitrone **4** offers the greater synthetic potential.

Acknowledgment. We thank the Institute of General Medical Sciences (NIH) for financial assistance (GM 25303). Moreover, we thank Dr. A. R. Mattocks (Medical Research Council Laboratories; Surrey, England), Dr. C. C. J. Culvenor (CSIRO), Dr. D. J. Robins (Glasgow), and Dr. M. Suffness (Developmental Therapeutics Program, NCI) for samples of *d*-retronecine.

References and Notes

(1) For example, see: (a) Tufariello, J. J.; Tette, J. P. *J. Chem. Soc., Chem. Commun.* **1971**, 469–470. (b) Tufariello, J. J.; Tegeler, J. J. *Tetrahedron Lett.* **1976**, 4037–4040. (c) Oppolzer, W.; Petrzilka, M. *J. Am. Chem. Soc.* **1976**, *98*, 6722–6723. (d) Confalone, P. N.; Lollar, E. D.; Pizzolato, G.; Uskokovic, M. *Ibid.* **1978**, *100*, 6291–6292. (e) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, Sk. Asrof *Ibid.* **1979**, *101*, 2435–2442.
(2) For example, 3-oxo-3,4,5,6-tetrahydropyridine 1-oxide has been prepared from 2-methyl-1-pyrroline 1-oxide in <6% yield using selenium dioxide: Brown, R. F. C.; Subrahmanyan, L.; Whittle, C. P. *Aust. J. Chem.* **1967**, *20*, 339–347. A synthesis of 5,5-dimethylpyrroline 1-oxide, which is incapable of tautomerization into a pyrrole, could not be adapted to the synthesis of **1**: Clark, V. M.; Sklarz, B.; Todd, A. *J. Chem. Soc.* **1959**, 2123–2127.
(3) Geissman, T. A.; Waiss, A. C. *J. Org. Chem.* **1962**, *27*, 139–142.
(4) For a review, see Warren, F. L. *Fortschr. Chem. Org. Naturst.* **66**, *24*, 329–406.
(5) For recent synthetic efforts directed toward the saturated pyrrolizidine alkaloids, see: Robins, D. J. *Alkaloids (London)* **1978**, *8*, 47–61. Danishevsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72. Pinnick, H. W.; Chang, Y.-H. *J. Org. Chem.* **1978**, *43*, 4662–4663.
(6) Culvenor, C. C. J.; Dowling, D. T.; Edgar, J. A.; Jago, M. V. *Ann. N.Y. Acad. Sci.* **1969**, *163*, 837–847.
(7) Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. "The Pyrrolizidine Alkaloids"; North Holland Publishing Co.: Amsterdam, 1968.
(8) Tufariello, J. J.; Kendall, P. M., unpublished observations.
(9) Leonard, N. J.; Fischer, F. E.; Barthel, E.; Fugueras, J.; Wildman, W. C. *J. Am. Chem. Soc.* **1951**, *73*, 2371–2373. Cavalla, J. F.; Davoll, J.; Dean, M. J.; Franklin, C. S.; Temple, D. M.; Winder, C. V. *J. Med. Pharm. Chem.* **1961**, *4*, 1–19.
(10) For a related transformation similarly rationalized, see Bonnett, R.; Ho. S. C.; Raleigh, J. A. *Can. J. Chem.* **1965**, *43*, 2717–2723.
(11) Although two diastereomeric adducts are formed, the depiction of **8a** in Scheme I is that of the major stereoisomer. The reasons for this stereochemical assignment will be detailed in a full report.
(12) Murray, B. G.; Turner, A. F. J. *Chem. Soc. C* **1966**, 1338–1339. Huisgen, R.; Hauck, H.; Grashey, R.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2568–2584. Joucla, M.; Tonnard, F.; Gree, D.; Hamelin, J. *J. Chem. Res. (M)* **1978**, 2901–2912.
(13) Culvenor, C. C. J.; Assen, A. J.; *Aust. J. Chem.* **1969**, *27*, 2657–2662.
(14) Brown, H. C.; Yoon, N. W. *J. Am. Chem. Soc.* **1968**, *90*, 2927–2938. Brown, H. C.; Hess, H. M. *J. Org. Chem.* **1969**, *34*, 2206–2209.

