

Tris(trimethylsilyl)methane is *not* an effective mediator of radical reactions

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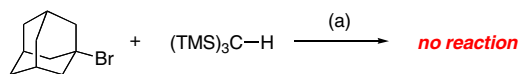
Abstract—The reductive dehalogenation of organohalides by tris(trimethylsilyl)methane has been re-investigated. Contrary to claims made in a recent publication (*Tetrahedron Lett.* **2006**, *47*, 5163–5165), (TMS)₃CH does not reduce organohalides. In competition experiments between (TMS)₃CH and the poor chain mediator Et₃SiH, the latter performed the reduction. Computational investigations support these experimental findings and indicate that the C–H bond of (TMS)₃CH is too strong for this compound to serve as an effective mediator of radical reactions.

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The introduction of tributyltin hydride as a mild and effective mediator of free radical chain reactions led to an upsurge in the development of new synthetic methods and strategies involving radical intermediates.¹ Bu₃SnH is not, however, an ideal reagent. Organotin compounds are toxic² and difficulties are often encountered in the separation of organotin by-products from the desired products of the radical reactions they mediate. Over the years several alternative reagents have been introduced, the most successful of which are Chatgililoglu's tris(trimethylsilyl)silane³ and Barton's ethyl piperidinium hypophosphite (EPHP).⁴ These and related reagents can be used as replacements for Bu₃SnH in many radical reactions.⁵ Nevertheless, (TMS)₃SiH is expensive⁶ and not easy to prepare.⁷ In contrast, EPHP is cheap⁸ and easily made⁹ but must be used in large excess with copious amounts of initiator. We were excited, therefore, to read a recent publication in this *Journal* introducing a new radical reducing agent tris(trimethylsilyl)methane, (TMS)₃CH.¹⁰ This compound appeared to offer significant advantages over existing reagents since, in addition to the fact that it is very easy to synthesize on multigram scale,¹¹ the

reported rate constant for H atom transfer from (TMS)₃CH to primary alkyl radicals is similar to that of (TMS)₃SiH.¹⁰ We were fascinated by the possibilities presented by (TMS)₃CH and embarked upon a program involving its use. Despite our best efforts, however, we have been unable to replicate the findings of the 2006 communication and report here the results of our own experimental and computational investigations with (TMS)₃CH, which we believe show that it is *not* an effective radical reducing agent.

Primary, secondary, and tertiary alkyl halides and aryl halides were reported to undergo reductive dehalogenation with (TMS)₃CH on heating in the presence of AIBN or 1,1'-azobis(cyclohexanecarbonitrile) (VAZO 88) or under unspecified photochemical conditions. We initially attempted to repeat the reported conversion of 1-bromoadamantane to adamantane using the thermal procedures described in the Letter (*Scheme 1*).^{10,12}



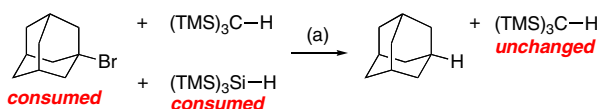
Scheme 1. Attempted radical reductions of 1-bromoadamantane. Reagents and conditions: (a) (TMS)₃CH (2 mol equiv), benzene (substrate concn 0.1 M), AIBN or VAZO 88 (0.2–2 mol equiv), with or without anisole (internal standard), 80 °C, 14–24 h.

Keywords: Radicals; Synthetic methods; Ab initio calculations.

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Thus, AIBN (0.2 mol equiv) was added to a degassed mixture of 1-bromoadamantane and $(\text{TMS})_3\text{CH}$ (2 mol equiv) in benzene (0.1 M in substrate) and the resulting solution was heated to reflux for 14 h. Despite many attempts with various batches of commercial¹³ and freshly prepared¹¹ $(\text{TMS})_3\text{CH}$, we found no reaction under these conditions.^{10,12} Furthermore, when the reaction was conducted with larger amounts of AIBN (up to 2 mol equiv) or VAZO (up to 2 mol equiv) in refluxing benzene, no adamantane was present in the reaction mixture. We replaced 1-bromoadamantane with iodobenzene and bromocyclohexane and obtained the same result: no products of reductive dehalogenation could be detected in the reaction mixtures by GC analysis and, in runs containing an internal GC standard, the $(\text{TMS})_3\text{CH}$ remained unchanged.

