

Tris(trimethylsilyl)methane as an internal ^{13}C NMR chemical shift thermometer†

William H. Sikorski, Aaron W. Sanders and Hans J. Reich*

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706, USA

Received 12 January 1998; accepted 10 February 1998

ABSTRACT: Tris(trimethylsilyl)methane has excellent properties for an internal chemical shift thermometer to measure temperatures in ^{13}C DNMR spectroscopy [$\Delta\delta$ between the ^{13}C signals of $\text{Si}(\text{CH}_3)_3$ and CH carbons]. It is chemically inert, soluble in most organic solvents and has an almost linear dependence of $\Delta\delta$ on temperature. The sensitivity (approximately 1°C Hz^{-1} at 90 MHz) allows the measurement of temperature to within 1°C . The chemical shift is solvent dependent, so each solvent mixture must be calibrated. Calibrations are presented for seven solvents. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{13}C NMR; tris(trimethylsilyl)methane; chemical shift thermometer; temperature measurement; silanes

INTRODUCTION

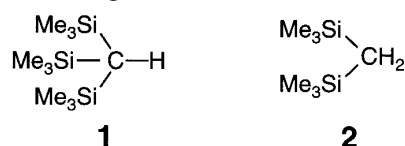
There are three principal techniques for the measurement of rates by NMR spectroscopy: (1) the use of peak integrations to monitor reactant and/or product concentrations for classical kinetic studies on the laboratory time-scale, (2) dynamic NMR spectroscopy (DNMR) and (3) saturation transfer (Hoffman-Forsén) experiments allowing measurements of the rates of reversible reactions at equilibrium on the millisecond to second time-scale (conformational processes, ligand reorganizations, pyramidal inversions and chemical reactions).¹ Accurate temperature measurement is an important requisite for obtaining reliable data in all three experiments, but the DNMR experiment has particularly demanding requirements. Since the actual set temperatures of NMR temperature control devices are often inaccurate, the primary standards for precision NMR temperature measurement are usually thermistor or thermocouple devices. Since NMR experiments are not compatible with the insertion of an electronic device into the sample during the measurement of spectra, it is common to use chemical shift thermometers as secondary standards.

For ^1H NMR spectroscopy, the most commonly used chemical shift thermometer is methanol,^{2a,b} which works over the temperature range from -100 to 60°C . Both the methanol ^1H thermometer and others that have been proposed for ^1H [ethylene glycol,^{2b} $\text{Yb}(\text{fod})_3\text{-Me}_2\text{CO}$ ^{3a}], ^{13}C [$\text{MeI-Me}_4\text{Si}$,^{3c} $\text{CCl}_4\text{-Me}_2\text{CO}$,^{3d} $\text{HOAc-Dy}(\text{NO}_3)_3$,^{3e} Cl_2CHCOOH ,^{3g} $\text{Yb}(\text{fod})_3\text{-Me}_2\text{CO}$ ^{3a}], ^{19}F [$\text{C}_6\text{F}_6\text{-CHFCl}_2$,^{3b} $\text{CFCl}_3\text{-CF}_2\text{Cl}_2$ ^{3b}] or ^{59}Co [$\text{Co}(\text{acac})_3$ ^{3f}] NMR are inherently *external* temperature calibration devices,

which restricts their temperature ranges and makes them susceptible to all the errors and inconvenience associated with sample substitution or capillary insertion. Many of these also measure *intermolecular* chemical shifts, which creates potential problems with sample preparation and purity. An ideal shift thermometer would (1) be a non-interactive robust molecule useable as an *internal* standard, (2) utilize an *intramolecular* shift so that only a single material needs to be added, (3) be effective over a wide range of temperatures, (4) give a linear response of chemical shift to temperature, (5) have a sufficiently strong $\Delta\delta$ *vs.* T dependence that accurate temperatures can be measured and (6) give solvent-independent shifts. To help address this fundamental need, we have identified a ^{13}C chemical shift thermometer, tris(trimethylsilyl)methane (1), which fulfils all of these requirements except item (6). It can be added directly to nearly any organic solution under study, as it has no significant Lewis acidity or basicity and is demonstrably stable to media which are acidic, basic, oxidative or reductive. Bis(trimethylsilyl)methane (2) is also a candidate, but we selected 1 because of its greater temperature sensitivity and lower volatility, which makes the preparation of ^{13}C -enriched material more convenient.

RESULTS AND DISCUSSION

Figure 1 shows a variable-temperature study of ^{13}C -enriched 1 in an ethereal solvent mixture that we routinely use for our low-temperature NMR studies of organolithium reagents.⁴ The chemical shift of the



* Correspondence to: H. J. Reich, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706, USA.

† Dedicated to Professor John D. Roberts on the occasion of his 80th birthday.