Joseph J. Tufariello,* George E. Lee
Department of Chemistry
State University of New York at Buffalo
Buffalo, New York 14214
Received July 9, 1979

Structural Dependence of ^{18}O Isotope Shifts in ^{13}C NMR Spectra

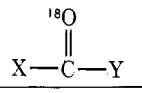
Sir:

Isotopic substitution with ^{18}O causes shifts in the NMR resonance positions of attached nuclei such as ^{55}Mn, ^{95}Mo, and ^{31}P which are useful in mechanistic studies.[1] Recently Risley and Van Etten confirmed[2] theoretical prediction[3] of an ^{18}O isotopic effect on ^{13}C NMR spectra by observing an upfield shift for [^{18}O]-*tert*-butyl alcohol. We now report that the ^{18}O-induced upfield shift in natural-abundance ^{13}C NMR spectra appears to be a general phenomenon, and that its magnitude is dependent on structure.

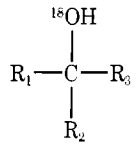
The ^{18}O-labeled compounds listed in Table I were prepared,[4] and their natural-abundance ^{13}C NMR spectra were measured on a Bruker WH 400 instrument at 100.6 MHz in the Fourier

0002-7863/80/1502-0374$01.00/0

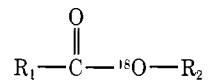
Table I. Upfield Shifts at 100.6 MHz on Carbons Attached to ^{18}O[a]



X	Y	shift in Hz
phenyl	CH_3	5.0
phenyl	phenyl	4.6
phenyl	H	4.2
$CH_3(CH_2)_6$	H	4.8
cyclohexyl	CH_3	5.2
	cyclohexanone	5.3
	pulegone	4.5
cyclohexyl	$OCH_2CH_2CH_3$	3.9
cyclohexyl	O-cyclohexyl	3.7
phenyl	$O\text{-}CH_2CH_2CH_3$	3.3
cyclohexyl	NH_2	3.6[b]
cyclohexyl	$HNCH_2CH_2CH_3$	3.3
cyclohexyl	$N(CH_2CH_2CH_3)_2$	3.3
phenyl	NH_2	3.0[c]
phenyl	$HNCH_2CH_2CH_3$	2.8
phenyl	$N(CH_2CH_2CH_3)_2$	3.0
	2-pyrrolidone	2.8



R_1	R_2	R_3	shift in Hz
CH_3	CH_3	CH_3	3.5[d]
cyclohexyl	CH_3	CH_3	3.2
cyclohexyl	CH_3	H	2.6
	cyclohexanol		2.2
$CH_3(CH_2)_6$	H	H	2.1
phenyl	CH_3	H	2.3
phenyl	phenyl	H	2.0
phenyl	H	H	1.9
	α-D-glucose (^{18}O on C_1)		1.5[e]
	β-D-glucose (^{18}O on C_1)		1.3[e]



R_1	R_2	shift in Hz C=O	shift in Hz R_2
phenyl	$CH_2CH_2CH_3$	1.5	3.2
cyclohexyl	$CH_2CH_2CH_3$	1.5	3.0
α-D-glucose pentaacetate (^{18}O on C_1)		1.0	2.4
β-D-glucose pentaacetate (^{18}O on C_1)		1.0	2.6

[a] Spectra were run in $CDCl_3$ unless noted; all shifts are ±0.1 Hz. [b] Me_2SO-d_6. [c] Acetone-d_6. [d] Calculated from ref 2. [e] Pyridine-d_5.

transform mode.[5] Labeled aldehydes and ketones were made by exchange with 50 atom % excess [^{18}O]water[6] containing a trace of HCl (24 h, 25 °C).[7] Sodium borohydride reduction (4-fold excess, THF–methanol, 3 h, 25 °C) of these compounds produced the corresponding ^{18}O alcohols. Benzoic acid and cyclohexanecarboxylic acid were exchanged with [^{18}O]water[7a] and converted via the acid chlorides into the derived amides and esters which were labeled in the carbonyl oxygen.[8] Propyl benzoate and propyl cyclohexanecarboxylate labeled in the other oxygen were prepared similarly from [^{18}O]propanol obtained by reduction of exchanged propanal. D-Glucose was labeled by heating in [^{18}O]water[9] and converted into the α- and β-pentaacetates.[10] In a typical NMR experiment, the full proton-decoupled spectrum of 1 mmol of sample in 2.5 mL of solvent was recorded using a 10-mm probe, and the spectrum was rerun to expand the region containing the carbon bearing ^{18}O. Under these conditions, a total of 40 scans, 2000-Hz sweep