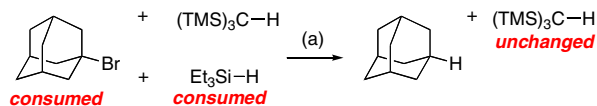
These results led us to suspect that an unidentified radical inhibitor was contaminating our reactions. Thus, a benzene solution of 1-bromoadamantane was exposed to equimolar amounts of $(\text{TMS})_3\text{SiH}$ and $(\text{TMS})_3\text{CH}$ under the standard conditions. This time, adamantane was formed cleanly (Scheme 2).



Scheme 2. Test for the presence of radical inhibitors. Reagents and conditions: (a) $(\text{TMS})_3\text{CH}$ (2 mol equiv), $(\text{TMS})_3\text{SiH}$ (2 mol equiv), benzene (substrate concn 0.1 M), AIBN (0.2 mol equiv), anisole (internal standard), 80 °C, 14 h, 100% conversion.

Closer analysis of the product mixture revealed that $(\text{TMS})_3\text{CH}$ was unchanged and that $(\text{TMS})_3\text{SiH}$ had been consumed. Whilst this result allayed our fears regarding inhibition of a radical chain process, we were cognizant of the fact that this outcome simply confirmed that $(\text{TMS})_3\text{SiH}$ was a more effective reducing agent than $(\text{TMS})_3\text{CH}$. To shed light on the efficiency of $(\text{TMS})_3\text{CH}$ as a reducing agent, a more stringent test was warranted. In the absence of polarity reversal catalysts,¹⁴ triethylsilane is known to be a poor radical reducing agent. It was reported¹⁰ that $(\text{TMS})_3\text{CH}$ transfers a hydrogen atom to a primary alkyl radical significantly faster than triethylsilane.¹⁵ Thus, a competition experiment between $(\text{TMS})_3\text{CH}$ and Et_3SiH should result in the consumption of the former.

A solution of benzoyl peroxide¹⁶ (2 mol equiv) was added, via a syringe pump over 5 h, to a solution of 1-bromoadamantane (1 mol equiv), $(\text{TMS})_3\text{CH}$ (10 equiv), and Et_3SiH (10 equiv) in benzene (0.1 M) at 80 °C (Scheme 3). The progress of the reaction was monitored by GC using anisole as an internal standard.¹⁷ After 22 h at 80 °C, GC analysis revealed the presence of adamantane, decreased amounts of triethylsilane and 1-bromoadamantane, and no change in the amount of $(\text{TMS})_3\text{CH}$. We entertained the possibility that $(\text{TMS})_3\text{CH}$ might somehow be catalyzing this reaction. When the experiment depicted in Scheme 3 was repeated without $(\text{TMS})_3\text{CH}$, however, the same level of conversion of 1-bromoadamantane into adamantane was



Scheme 3. Competition experiment between $(\text{TMS})_3\text{CH}$ and Et_3SiH . Reagents and conditions: (a) $(\text{TMS})_3\text{CH}$ (10 mol equiv), Et_3SiH (10 mol equiv), benzene (substrate concn 0.1 M), $(\text{BzO})_2$ (2 mol equiv, slow addition), anisole (internal standard), 80 °C, 14 h, 27% conversion.