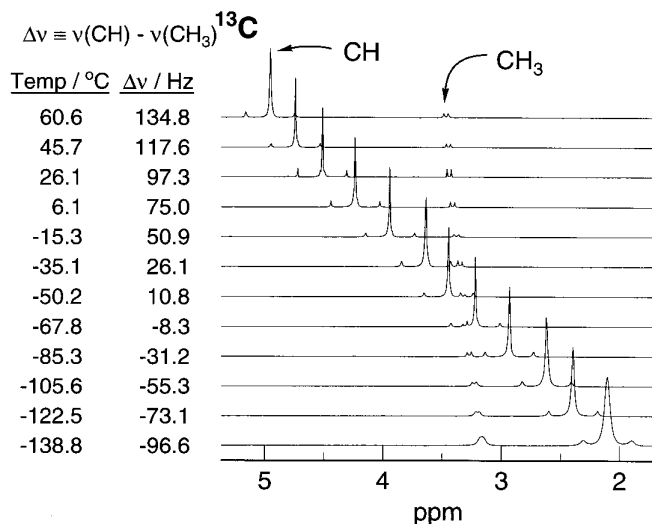


Figure 1. ^{13}C NMR spectra (90.56 MHz, 360 MHz proton frequency) from a variable-temperature study of 0.20 M tris(trimethylsilyl)methane (^{13}C -H) (1) in 3:2 THF-diethylether.

methine carbon (large signal) is highly temperature dependent, the CH_3 signal (doublet, $^2J_{\text{CC}} = 3.2$ Hz) much less so. Over the course of a 200 °C temperature range from -140 to +60 °C, the chemical shift difference between the two carbon signals, $\nu(\text{CH}) - \nu(\text{CH}_3)$, spans 230 Hz, giving a sensitivity of better than 1 Hz °C⁻¹ on a 360 MHz proton frequency instrument.

Calibration

We calibrated this shift thermometer in a variety of solvents. Figure 2 highlights the remarkable result that the chemical shift difference between the two carbons is an almost linear function of temperature in a variety of solvents, displaying nearly identical slopes in all cases. These calibrations were performed over the entire liquid

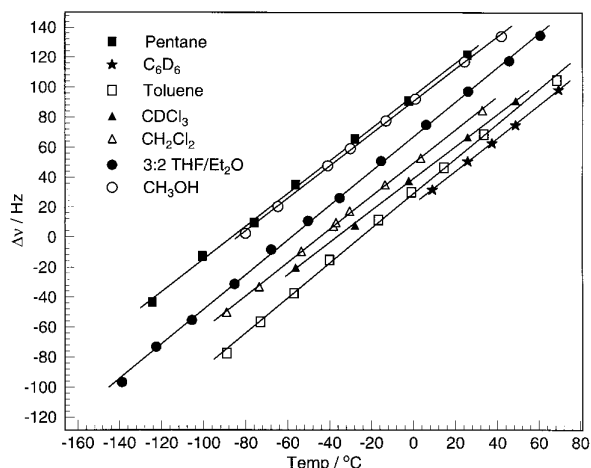


Figure 2. Graph relating the ^{13}C chemical shift difference in Hz between the methine and methyl carbons of tris(trimethylsilyl)methane (1) to temperature in pentane, benzene- d_6 , toluene, 3:2 THF-diethylether, chloroform- d , dichloromethane and methanol.

ranges of the respective solvents (except for toluene, which was only measured from -89 to 68 °C). Significantly, even at the temperature extremes, the compound is well behaved.

Various methods have been proposed for calibrating chemical shift thermometers, including direct measurement with a static thermistor probe,^{2a} detection of the melting of various solids either through the sharpening of the signals in the NMR spectrum,^{5a,c} or visual inspection of the sample,^{5b} and detection of the clearing points of liquid crystals (marked by the appearance of sharp signals in the NMR spectrum).^{5c} The MeOH thermometer has been calibrated repeatedly by Van Geet,² and his work highlights the careful attention to detail that is necessary to calibrate a chemical shift thermometer properly. Van Geet's studies included the important observation that there was a temperature gradient along the length of the tube (*ca.* 0.5 °C cm⁻¹ in his instrument), which was slightly larger when the sample was not spinning.^{2a} Hence it is important that a thermocouple or thermistor device be inserted accurately to the center of the receiver coil to obtain an accurate reading. Further, since the temperature probe is a heat conductor, its very presence alters the temperature of the solution.^{2b}

We have used two variations of a thermocouple-based procedure for calibrating our thermometer. The first was a sample substitution protocol, where the temperature was measured in one sample containing an inserted thermocouple and the spectrum was measured in a second one, otherwise identical. Each sample was equilibrated for an appropriate length of time (15 min for a 10 mm sample tube). Since the sample could not be spun during the temperature measurement, we measured spectra on non-spinning samples. A second procedure involved a single sample in an open tube. After sample equilibration the thermocouple was inserted into the sample such that the sensing element was at the center of the receiving coil, and the temperature was measured. The spectrum was then taken with the thermocouple raised, and the thermocouple was again lowered into the sample for a second temperature measurement. These measurements were performed on a spinning sample. The sample substitution and direct insertion methods gave slightly different results (1–2 °C) at the low and high temperature extremes.

The results reported in Fig. 1 lead to the equations in Table 1 for calculating the temperature, where $\Delta\delta = \delta(\text{CH}) - \delta(\text{CH}_3)$. We use $\Delta\delta$ rather than $\Delta\nu$ values here to make the equations independent of the spectrometer.

