Reversal of Stereoselectivity in the Reduction of *gem*-Dichlorides by Tributyltin Hydride and Tris(trimethylsilyl)silane. Synthetic and Mechanistic Implications

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The most useful reagent for the reduction of alkyl halides is probably Bu_3SnH ,¹ but due to its high toxicity its use for pharmaceutical applications is generally unacceptable. It was recently discovered that (Me_3Si)₃SiH reduces organic halides in high yields, and due to its low toxicity it is an attractive alternative to Bu_3SnH .² The two reagents have different spatial shapes: Bu_3SnH has flexible chain-type substituents while (Me_3 -Si)₃SiH has a spherical and more rigid shape. In this paper we demonstrate that *the different spatial shapes of* Bu_3SnH and (Me_3Si)₃SiH can lead to different, even reversed, product stereoselectivities, an unprecedented finding of synthetic significance. In addition, our experimental results coupled with ab initio calculations suggest that a mechanistic assumption commonly used to interpret the reduction products by Bu_3SnH^3 is not generally valid.

The gem-dihalides, 1-6 (Table 1) were reduced with both Bu₃SnH and (Me₃Si)₃SiH, and the ratios of the monoreduced stereoisomeric products are given in Table 1.⁴ The accepted two-step radical chain mechanism for the reduction of halides by both Bu₃SnH³ and (Me₃Si)₃SiH² is shown in Scheme 1 (for gem-dichlorocyclopropanes).

Reduction of 1,1-dichloro-cis-2,3-dimethylcyclopropane (1) and of cis-1,1,2,3-tetrachlorocyclopropane (2) with either of the two reagents yields similar product mixtures (Table 1). The preferred formation of the cis products (1b and 2b, respectively) can be understood as resulting from a preferred approach of the reducing reagents, M–H, to the fast equilibrating³ R-cis \rightarrow **R-trans** radicals from the sterically less hindered side, i.e., anti to the β -R substituents. In contrast, reduction of the bicyclic systems 3, 4, and 5 or of 4-tert-butyl-1,1-dichlorocyclohexane, 6, with Bu₃SnH or with (Me₃Si)₃SiH leads to different stereoselectivities (Table 1). Thus, the 3b/3a product ratio is 2.6 with Bu₃SnH and 7.1 with (Me₃Si)₃SiH. Reduction of 6 with Bu₃-SnH leads to a 6a/6b product ratio of 5.2, while with (Me₃-Si)₃SiH this ratio is only 1.4. The two reagents exhibit reversed stereoselectivities with 4 and 5; e.g., the 5a/5b product ratio is 1.3 with Bu₃SnH but only 0.22 with (Me₃Si)₃SiH (Table 1). Thus with Bu₃SnH, H formally enters preferentially from the endo side, while with (Me₃Si)₃SiH, H is introduced preferably from the exo side, leading predominantly to 4b and 5b.

To gain information on the structures of the reduction reaction transition states (TS) we have carried out ab initio calculations^{5,6} for the model reaction 1. Reaction 1 is calculated to be exothermic by 21.3 kcal/mol, and the activation enthalpy is 9.4

Table 1.	Reduction	Products	with	Bu ₃ SnH	and	(Me ₃ Si) ₃ SiH	of
Systems 1	-6						

starting dichloride			k'2/k2 ^b		
R ₁ = R ₂ = Ci	reducing agent	reduction pro	Bu ₃ SnH	(Me ₃ Si) ₃ SiH	
	Bu ₃ SnH (Me ₃ Si) ₃ SiH	1a R ₁ ≠ H, R ₂ = Cl 1 1	1b R ₁ ⊭ Cl, R ₂ = H : 4.0 : 5.2	6.0	7.8
	Bu₃SnH (Me₃Si)₃SiH	2a R ₁ = H, R ₂ = Cl 1 1	2b R ₁ = Cl, R ₂ ≠ H : 2.9 : 2.9	5.8	5.8
	Bu₃SnH (Me₃Si)₃SiH	3a R ₁ = H, R ₂ = Cl 1 1	3b R ₁ = Cl, R ₂ = H : 2.6 : 7.1	10.9	29.8
	Bu ₃ SnH (Me ₃ Si) ₃ SiH	4a R ₁ = H, R ₂ = Cl 1.9	4b R ₁ = CI, R ₂ = H : 1 : 1.3	3.4	8.3
	Bu ₃ SnH (Me ₃ Si) ₃ SiH	5a R ₁ ≕ H, R ₂ ≕ Cl 1.3 1	5b R ₁ = Cl, R ₂ = ⊭ : 1 : 4.6	-	-
	Bu ₃ SnH (Me ₃ Si) ₃ SlH	6a R ₁ = H, R ₂ = Cl 5.2 1.4	6b R ₁ = Cl, R ₂ = H : 1 : 1	1.6°	6.1 [°]