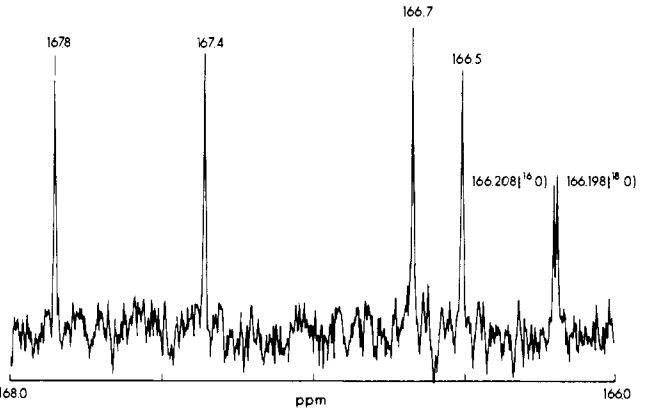


Figure 1. Natural abundance 100.6-MHz ^{13}C NMR spectrum of labeled [1-^{18}O]-α-D-glucose pentaacetate in $CDCl_3$. Chemical shift values are given in parts per million relative to Me_4Si.

width, 8.2-s acquisition time, 45° pulse angle, and 32K data block was adequate for the expansion. A number of experiments were repeated at higher resolutions to ensure accuracy. Since all of the compounds contained between 15 and 50% ^{18}O,[11] two peaks were always observed for the attached carbons, the upfield one being due to carbons substituted with ^{18}O.

The emerging trend in Table I is that the magnitude of the isotope shift for the carbon attached to a labeled carbonyl oxygen tends to decrease in the order ketones ≥ aldehydes ≥ esters ≥ amides. Conjugation with a phenyl ring reduces the shift by ~0.002–0.006 ppm (0.2–0.6 Hz at 100.6 MHz). Additional alkyl substitution has only a small effect. Changing the solvent from $CDCl_3$ to Me_2SO-d_6, pyridine-d_5, benzene-d_6, or methanol-d_4 caused no measurable change in the isotope shift of carbonyl-labeled propyl benzoate, although the actual NMR resonance positions were altered.

Tertiary alcohols tend to exhibit a larger isotope shift than primary or secondary alcohols. Benzylic alcohols show very slightly smaller chemical shift differences for the two isotopic species than completely saturated analogues. In contrast to the other compound classes, solvent effects for alcohols are substantial; the isotope shift for 1-phenylethanol was 2.3 Hz in $CDCl_3$, 2.1 Hz in benzene-d_6, and 2.0 Hz in pyridine-d_5. Hydroxylic solvents such as methanol-d_4 or D_2O caused broadening of the two signals normally observed for the mixture of labeled and unlabeled alcohols to a single peak encompassing the whole region. This may be due to the existence of various hydrogen-bonded forms in solution.

Mass spectrometry has been the general analytical technique for determination of extent and position of ^{18}O label in organic compounds,[12] but multiply oxygenated materials often require extensive prior degradation to ascertain the structures of the fragments. In a simple example, the 70-eV electron impact mass spectra of both [*carbonyl*-^{18}O]- and [*alkoxy*-^{18}O]propyl cyclohexanecarboxylate show the highest mass ions at *m/e* 129 and 131, corresponding to $C_7H_{13}O_2$. The present NMR method facilitates immediate localization of the label on the basis of the greater shift magnitude of the [*carbonyl*-^{18}O] compound and the occurrence of a second "split carbon" in the spectrum of the other isomer.[13] Conversely, knowledge of the position of label allows assignment of the ^{13}C NMR spectrum. Although the five carbonyl carbon resonances in unlabeled α-D-glucose pentaacetate are separated by <2 ppm, it is possible to identify the signal due to the anomeric acetate carbonyl using the spectrum of ^{18}O-labeled compound (Figure 1).

Theoretical calculation of isotope shift would require exact knowledge of changes in electron density and molecular geometry,[3,14] but these preliminary empirical studies suggest trends correlating structure and shift magnitude. In addition,

the effect appears to be a general phenomenon which complements mass spectrometry in ^{18}O-labeling studies.[15] We are currently investigating the influence of hybridization changes on shift magnitude and applications in secondary metabolism.

Acknowledgments. The author is grateful to Dr. T. Nakashima and Mr. G. Bigam for spectral measurements and useful discussions. This investigation was supported by University of Alberta General Research Fund Grant 55-32837 and Natural Sciences and Engineering Research Council of Canada (NSERC) Grant A0845. Initial measurements in December 1977 at Stanford Magnetic Resonance Laboratory were supported by NSF GP 23633 and NIH RR00711.