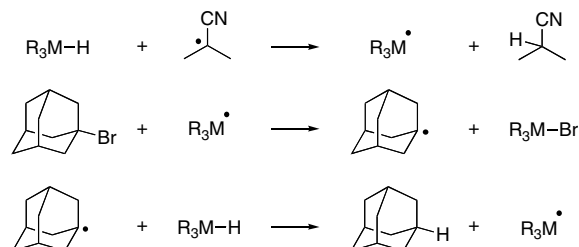
recorded. Furthermore, when the Scheme 3 competition experiment was repeated with the omission of Et_3SiH , no conversion of 1-bromoadamantane or $(\text{TMS})_3\text{CH}$ was observed.

We contemplated the possibility that the solvent was influencing the outcome of our reactions, since it is known that $\text{Et}_3\text{Si}^\bullet$ radicals add to benzene.¹⁸ Upon repeating the experiments described above in cyclohexane, however, similar results were obtained¹⁹ and no conversion of $(\text{TMS})_3\text{CH}$ was detected.

At this stage, we were confident that $(\text{TMS})_3\text{CH}$ was inferior to Et_3SiH as a radical reducing agent and that the procedures described in the 2006 communication¹⁰ were not reproducible. We reflected on the possibility that our reactions might be failing because they lacked a contaminant. Perhaps the original authors achieved successful transformations due to the presence of a catalyst of which they had no knowledge. We conducted a final set of experiments akin to those described above with added *tert*-dodecylthiol as a polarity reversal catalyst.²⁰ Reactions involving Et_3SiH in the presence of small amounts of thiol led to markedly faster conversions and higher conversions of the organohalide. To our dismay, $(\text{TMS})_3\text{CH}$ remained unchanged in all such tests.

Our experimental observations on the inefficiency of $(\text{TMS})_3\text{CH}$ as a chain carrier are supported by computational investigations. High-level *ab initio* calculations were used to model the radical reductive debromination of 1-bromoadamantane by the three chain carrier agents, according to the general pathway shown in Scheme 4. Relevant thermodynamic and kinetic parameters are given in Tables 1–3.

From Table 1, it is seen that $(\text{TMS})_3\text{CH}$ is the least susceptible of the three reagents toward initial hydrogen atom abstraction by the AIBN-derived 2-cyanopropyl radical. This lack of reactivity stems both from thermodynamic sources [the bond dissociation energy (BDE)]²¹



Scheme 4. Pathway modeled for radical reductive debromination of 1-bromoadamantane. $\text{R}_3\text{M-H}$ = $(\text{TMS})_3\text{C-H}$, $(\text{TMS})_3\text{Si-H}$ or $\text{Et}_3\text{Si-H}$.

Table 1. Kinetics and thermodynamics of hydrogen atom abstraction from the various chain carriers at 353.15 K^a

	$\Delta H^\ddagger/\Delta H$ (kJ mol ⁻¹)	$\Delta S^\ddagger/\Delta S$ (J mol ⁻¹ K ⁻¹)	$\Delta G^\ddagger/\Delta G$ (kJ mol ⁻¹)	Q	k (L mol ⁻¹ s ⁻¹)/K
(TMS) ₃ CH + ·C(CN)Me ₂ → (TMS) ₃ C· + H–C(CN)Me ₂	Rate (k)	38.7	–201.2	109.7	3.31 4.16 × 10 ⁻²
	Equilibrium (K)	31.4	7.4	28.8	— 5.58 × 10 ⁻⁵
(TMS) ₃ Si–H + ·C(CN)Me ₂ → (TMS) ₃ Si· + H–C(CN)Me ₂	Rate (k)	4.1	–170.4	64.2	1.63 1.09 × 10 ⁵
	Equilibrium (K)	–27.2	–8.0	–24.4	— 4.06 × 10 ³
Et ₃ SiH + ·C(CN)Me ₂ → Et ₃ Si· + H–C(CN)Me ₂	Rate (k)	40.6	–144.4	91.6	4.29 2.54 × 10 ¹
	Equilibrium (K)	15.3	–7.8	18.1	— 2.13 × 10 ⁻³

^a High-level ab initio calculations were performed at the G3(MP2)-RAD//B3-LYP/6-31G(d) level of theory. Partition functions and associated thermodynamic quantities were calculated using the standard formulae for the statistical thermodynamics of an ideal gas under the rigid rotor/harmonic oscillator approximation, and the reaction rates incorporate Eckart tunneling corrections (Q). For more details see the Supplementary data.