^a Determined by NMR. No significant changes in the product ratios were observed during the reaction course. ^b See Scheme 1. ^c Using chlorocyclohexyl radical as a model.

Scheme 1. Schematic Mechanism for the Reduction of *gem*-Dichlorocyclopropanes by Bu₃SnH and (Me₃Si)₃SiH



kcal/mol (MP3/6-31G*//6-31G*).

 $CH_3^{\bullet} + HSi(SiH_3)_3 \longrightarrow [H_3C - H - Si(SiH_3)_3]^{\bullet \bullet} \longrightarrow$

 $H_4C + (H_3Si)_3Si^{\bullet}$ (1)

The transition structure for reaction 1 (characterized at $6-31G^{*5,6}$) is essentially linear, and it occurs relatively "early" along the reaction coordinate; i.e., the calculated C-H, Si-H, and C-Si distances are 1.519 Å (1.084 Å in CH₄), 1.683 Å (1.484 Å in (H₃Si)₃SiH), and 3.202 Å, respectively.

Examination of molecular models (and the results of forcefield calculations) which use the ab initio calculated transition state geometry indicates that γ -substituents (not β -substituents as in 1 and 2)⁷ are required to induce steric differentiation between the two reagents, in agreement with the experimental results in Table 1. This results from the relatively long Si-H and Sn-H bonds and the relatively "early" TS, which make

⁽¹⁾ For a recent review, see: Neumann, W. P. Synthesis 1987, 665.

⁽¹⁾ Tol a recent rootw, see: Acumani, W. T. Synhests Dyn, 605.
(2) (a) Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgilialoglu, C.; Griller, D.; Lesage, M. J. Org. Chem. 1988, 53, 3641. (c) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. J. Org. Chem. 1991, 56, 678.
(2) (a) Pache C.; Welberglu; H. M. In Conference Derived Receiver.

^{(3) (}a) Boche, G.; Walborsky, H. M. In Cyclopropane Derived Reactive Intermediates; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1990. (b) Walborsky, H. M. Tetrahedron 1981, 37, 1625.
(4) The reductions were carried at 80 °C in d₆-benzene in a vacuum-

⁽⁴⁾ The reductions were carried at 80 °C in d_6 -benzene in a vacuumsealed NMR tube using a 1:1 ratio of the dichloride and of the reducing agent and a catalytic amount (5–10%) of AIBN. The product ratios were determined by NMR.

⁽⁵⁾ Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. Ab Initio Molecular Orbital Theory; John Wiley & Sons: New York, 1986.

⁽⁶⁾ The Gaussian 92, Version C, program was used: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defress, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1992.

⁽⁷⁾ Examination of molecular models and force-field calculations show that increase in the size of the β -substituents (e.g., to *t*-Bu in 1) would increase the **b**/a product ratio to the same extent, for the two reagents.