References and Notes

(1) (a) Buckler, K. U.; Haase, A. R.; Lutz, O.; Muller, M.; Nolle, A. *Z. Naturforsch. A* **1977**, *32*, 126–130; (b) Webb, D. R.; McDonald, G. G.; Trentham, D. R. *J. Biol. Chem.* **1978**, *253*, 2908–2911. (c) Bock, J.; Cohn, M. *Ibid.* **1978**, *253*, 4082–4085. (d) Cohn, M.; Hu, A. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 200—203. (e) Van Etten, R. L.; Risley, J. M. *Ibid.* **1978**, *75*, 4784–4787. (f) Jarvest, R. L.; Lowe, G. *J. Chem. Soc., Chem. Commun.* **1979**, 364–366. (g) Cohn, M.; Nageswara Rao, B. D. *Bull. Magn. Reson.* **1979**, 38–60.
(2) Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 252–253.
(3) (a) Raynes, W. T.; Stanney, G. *J. Magn. Reson.* **1974**, *14*, 378–380. (b) Jameson, C. J., *J. Chem. Phys.*, **1977**, *66*, 4983–4988.
(4) All compounds were checked for purity by thin layer or gas chromatography and showed spectral characteristics (^1H NMR, ^{13}C NMR, IR, and mass spectra) consistent with the assigned structures.
(5) Our first experiments were done with pulegone using Stanford Magnetic Resonance Laboratory's HXS-360 at 90 MHz. We are grateful to Drs. W. Conover and G. Sullivan for making these measurements.
(6) Labeled water was purchased from KOR Isotopes or donated by the Stable Isotopes Resource of Los Alamos Scientific Laboratory.
(7) (a) Samuel, D.; Silver, B. L. *Adv. Phys. Org. Chem.* **1965**, *3*, 123–186. (b) Byrn, M.; Calvin, M. *J. Am. Chem. Soc.* **1966**, *88*, 1916–1922.
(8) Bender, M. L.; Matsui, H.; Thomas, R. J.; Tobey, S. W. *J. Am. Chem. Soc.* **1961**, *83*, 4193–4196.
(9) Gorin, P. A. J.; Mazurek, M. *Carbohydr. Res.* **1978**, *67*, 479–483.
(10) Wolfram, M. L.; Thompson, A. *Methods Carbohydr. Chem.* **1963**, *2*, 211–212.
(11) The extent of ^{18}O labeling was determined by mass spectral analysis on an AEI MS2 instrument.
(12) Klein, E. R.; Klein, P. D. *Biomed. Mass Spectrom.* **1978**, *5*, 425–432.
(13) We recently observed an isotope shift of 0.5 Hz at the methylene carbon β to ^{18}O in the propyl side chains of [*alkoxy*-^{18}O]-labeled propyl benzoate and propyl cyclohexanecarboxylate. Investigations on the generality of this "β effect" are in progress.
(14) Batiz-Hernandez, H.; Bernheim, R. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1967**, *3*, 63–85.
(15) Since the completion of this work, reports have appeared on ^{18}O isotope shifts in ^{13}C NMR spectra of metal carbonyl derivatives: (a) Darensbourg, D. J. *J. Organomet. Chem.* **1979**, *174*, C70–C76. (b) Darensbourg, D. J.; Baldwin, B. J. *J. Am. Chem. Soc.* **1979**, *101*, 6447.

John C. Vederas
Department of Chemistry, University of Alberta
Edmonton, Alberta, Canada T6G 2G2
Received August 27, 1979

Disproportionation of Trimethylsilyl at 25 °C. Mercury Photosensitization of Trimethylsilane

Sir:

While the disproportionation of trimethylsilyl radicals has been invoked under pyrolysis conditions,[1] this reaction has been suggested on a number of occasions to be negligible at or near room temperature.[2-6] Nay, Woodall, Strausz, and Gunning have examined the mercury photosensitization of trimethylsilane with some care.[6] This method was also used by Cadman, Tilsley, and Trotman-Dickenson to generate $(CH_3)_3Si$ for a gas-phase rotating-sector experiment.[3] Both groups indicated they did not expect reaction 1 to be important and found no evidence to contradict that expectation. Recent developments suggest a reexamination of this system may be justified.