The digital resolution under the conditions that we measured our spectra was 0.64 Hz. Hence temperatures determined using this method are probably accurate to within 1 °C. Although higher digital resolution could easily be achieved (with temperature measurements to within 0.2 °C), it is very difficult to calibrate the thermometer that accurately and other sources of error such as heating by the decoupler, signal broadening and the effects of spinning the sample prevent achieving higher accuracy.

Table 1. Calibrations for the tris(trimethylsilyl)methane chemical shift thermometer

Pentane	Temp. (°C) = 83.231($\Delta\delta$) - 86.6	(-124 to 26 °C)
C ₆ D ₆	Temp. (°C) = 82.249($\Delta\delta$) - 19.9	(9 to 69 °C)
Toluene	Temp. (°C) = 77.931($\Delta\delta$) - 24.9	(-89 to 68 °C)
CDCl ₃	Temp. (°C) = 84.711($\Delta\delta$) - 36.5	(-56 to 49 °C)
CH ₂ Cl ₂	Temp. (°C) = 81.729($\Delta\delta$) - 44.5	(-89 to 33 °C)
3:2 THF-Et ₂ O	Temp. (°C) = 78.675($\Delta\delta$) - 58.1	(-139 to 60 °C)
MeOH	Temp. (°C) = 83.925($\Delta\delta$) - 83.9	(-80 to 42 °C)

Stability of tris(trimethylsilyl)methane

To be used as an internal standard, the compound needs to be inert. To test this, we subjected **1** to a variety of conditions. It had already been demonstrated to be resistant to strong bases (metalation with MeLi in THF-Et₂O has been reported to require 20 h at room temperature,⁶ although through NMR observations we have determined that 3 days are actually required for complete metalation). In our own NMR studies of lithium reagents, we have been making routine use of this chemical shift thermometer, and its presence has never been a problem. We have specifically tested the stability of **1** to basic conditions (NaOH-MeOH), acidic conditions (CF₃COOH-CDCl₃), oxidative conditions (*m*-chloroperbenzoic acid-CH₂Cl₂) and reducing conditions (NaBH₄-MeOH) and found it to be unaffected after 1 week at room temperature.

Using the chemical shift thermometer

The advantages of an internal chemical shift thermometer are substantial, and include the following: the temperature being recorded is always the true temperature at the position of the receiver coil at the time of the acquisition (or, if acquiring in a nucleus other than ¹³C, immediately before or after, with almost no disturbance of the sample); reliable operation is limited only by the practical limits of the freezing and boiling points of the solvent; and the DNMR experiment itself becomes decoupled from the temperature calibration (calibrations of a solvent can even be performed long after an experiment has been done, even on a different spectrometer if the DNMR experiment was performed with the internal standard present). Because the thermometer is part of the solution, one does not need to use a capillary (temperature gradients across the capillary wall are a potential problem, and the presence of the capillary can affect signal quality), nor does one need to exchange NMR tubes to measure the temperature, which is inherently imprecise, and very time consuming since numerous samples need to be equilibrated. Furthermore, exchanging tubes can be a real problem for low-temperature studies of sensitive samples or classical kinetic studies followed by NMR where sample warming must be avoided.

The fact that only the CH signal of **1** shows a substantial temperature dependence has a valuable conse-

quence. If there are significant temperature gradients across a sample, or if the temperature changed during a lengthy acquisition, there will be differential broadening of the two signals, thus providing an internal check on the physical and temporal temperature homogeneity while the spectrum is acquired. This is illustrated in a high-resolution experiment of a sample containing a 2:1 ratio of ¹³C labeled and unlabeled **1** designed to measure the ¹³C-¹³C isotope shift of the Me groups for (Me₃Si)₃¹³CH (Fig. 3). Here the linewidth of the CH₃ signals is 0.15 Hz whereas that of the CH signal 0.75 Hz. Hence there was an approximately 0.7 °C temperature shift during the experiment, or temperature gradient across the sample. Since a spectrum taken subsequently had much sharper lines for the CH signal, this was probably a shift in temperature with time.

An inherent problem with an internal chemical shift thermometer is that the sample becomes contaminated. If a compound is to be recovered, it needs to be separated from the chemical shift thermometer. Tris(trimethylsilyl)methane has a boiling point of 80 °C at 2 mmHg and, although it contains no chromophore, it is extremely non-polar and can generally be removed by chromatography.

The spectra in Fig. 1 illustrate some other limitations of this method. The signals move across the 2–5 ppm region of the ¹³C NMR (in all solvents tested), which could lead to some interference if a compound under study has signals in this location. Fortunately, this region is usually fairly bare, although studies of other

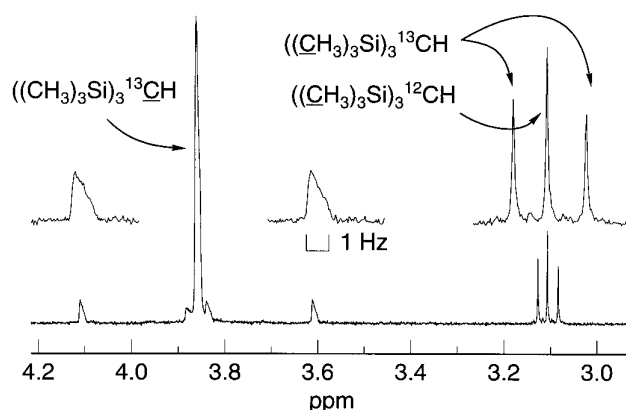


Figure 3. ¹³C NMR spectrum of a 2:1 ratio of ¹³C labeled and unlabeled **1** in acetone-*d*₆. The isotope shift of the SiMe₃ carbon is 0.15 Hz upfield (1.65 ppb). ²*J*_{C, Si, C} = 3.31 Hz.

alkylsilanes, for instance, could be compromised. Since the chemical shifts of the SiMe_3 and CH carbons cross, there is a 'blind' spot of 1–2 °C when the two signals are too close to be distinguished (e.g. –58 °C in 3:2 THF– Et_2O).