Table 2. Thermodynamics of bromine atom abstraction from 1-bromoadamantane by the various chain carrier radicals at 353.15 K^a

	ΔH (kJ mol ⁻¹)	ΔS (J mol ⁻¹ K ⁻¹)	ΔG (kJ mol ⁻¹)	K
(TMS) ₃ C· + adamantyl–Br → (TMS) ₃ CBr + adamantyl·	42.5	–24.1	51.0	2.82 × 10 ⁻⁸
(TMS) ₃ Si· + adamantyl–Br → (TMS) ₃ SiBr + adamantyl·	–51.0	–10.7	–47.2	9.61 × 10 ⁶
Et ₃ Si· + adamantyl–Br → Et ₃ SiBr + adamantyl·	–108.4	4.0	–109.8	1.72 × 10 ¹⁶

^a High-level ab initio calculations were performed at a modified G3(MP2)-RAD//B3-LYP/6-31G(d) level of theory. Partition functions and associated thermodynamic quantities were calculated using the standard formulae for the statistical thermodynamics of an ideal gas under the rigid rotor/harmonic oscillator approximation. For more details see the Supplementary data.

Table 3. Thermodynamics of hydrogen atom abstraction from the various chain carriers by the adamantyl radical at 353.15 K^a

	ΔH (kJ mol ⁻¹)	ΔS (J mol ⁻¹ K ⁻¹)	ΔG (kJ mol ⁻¹)	K
adamantyl· + (TMS) ₃ CH → (TMS) ₃ C· + adamantane	–11.4	17.5	–17.6	4.03 × 10 ²
adamantyl· + (TMS) ₃ SiH → (TMS) ₃ Si· + adamantane	–70.0	2.0	–70.7	2.87 × 10 ¹⁰
adamantyl· + Et ₃ SiH → Et ₃ Si· + adamantane	–27.5	2.3	–28.3	1.68 × 10 ⁴

^a High-level ab initio calculations were performed at the G3(MP2)-RAD//B3-LYP/6-31G(d) level of theory. Partition functions and associated thermodynamic quantities were calculated using the standard formulae for the statistical thermodynamics of an ideal gas under the rigid rotor/harmonic oscillator approximation. For more details see the Supplementary data.

for (TMS)₃CH at 0 K, at 401.5 kJ mol⁻¹, is calculated to be some 57.5 kJ mol⁻¹ greater than that for (TMS)₃SiH (344.0 kJ mol⁻¹)²², and from kinetic effects [(TMS)₃CH is calculated to be a factor of 3 × 10⁶ slower as a hydrogen atom donor than its Si–H analogue].²³ In comparison to the two TMS-substituted reagents, Et₃SiH falls in an intermediate position, having a moderately low rate constant²⁴ and a reasonably unfavorable equilibrium constant for the initial hydrogen abstraction. The barrier (ΔH^\ddagger) for the initial hydrogen abstraction from (TMS)₃CH is very similar to that for Et₃SiH. However, the reagent (TMS)₃CH also suffers from entropic disadvantages, as in the transition state the distance between the abstracting and incipient radical centers is much smaller (and steric clashing is consequently more severe) than for the silanes: the distance C···H···C in the transition state for hydrogen abstraction from (TMS)₃CH is 2.8 Å, compared with Si···H···C distances of 3.2 Å in the silane transition states.