Table 2. Calculated Energy Differences (ΔE) , Equilibrium Constants (K_{eq}) , Energies of Activation (ΔE^*) , and Inversion Rates (k_i) for Various Cyclopropyl Radicals and Chlorocyclohexyl Radical at 6-31G*

radicala	∆E b kcai/mol	К _{еq} с (80 ⁰ С)	% ^d	∆E ^{‡ e} kcal/mol	k _i f s ⁻¹
cyclopropyl	0.0	0.0	50	3.9	8.7x10 ^{9 g}
α-chloro- cyclopropyl	0.0	0.0	50	7.9	1.1x10 ⁷
CH ₃ CH ₃ R-1-trans	0.3	1.5	60	7.6	1.7x10 ⁷
	0.5	2.0	67	4.5	3.1x10 ⁹
R-2-trans	1.0	4.2	81	7.6	1.7x10 ⁷
R-3-trans	1.3	6.4	87	7.7	1.4x10 ⁷
CI	1.5	8.5	90	2.5	9.1x10 ¹⁰

^{*a*} The more stable structure of the radical is shown. ^{*b*} Calculated energy differences between the isomeric radicals. ^{*c*} Calculated from ΔE at the reaction temperature. ^{*d*} Percentage of the more stable radical at equilibrium. ^{*f*} Calculated inversion barriers starting from the more stable structure. ^{*f*} At 25 °C. Calculated from ΔE^* and the Eyring equation. ^{*s*} The experimental value (ESR) of $10^{11} < k_i \le 10^{12} \text{ s}^{-1}$ at 71 °C (Johnston, L. J.; Ingold, K. U. J. Am. Chem. Soc. **1986**, 108, 2343) is somewhat higher.

the spatial differences between the chain-like *n*-butyl groups and the spherical $(Me_3Si)_3SiH$ become important only in interactions with groups which are located at relatively remote positions (e.g., γ -position) from the radical center which is being approached at the TS for H transfer. As expected, γ -substituents have larger steric interactions at the TS with the spherical $(Me_3-Si)_3SiH$ than with the more flexible Bu₃SnH. Consequently, $(Me_3Si)_3SiH$ shows a higher selectivity than Bu₃SnH in transferring its H atom from the least sterically hindered side leading in general to higher **b/a** product ratios (Table 1).

The above results also have important mechanistic implications. A recent comprehensive review on the reduction of cyclopropyl halides has reached the following conclusions (Scheme 1):³ (1) The intermediate cyclopropyl radicals, **R-cis** and **R-trans**, isomerize faster than they abstract an H atom from M-H (i.e., $k_1, k_{-1} \gg k_2, k'_2$). (2) The rates of H atom transfer from Bu₃SnH to both sides of the cyclopropane ring are equal (i.e., $k_2 = k'_2$). It was therefore concluded that the product ratios are determined *only* by the **R-cis** — **R-trans** equilibrium. Consequently product ratios were used to determine unknown equilibrium constants of isomeric radicals,³ i.e., eq 2.

$$[\mathbf{P}-\mathbf{cis}]/[\mathbf{P}-\mathbf{trans}] = [\mathbf{R}-\mathbf{cis}]/[\mathbf{R}-\mathbf{trans}]$$
(2)

Our finding that Bu₃SnH and (Me₃Si)₃SiH give *different* product ratios with the same precursor contradicts the above assumptions. Thus, if the radicals indeed reach equilibrium before their trapping $(k_1, k_{-1} \gg k_2, k'_2)$, then at least for one of the reagents $k_2 \neq k'_2$, in contrast to assumption 2 above.

To gain independent information on the above assumptions, we have calculated at $6-31G^*//6-31G^* \,^6$ inversion barriers, ΔE^4 and the corresponding inversion rates, k_i , for several radicals (Table 2). Comparison of the calculated k_i values (all >1.4 ×

 $10^7 \, {\rm s}^{-1}$) with experimentally known rates of H abstraction⁸ (e.g., 1.85 \times 10⁶ and 2.55 \times 10⁵ $M^{-1} \, {\rm s}^{-1}$ for the reaction of tertiary alkyl radicals with Bu₃SnH and (Me₃Si)₃SiH, respectively, at 25 °C⁹) supports the assumption³ that α -chlorocyclopropyl radicals interconvert faster than they abstract a hydrogen.¹⁰