The spectra in Fig. 1 were measured on a 99% ^{13}C -enriched sample (see below for the preparation); here the areas of the CH and $\text{Si}(\text{CH}_3)_3$ signals are in an approximately 10:1 ratio. The intensity ratio is further exacerbated by the doublet splitting of the minor SiMe_3 peak. Unlabeled material can also be used (see Fig. 4); here the signals are in a 1:9 ratio (both signals can be detected in 80 scans of a 2% solution in a 10 mm tube; below this concentration the minor CH signal becomes hard to detect). A very effective alternative is to use a 1:10 ratio of ^{13}C -labeled and unlabeled material (Fig. 4). This uses very little of the expensive labeled material and balances the intensities of the two carbon signals (both singlets) while maintaining a slight difference for identification purposes (the methyl and methine carbons are present in an approximately 5:4 ratio). With this mixture, only 5 mol% relative to the compound under investigation (0.2 vol.% of the sample) is necessary for an adequate signal-to-noise ratio.

The dispersion of lines in Fig. 2 illustrates a potential problem with the method. The fact that different solvents give curves with substantially different offsets raises the question of whether calibration curves are affected by solutes. At the extremes, the offset between the calibrations for pentane (or methanol) and benzene (or toluene) is the equivalent of 60 °C. The addition of 5% of an aromatic substrate (benzene) to a pentane solution might cause a 3 °C error if the calibration curve for pure pentane were used. We have found that calibrations for mixed solvents can be extrapolated owing to the nearly linear dependence on the volume ratio (Fig. 5). Thus for 2:1 and 1:2 (v/v) MeOH– CDCl_3 the actual temperatures differed by 0.4 and –1.1 °C, respectively from the calculated values assuming a linear dependence. For 2:1 and 1:2 (v/v) pentane–toluene the deviations were –1.4 and 1.3 °C, respectively. We carried out some spot checks and found that, for example, the addition of 1 M styrene oxide to 3:2 THF–diethylether gave no detectable change in the $\Delta\delta$

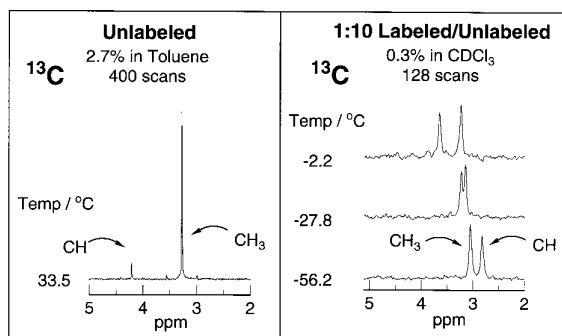


Figure 4. Typical ^{13}C spectra obtained for the signals of **1** for a 2.7 vol.% solution of natural abundance **1** (left) in toluene and a 0.29 vol.% sample of 9% enriched **1** (right) in CDCl_3 .

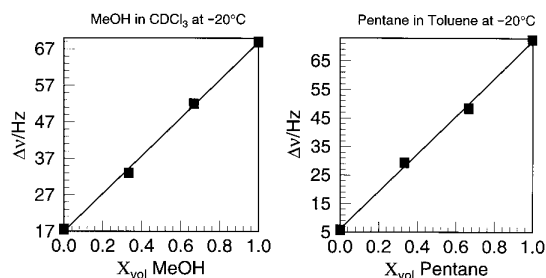


Figure 5. Calibration of **1** in mixed solvents. Plot of chemical shift between CH and CH_3 carbons at –20 °C vs. volume fraction for methanol–chloroform (left) and pentane–toluene (right).

value, but the user should be careful to perform calibrations of the thermometer using samples that are representative of the actual experiment, especially if substrates and solvents are likely to have large $\Delta\delta$ offsets and high concentrations are to be used.

On the positive side, the curves show only minimal, barely detectable, deviations from linearity. The small systematic deviations occur only at the highest and lowest temperatures near the boiling points and freezing points of the solvent, where systematic errors are likely to be largest (e.g. solvent reflux). This means that only two or three temperatures need to be calibrated, preferably no more than 50 or 60 °C apart, near the upper and lower limits of the DNMR experiment. In fact, the slopes for all solvents are so similar that a single calibration point will lead to acceptable results over a narrow temperature range. Hence calibration of a realistic solvent–substrate mixture is still much less work (and more reliable) than a normal sample-substitution protocol which needs to be performed at multiple temperatures, and every time an experiment is re-run.