The abstractions of bromine from 1-bromoadamantane are exothermic for Et₃Si· and (TMS)₃Si· but endothermic for (TMS)₃C· (Table 2). There is a large difference between the exothermicity of the reaction involving the carbon-centered radical with those involving the silyl radicals. This difference is related to the relative bond

strengths of Si–Br and C–Br bonds and is in accord with the literature data for related compounds. For example, the BDE of the Si–Br bond in Me₃Si–Br²⁵ is 424.2 kJ mol⁻¹, whereas the BDE of Me₃C–Br²⁶ is only 292.9 kJ mol⁻¹.

Hydrogen atom abstractions from the chain carriers by the adamantyl radical are also exothermic (Table 3). As expected, the enthalpies follow the same order as in the first step, with abstraction from the (TMS)₃CH molecule least favorable. Our calculations are consistent with our experimental observations but are at odds with the reported¹⁰ rate data for H atom abstraction from (TMS)₃CH by primary alkyl radicals.

We believe that our experimental and computational results demonstrate that chain-carrier efficiency varies in the order (TMS)₃SiH > Et₃SiH ≫ (TMS)₃CH. The distinction between the two SiH reagents may be attributed predominantly to the kinetic attributes of hydrogen atom abstraction. On the other hand, for (TMS)₃CH there is not only a higher barrier to the initial C–H abstraction, but the subsequent bromine abstraction is even less energetically favorable. We therefore conclude that tris(trimethylsilyl)methane is not an effective radical reducing agent.²⁷

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Supplementary data

Supplementary data associated with this article (computational methods and tables of geometries and total energies) can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.055.

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- No reaction was observed upon attempted initiation of the radical reaction with either AIBN or VAZO 88.
- Experimental procedure*: A solution of 1-bromoadamantane (20 mg, 0.09 mmol), anisole (10 μL), triethylsilane (150 μL , 0.9 mmol, 10 mol equiv), and/or tris(trimethylsilyl)methane (260 μL , 0.9 mmol, 10 mol equiv) in benzene (1 mL) was heated to 80 °C. A solution of benzoyl peroxide (50 mg, 0.2 mmol, 2 equiv) in benzene (1 mL) was added, via syringe pump, over 5 h. A diluted sample of the reaction mixture was injected directly into an Agilent 6850 series GC instrument fitted with an Agilent 19091 J-233E, HP5 5% phenyl methyl siloxane column (capillary size: 30.0 m \times 250 μm \times 1.00 μm).
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- This value compares favorably with the experimental BDE for (TMS)₃Si–H of 347 kJ mol⁻¹: Becerra, R.; Walsh, R.. In *The Chemistry of Organic Silicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; John Wiley & Sons: Chichester, 1998; Vol. 2, Part 1, pp 153–180. The experimental BDE for Et₃Si–H (reported in the same paper) is 392 kJ mol⁻¹. To our knowledge the BDE for (TMS)₃C–H has not been reported.
- Experimental rate constants (at 298 K) are 3.7, 1.4, and $2.6 \times 10^5 \text{ L mol}^{-1} \text{ s}^{-1}$ for H atom abstraction from (TMS)₃Si–H by primary, secondary, and tertiary alkyl radicals, respectively: Chatgililoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* **1991**, 56, 6399–6403. Our calculated rate constant for H atom abstraction from (TMS)₃Si–H by the 2-cyanopropyl radical of $1.09 \times 10^5 \text{ L mol}^{-1} \text{ s}^{-1}$ (Table 1) is in good agreement with this experimental value.
- The experimental rate constants (at 298 K) for H atom abstraction from Et₃Si–H by a primary alkyl radical is $6.4 \times 10^2 \text{ L mol}^{-1} \text{ s}^{-1}$: Chatgililoglu, C.; Ferreri, C.; Lucarini, M. *J. Org. Chem.* **1993**, 58, 249–251. Our calculated rate constant for H atom abstraction from Et₃Si–H by the 2-cyanopropyl radical of $2.54 \times 10^1 \text{ L mol}^{-1} \text{ s}^{-1}$ (Table 1) is in good agreement with this experimental value.
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