Calculations at 6-31G* show that the radicals R-1 to R-4 prefer the conformation in which the α -Cl is directed anti to the larger substituent on the cyclopropyl ring; e.g., R-3-trans and R-4-trans are calculated to be by 1.0 and 1.3 kcal/mol, respectively, more stable than the isomeric R-3-cis and R-4cis, and thus their equilibrium constants, Keq, at 80 °C are 4.2 and 6.4, respectively (Table 2). As the observed product ratios [3a]/[3b] (0.38 with Bu₃SnH and 0.14 with (Me₃Si)₃SiH (Table 1)) are different from the [R-3-trans]/[R-3-cis] value of 4.2, it is clear that eq 2 is not obeyed, in contrast to previous suggestions.³ The discrepancy between the experimentally observed product ratios and those expected from the calculated equilibrium constants of the radicals leads to the conclusion that the rates of trapping of the isomeric radicals are different, i.e., $k'_2 \neq k_2$ (Scheme 1). Combination of the calculated K_{eq} values of the isomeric radicals (Table 2) with the experimentally determined product ratios (Table 1) allows estimation of the k'_2/k_2 ratios (Table 1). As expected from molecular models, the estimated k'_2/k_2 ratios show that there is a stronger preference for (Me₃Si)₃SiH than for Bu₃SnH to transfer an H atom from the less hindered side of the ring. For example, for 3, k'_2/k_2 is $2.6 \times 4.2 = 10.9$ for Bu₃SnH, but it is $7.1 \times 4.2 = 29.8$ for (Me₃Si)₃SiH.

A similar analysis clarifies why the reduction of 4 by Bu₃-SnH produces mainly 4a, apparently suggesting that H is introduced preferably from the more hindered side of the cyclopropyl ring. In this case the estimated k'_2/k_2 is 3.4, indicating that Bu₃SnH indeed prefers to transfer its H atom from the sterically least hindered side; the observed [4a]/[4b] ratio of 1.9 results from the significantly higher stability of **R**-4trans relative to **R**-4-cis ($K_{eq} = 6.4$). With (Me₃Si)₃SiH, the larger k'_2/k_2 of 8.3 overwhelms the radical equilibrium of 6.4 and 4b is the major product despite the fact that **R**-4-trans dominates the radical equilibrium.¹¹ Similarly, the preferred reduction of 6 from the more hindered axial direction (less so for (Me₃Si)₃SiH) results from the fact that K_{eq} for the radical (8.5) is larger than the k'_2/k_2 of 1.6 (8.5/5.2) for Bu₃SnH and of 6.1 (8.5/1.4) for (Me₃Si)₃SiH.

In summary, we have shown that in properly designed systems $(Me_3Si)_3SiH$ and Bu_3SnH lead to a different and even reversed reduction stereoselectivity. These findings may prove to be of special importance in the reduction of prochiral centers. We have also shown unequivocally that in general product ratios cannot be equated with the stereochemical preferences of the intermediate radicals.

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(11) A fast H transfer before radical equilibrium is reached can be excluded because $(Me_3Si)_3SiH$ transfers H ca. 10 times slower than Bu_3-SnH .^{8a}

^{(8) (}a) Chatgilialoglu, C.; Dickhaut, J.; Giese, B. J. Org. Chem. 1991, 56, 6399. (b) Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywick-reyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. J. Am. Chem. Soc. 1985, 107, 4594.

⁽⁹⁾ The concentrations of the reducing agents were ca. 1 M so that the first- and second-order rate constants can be compared directly.

⁽¹⁰⁾ Experimental rates of H abstraction from Bu₃SnH or (Me₃Si)₃SiH by α-chlorocyclopropyl radicals are not available. However, supporting this conclusion is the fact that reduction with Ph₃SnH of either endo- or exo-7-bromo-7-chlorobicyclo[4.1.0]heptane yields an identical product mixture (Altman, L. J.; Baldwin, R. C. Tetrahedron Lett. 1971, 2531). As Ph₃SnH transfers H to radicals ca. 17 times faster than Bu₃SnH (Carlsson, D. J.; Ingold, K. U. J. Am. Chem. Soc. 1968, 90, 1055) and ca. 170 times faster than (Me₃Si)₃SiH,^{8a} it is expected that α-chlorocyclopropyl radicals isomerize faster than they abstract H from Bu₃SnH or (Me₃Si)₃SiH.