Bis(trimethylsilyl)methane (**2**) as a shift thermometer

We have documented the utility of **1** as a NMR chemical shift thermometer. Bis(trimethylsilyl)methane (**2**) is also a candidate and shares many of the desirable properties of **1**, and even has some advantages over it. For example, the peak ratio at natural abundance is 6:1 vs. 9:1 for **1** (reducing the need for labeled material), and the two signals do not cross, so there is no 'blind spot'. Compound **2** is also substantially more volatile than **1** (b.p. 133 °C), which is an advantage for sample purification, but could restrict its use in high-temperature situations. A disadvantage is that the chemical shift sensitivity, which is already marginal for **1** (1.15 Hz °C^{–1}), is smaller (0.8 Hz °C^{–1}) for **2**. It has not been established what the chemical shift dependence on solvent is, or whether the temperature dependence is as linear as found for **1**.

Preparation of labeled tris(trimethylsilyl)methane

Although DNMR studies can effectively be performed with an approximately 2% solution of **1**, the sensitivity

is greatly increased (by at least an order of magnitude) by using material that is partially ^{13}C labeled at the methine carbon (see above). We developed a clean, efficient synthesis of ^{13}C -labeled tris(trimethylsilyl)methane from commercially available ^{13}C -paraformaldehyde (Scheme 1). This synthesis involves several *in situ* electrophilic traps which take advantage of the differing reactivities of the starting materials, products and electrophiles towards metalating agents. The first step is precedented.⁷ The second step is based on the observation that at -78°C , LDA does not react detectably with Me_3SiCl .⁸ However, bis(phenylseleno)methane (**3**) metalates readily at -78°C and is quenched by the Me_3SiCl as it is formed. This reaction succeeds because the product, bis(phenylseleno)trimethylsilylmethane (**4**), cannot be metalated by lithium diisopropylamide (LDA) at -78°C .

The third step takes advantage of an ideal balance of reactivities of the starting material, product and Me_3SiCl towards *n*-BuLi. Thus, the Se—C bond of bis(phenylseleno)trimethylsilylmethane is cleaved more rapidly than *n*-BuLi is trapped by Me_3SiCl . This permits phenylseleno(trimethylsilyl)methylolithium to be formed and trapped *in situ*. The product, bis(trimethylsilyl)phenylselenomethane (**5**), reacts sluggishly with *n*-BuLi at -78°C , so any excess *n*-BuLi is trapped by Me_3SiCl .

The final phenylseleno group is substituted in a sequential reaction by adding *n*-BuLi, warming to -20°C for 30 min and trapping with Me_3SiCl , producing $1\text{-}^{13}\text{C}$ in 71% overall yield from $[^{13}\text{C}]$ paraformaldehyde. This synthetic sequence allows one to arrive cleanly at any of the intermediates, and this synthetic approach can be easily modified to construct a variety of derivatives.

CONCLUSION

The primary advantage of the use of **1** as an NMR thermometer over other published NMR temperature measurement techniques is that it can be added directly to the solution being studied and measures the true internal temperature of the sample. It is soluble in all common organic solvents, very little is needed and its

chemical shifts maintain strong linear correlations in all solvents tested. An internal temperature thermometer has numerous advantages over other methods, and **1** fulfils most of the requirements of an ideal compound: it is unobtrusive (its peaks are in a usually bare region of the ^{13}C NMR spectrum), it is unreactive and it has no acidic or basic properties.

EXPERIMENTAL

Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl before use. Glassware was placed overnight in a 110°C oven or flame-dried before purging with N_2 to remove moisture. Common lithium reagents were titrated using *n*-propanol in THF with 1,10-phenanthroline as an indicator.⁹ Lithium diisopropylamide (LDA) was freshly prepared according to a literature procedure.^{4b} Temperatures of -78°C were achieved with a dry ice-acetone bath and -20°C with a chemical freezer.

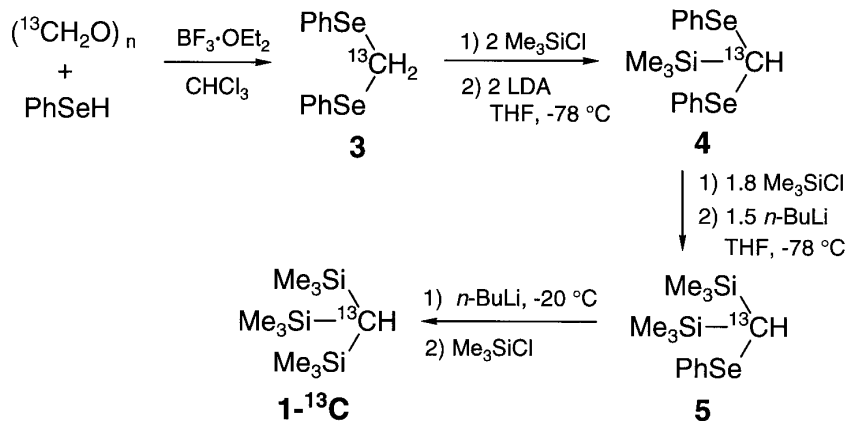
Commercially available starting materials and reagents (obtained from Aldrich Chemical unless stated otherwise) included benzeneselenol (PhSeH), boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$), ^{13}C -labeled paraformaldehyde (Cambridge Isotope Laboratories), trimethylsilyl chloride (Me_3SiCl), and tris(trimethylsilyl)methane ($(\text{Me}_3\text{Si})_3\text{CH}$).