$$2(CH_3)_3Si \rightarrow (CH_3)_3SiH + [(CH_3)_2SiCH_2] \quad (1)$$

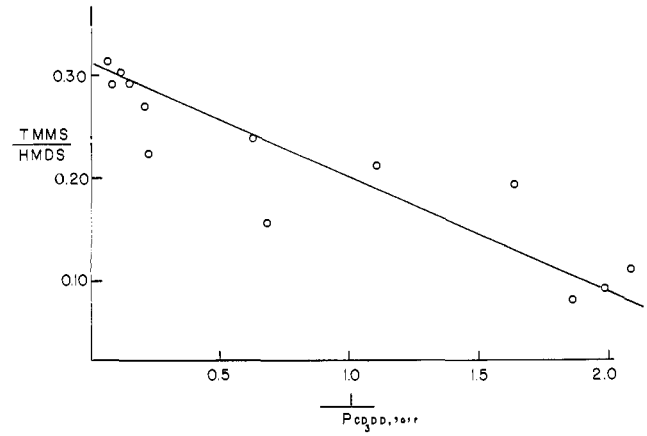


Figure 1. Ratio of the quantum yield of trimethylmethoxysilane to hexamethyldisilane plotted vs. reciprocal methanol-d_4 pressure (in Torr). Least-squares fit intercept is 0.31 ± 0.08.

$[(CH_3)_2SiCH_2]$ produced in the gas phase by pyrolysis dimerizes to 1,1,3,3-tetramethyl-1,3-disilacyclobutane in good yield.[7] The dimer, however, apparently does not form near room temperature when $[(CH_3)_2SiCH_2]$ is produced by gas-phase photolysis.[8] Since the other product of reaction 1 is the starting material, $(CH_3)_3SiH$, this reaction could easily go unnoticed while still occurring.

In a recent discussion of the photolysis of tetramethylsilane,[9] we reported a ratio of the rate of reaction 1 to reaction 2 of 0.48 ± 0.2. The large uncertainty in our value for k_1/k_2, the ready availability of trimethylsilyl radicals from Hg photosensitization of trimethylsilane, and the possibility that reaction 1 was overlooked in earlier work all suggest that this system be reexamined with emphasis on possible detection of $[(CH_3)_2SiCH_2]$.

$$2(CH_3)_3Si \rightarrow (CH_3)_6Si_2 \quad (2)$$

Small amounts of methanol have been demonstrated to be an effective, though not quantitative, trap for $[(CH_3)_2SiCH_2]$ in the gas phase.[8] Trimethylsilane, 120 Torr, and 0.6 to 12 Torr of perdeuterated methanol in a quartz vessel fitted with a Teflon stopcock (Kontes) and containing a small droplet of Hg were placed in a Rayonet photochemical reactor fitted with low pressure mercury lamps. Products were analyzed as reported previously using a gas chromatograph and mass spectrometer.[8]

Trimethylmethoxysilane, the expected addition product of $[(CH_3)_2SiCH_2]$ and CH_3OH, is found in good yield in these experiments. Figure 1 plots the ratio of $(CH_3)_2CH_2DSiOCD_3/(CH_3)_6Si_2$ vs. $[CD_3OD]^{-1}$. The intercept of this plot is presumed to correspond to the limiting yield of $(CH_3)_2CH_2DSiOCD_3$ and this is a direct measure of k_1/k_2. This value is 0.31 ± 0.08. Since the quenching cross section[6] for Me_3SiH is about three times larger than that for methanol,[10] and since $P(Me_3SiH)/P(CD_3OD) \geq 10$, it seems highly unlikely that $(CH_3)_2CH_2DSiOCD_3$ arose owing to sensitization of the methanol. The incorporation of all of the methanol-d_4 deuterium into the trimethylmethoxysilane is also consistent with its production as an addition of methanol-d_4 to $[(CH_3)_2SiCH_2]$. In their earlier work, Nay et. al. found the limiting quantum yield of $(CH_3)_6Si_2$ to be 0.78 while products of less methylated silanes corresponded to a unit quantum yield. If the difference between $\Phi[(CH_3)_6Si_2]$ and unity is ascribed to reaction 1, then $k_1/k_2 = 0.28$, a value similar to that determined in this work.

It appears to us that disproportionation of $(CH_3)_3Si$ is a self-reaction competitive with combination of these radicals. Failure to discern it in earlier work[2-6] most likely is the result

0002-7863/80/1502-0376$01.00/0