NMR spectroscopy

For the characterization of synthesized compounds, ^1H and ^{13}C NMR spectra were acquired on a Bruker AC-300 spectrometer with CDCl_3 as the solvent and tetramethylsilane as the internal standard.

Temperature calibrations

The temperature calibrations were performed in 10 mm NMR tubes using a wide-bore AM-360 spectrometer at 360.148 MHz (^1H) and 90.556 MHz (^{13}C). Least squares data is reported in Table 2. The digital resolution was 0.15 Hz for ^1H and 0.64 Hz for ^{13}C . ^{13}C



Scheme 1. Synthesis of ^{13}C -labeled tris(trimethylsilyl)methane ($1\text{-}^{13}\text{C}$).

Table 2. Least-squares fit of $\Delta\delta$ vs. temperature for seven solvents (Fig. 2)

Solvent	Slope (Hz °C ⁻¹)	y-Intercept (Hz)	Correlation coefficient (<i>r</i>)
Pentane	1.088 ± 0.016	94.20 ± 1.16	0.9997
C ₆ D ₆	1.101 ± 0.010	21.92 ± 0.44	0.9999
Toluene	1.162 ± 0.016	28.92 ± 0.81	0.9994
3:2 THF–Et ₂ O	1.151 ± 0.009	66.90 ± 0.66	0.9997
CDCl ₃	1.069 ± 0.014	39.00 ± 0.52	0.9997
CH ₂ Cl ₂	1.108 ± 0.009	49.34 ± 0.45	0.9998
MeOH	1.079 ± 0.011	90.55 ± 0.49	0.9997

NMR spectra were Fourier transformed with a line broadening parameter of 2 Hz. When non-deuterated solvents were used, the spectrometer was run unlocked, and shimming was performed on the ¹³C FID of an isolated carbon.

To a 10 mm thin-walled NMR tube, truncated to 6 in, were added 3.0 ml of the appropriate solvent and 80 µl of tris(trimethylsilyl)methane (natural abundance) or 8 µl of 10% ¹³C-enriched tris(trimethylsilyl)methane.

Sample substitution method. The temperatures were measured using a thermocouple submerged in a second 10 mm NMR tube containing the same solvent mixture and volume as the sample (a second NMR tube was necessary because the presence of the thermocouple led to extremely poor resolution). Both the compound sample and the temperature probe sample were allowed to equilibrate thermally for 15 min to a given spectrometer console setting. The spinner air was not turned on at any point. The decoupler power was kept on at all times (it detectably heats the sample) except for the few seconds during which the temperature was actually recorded, as irradiation of the thermocouple led to non-sensical and sporadic readings in the temperature display unit.

Direct thermocouple insertion. The open tube was placed in the spectrometer. The temperature was taken before and after each ¹³C spectrum by inserting a thermocouple directly into the NMR tube inside the spectrometer. This was accomplished by threading the thermocouple into a 3 ft long piece of glass tubing, with the thermocouple protruding 1 in from the glass. The glass rod was lined up with the tube by using a brass scaffold inserted down the bore of the magnet to just above the tube. A rubber stop was used to adjust the height of the thermocouple and allow it to be placed at the same position each time. The decoupler was turned off only briefly as the temperature was recorded. Any point in which the temperature differed by more than 1 °C before and after the spectrum was obtained was retaken.

Tests of chemical stability of 1

To a dried 5 mm thin-walled NMR tube were added 0.5 ml of CDCl₃, 28 µl (0.1 mmol) of tris(trimethylsilyl)methane and 0.1 mmol of benzene as an internal

integration standard. The ¹H NMR spectrum was recorded. The tube was then charged with 62 µl (0.8 mmol, 8 equiv.) of trifluoroacetic acid. The tube was sealed with a cap and Parafilm and placed in an 18 °C constant-temperature bath. The tube was removed periodically over 1 week and the ¹H NMR spectrum recorded. There was no degradation of the tris(trimethylsilyl)methane signal vs. benzene within the limits of the integrations (± 5%) over 1 week. This procedure was repeated using 0.5 ml (8 equiv.) of 1.6 M *m*CPBA in CDCl₃, 0.5 ml (8 equiv.) of 1.6 M NaOH in CD₃OD and 0.5 ml (8 equiv.) of 1.6 M NaBH₄ in CD₃OD. No degradation was observed within the limits of the integrations in any of the samples over 1 week.

Materials

¹³C-Labeled Bis(phenylseleno)methane (3). This synthesis was performed according to a literature procedure.⁷ To a dried, argon-purged, 5 ml round-bottomed flask with a septum and stirrer bar were added 41.1 mg (1.32 mmol) of ¹³C-labeled paraformaldehyde, 3 ml of CHCl₃ and 315 µl (466 mg, 2.97 mmol) of PhSeH. The flask was cooled to 0 °C and 210 µl (235 mg, 1.66 mmol) of BF₃·OEt₂ were added, turning the heterogeneous solution a pale yellow. The spectrum of the closed system was covered with a thin layer of grease to limit formaldehyde evaporation, the flask was allowed to warm to room temperature and the reaction mixture was stirred for 4 days. The solution was taken up in 15 ml of 1:1 Et₂O–hexane, washed with 15 ml of 10% NaOH, 15 ml of H₂O and 15 ml of brine, dried over anhydrous MgSO₄ and decanted. Volatile materials were removed by rotary evaporation, and the last traces were removed with a vacuum pump (0.01 mmHg), yielding 0.434 g (1.33 mmol, 100% crude yield) of an orange liquid, which was used without further purification. ¹H NMR (300 MHz, CDCl₃): δ 4.20 (CH₂, d, ¹J_{H,C} = 156.45 Hz, ²J_{H,Se} = 12.13 Hz), 7.22–7.29 (Ph, m, 6H), 7.48–7.55 (Ph, m, 4H). ¹³C NMR (75.4 MHz, CDCl₃): δ 20.97 (CH₂, ¹J_{C,Se} = 87.10 Hz), 127.46 (CH), 129.06 (CH), 130.78 (C), 132.87 (CH).

¹³C-Labeled bis(phenylseleno)trimethylsilylmethane (4). The unlabeled compound has been reported.¹⁰ To a dried, N₂-purged, 25 ml round-bottomed flask with a septum and stirrer bar were added 0.17 g (0.52 mmol) of 3, 0.13 ml (0.11 g, 1.02 mmol) of Me₃SiCl and 10 ml of THF. A positive N₂ pressure was maintained throughout the reaction. The solution was cooled to –78 °C and 1.0 ml (1.06 mmol) of 1.06 M LDA in THF–hexane was added. The reaction mixture was kept at this temperature for 2 h and quenched with 1 ml of MeOH, to generate the easily removed Me₃SiOMe (b.p. 57 °C). Using quantitative transfers, the solution was taken up in 30 ml of 1:1 Et₂O–hexane and washed with 15 ml of 10% HCl and 2 × 15 ml of H₂O. Volatile materials were removed by rotary evaporation. Purification by preparative TLC (with hexane as eluent, R_f = 0.50) yielded 0.167 g (0.418 mmol, 80.6%) of a pale yellow liquid. ¹H NMR (300 MHz, CDCl₃): δ 0.16 (CH₃, d, ³J_{H,C} = 2.21 Hz, 9H), 3.82 (CH, d, ¹J_{H,C} = 141.74 Hz), 7.15–7.25 (Ph, m, 6H), 7.43–7.48 (Ph, m, 4H). ¹³C NMR (75.4 MHz, CDCl₃): δ –1.41 (CH₃, d, ²J_{CC} = 3.82 Hz), 31.45 (CH, ¹J_{C,Se} = 94.10

Hz, $^1J_{\text{C, Si}} = 47.05$ Hz), 127.50 (CH), 128.81 (CH), 131.54 (C), 133.93 (CH).

^{13}C -Labeled bis(trimethylsilyl)phenylselenomethane (5). To a dried, N_2 -purged, 50 ml round-bottomed flask with a septum and stirrer bar were added 0.167 g (0.418 mmol) of **4**, 95 μl (0.75 mmol) of Me_3SiCl and 10 ml of THF. A positive N_2 pressure was maintained throughout the reaction. The solution was cooled to -78°C and vigorously stirred while 0.1 mmol) of 1.06 M LDA in THF-hexane was added (to destroy any protic material) followed by 0.29 ml (0.62 mmol) of 2.13 M *n*-BuLi in pentane. The reaction mixture was stirred at this temperature for 15 min before being quenched with 1 ml of MeOH. The solution was warmed to room temperature, taken up in 30 ml of 1:1 Et_2O -hexane and washed with 3×20 mL of H_2O . Volatile materials were removed by rotary evaporation and the compound was purified by preparative TLC (with hexane as eluent, $R_f = 0.53$, preceding *n*-BuSePh, $R_f = 0.38$) yielding 0.130 g (0.412 mmol, 98.6%) of a pale yellow liquid. ^1H NMR (300 MHz, CDCl_3): δ 0.13 (CH_3 , d, $^3J_{\text{H,C}} = 1.84$ Hz, 18 H), 1.29 (CH, d, $^1J_{\text{H,C}} = 117.47$ Hz), 7.12–7.24 (Ar, m, 3H), 7.43–7.48 (Ar, m, 2H). ^{13}C NMR (75.4 MHz, CDCl_3): δ 0.36 (CH_3 , d, $^2J_{\text{CC}} = 3.82$ Hz), 15.80 (CH, $^1J_{\text{C, Se}} = 70.57$ Hz, $^1J_{\text{C, Si}} = 43.87$ Hz), 126.17 (CH), 128.80 (CH), 131.45 (CH), 133.73 (C).

^{13}C -Labeled tris(trimethylsilyl)methane (1- ^{13}C).¹¹ To a dried, N_2 -purged, 25 ml round-bottomed flask with a septum and stirrer bar were added 0.130 g (0.412 mmol) of **5** and 10 ml of THF. A positive N_2 pressure was maintained throughout the reaction. The solution was cooled to -78°C and 0.23 ml (0.49 mmol) of 2.13 M *n*-BuLi in pentane was added dropwise. The solution was warmed to -20°C and held at this temperature for 30 min. To a separate dried and purged 10 ml round-bottomed flask were added 68 μl (0.54 mmol) of Me_3SiCl and 5 ml of THF. This flask was also cooled to -20°C , the Me_3SiCl solution was transferred via a cannula to the flask containing the anion and the resulting mixture was allowed to warm to room temperature and stirred for 15 min before 1 ml of MeOH was added to trap the remaining Me_3SiCl . The solution was taken up in 30 ml of 1:1 Et_2O -hexane and washed with 2×30 ml of H_2O . Volatile materials were removed by rotary evaporation and the product was isolated by preparative TLC using hexane as the eluent, cutting away everything (no chromophore!) that ran ahead of the PhSeBu band ($R_f = 0.38$), and yielding 0.087 g (0.372 mmol, 90.4% or 71.3% overall from ^{13}C -labeled paraformaldehyde) of **1** (pale yellow liquid). ^1H NMR (300 MHz, CDCl_3): δ -0.73 (CH, d, $^1J_{\text{H,C}} = 100.19$ Hz, $^2J_{\text{H, Si}} = 9.74$ Hz, 1H), 0.15 (CH_3 , d, $^3J_{\text{H,C}} = 1.47$ Hz, $^2J_{\text{H, Si}} = 6.25$ Hz, 27 H). ^{13}C NMR (75.4 MHz, CDCl_3): δ 3.37 (CH_3 , d, $^2J_{\text{CC}} = 3.18$ Hz), 4.05 (CH, $^1J_{\text{C, Si}} = 37.51$ Hz). Mass spectrum: $[\text{M} - \text{CH}_3]^+ = 218.1254$ (calc. for $^{13}\text{CC}_9\text{H}_{28}\text{Si}_3 - \text{CH}_3$, 218.1298).

Acknowledgements

This work was supported by the National Science Foundation under Grant No. CHE-9703589. The spectrometers are funded by the National Science Foundation and the National Institute of Health through Grant Nos NSF CHF-8306121, NIH 1 S10 RR02388-01 (Bruker AM-360) and NSF CHE-9208463, NIH 1 S10 RR08389-01 (Bruker AC-300).

REFERENCES

1. J. Sandström, *Dynamic NMR Spectroscopy*. Academic Press, London (1982).
2. (a) A. L. Van Geet, *Anal. Chem.* **40**, 2227 (1968); (b) A. L. Van Geet, *Anal. Chem.* **42**, 679 (1970); see also D. S. Raiford, C. L. Fisk and E. D. Becker, *Anal. Chem.* **51**, 2050 (1979).
3. (a) H. J. Schneider, W. Freitag and M. Schommer, *J. Magn. Reson.* **18**, 393 (1975); (b) J. Bornais and S. Brownstein, *J. Magn. Reson.* **29**, 207 (1978); (c) D. W. Vidrine and P. E. Peterson, *Anal. Chem.* **48**, 1301 (1976); (d) J. J. Led and S. B. Petersen, *J. Magn. Reson.* **32**, 1 (1978); (e) P. J. Smolenaeres, M. T. Kelso and J. K. Beattie, *J. Magn. Reson.* **52**, 118 (1983); (f) G. C. Levy, J. T. Bailey and D. A. Wright, *J. Magn. Reson.* **37**, 353 (1980); (g) L. D. Field, S. Sternhell and W. Veigel, *Org. Magn. Reson.* **22**, 221 (1984).
4. (a) H. J. Reich and R. R. Dykstra, *Angew. Chem., Int. Ed. Engl.* **32**, 1469 (1993); H. J. Reich and K. J. Kulicke, *J. Am. Chem. Soc.* **117**, 6621 (1995); (b) H. J. Reich, J. M. Renga and I. L. Reich, *J. Am. Chem. Soc.* **97**, 5434 (1975).
5. (a) O. Yamamoto and M. Yanagisawa, *Anal. Chem.* **42**, 1463 (1970); (b) C. Piccinni-Leopardi, O. Fabre and J. Reisse, *Org. Magn. Resonance* **8**, 233 (1976); (c) H. Friebolin, G. Schilling and L. Pohl, *Org. Magn. Reson.* **12**, 569 (1979).
6. M. A. Cook, C. Eaborn, A. E. Jukes and D. R. M. Walton, *J. Organomet. Chem.* **24**, 529 (1970).
7. J. Gabriel and D. Seebach, *Helv. Chim. Acta* **67**, 1070 (1984).
8. E. J. Corey and A. W. Gross, *Tetrahedron Lett.* **25**, 495 (1984).
9. S. C. Watson and J. F. Eastham, *J. Organomet. Chem.* **9**, 165 (1967).
10. B.-T. Gröbel and D. Seebach, *Chem. Ber.* **110**, 852 (1977).
11. Compound 1- ^{13}C can also be efficiently prepared by reductive silylation of $^{13}\text{CHCl}_3$ (A. Guijarro, M. Yus, *Tetrahedron* **52**, 1797 (1996)).