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

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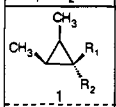
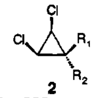
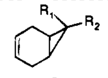
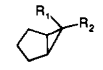
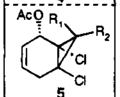
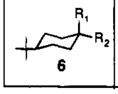
The most useful reagent for the reduction of alkyl halides is probably Bu_3SnH,[1] but due to its high toxicity its use for pharmaceutical applications is generally unacceptable. It was recently discovered that $(Me_3Si)_3SiH$ reduces organic halides in high yields, and due to its low toxicity it is an attractive alternative to Bu_3SnH.[2] The two reagents have different spatial shapes: Bu_3SnH has flexible chain-type substituents while $(Me_3Si)_3SiH$ 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 Bu_3SnH and $(Me_3Si)_3SiH$, 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 Bu_3SnH[3] and $(Me_3Si)_3SiH$[2] 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 equilibrating[3] **R-cis** ⇌ **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 Bu_3SnH or with $(Me_3Si)_3SiH$ leads to different stereoselectivities (Table 1). Thus, the **3b**/**3a** product ratio is 2.6 with Bu_3SnH and 7.1 with $(Me_3Si)_3SiH$. Reduction of **6** with Bu_3SnH leads to a **6a**/**6b** product ratio of 5.2, while with $(Me_3Si)_3SiH$ 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 Bu_3SnH but only 0.22 with $(Me_3Si)_3SiH$ (Table 1). Thus with Bu_3SnH, H formally enters preferentially from the endo side, while with $(Me_3Si)_3SiH$, H is introduced preferably from the exo side, leading predominantly to **4b** and **5b**.

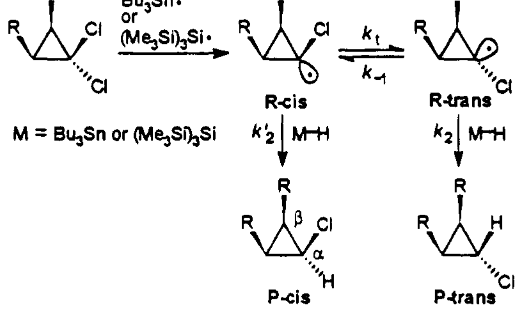
To gain information on the structures of the reduction reaction transition states (TS) we have carried out ab initio calculations[5,6] for the model reaction 1. Reaction 1 is calculated to be exothermic by 21.3 kcal/mol, and the activation enthalpy is 9.4 kcal/mol (MP3/6-31G*//6-31G*).

Table 1. Reduction Products with Bu_3SnH and $(Me_3Si)_3SiH$ of Systems **1**−**6**

starting dichloride $R_1 = R_2 = Cl$	reducing agent	reduction product ratio[a]			k'_2/k_2[b]	
					Bu_3SnH	$(Me_3Si)_3SiH$
 **1**		**1a** $R_1 = H, R_2 = Cl$		**1b** $R_1 = Cl, R_2 = H$	6.0	7.8
	Bu_3SnH	1	:	4.0		
	$(Me_3Si)_3SiH$	1	:	5.2		
 **2**		**2a** $R_1 = H, R_2 = Cl$		**2b** $R_1 = Cl, R_2 = H$	5.8	5.8
	Bu_3SnH	1	:	2.9		
	$(Me_3Si)_3SiH$	1	:	2.9		
 **3**		**3a** $R_1 = H, R_2 = Cl$		**3b** $R_1 = Cl, R_2 = H$	10.9	29.8
	Bu_3SnH	1	:	2.6		
	$(Me_3Si)_3SiH$	1	:	7.1		
 **4**		**4a** $R_1 = H, R_2 = Cl$		**4b** $R_1 = Cl, R_2 = H$	3.4	8.3
	Bu_3SnH	1.9	:	1		
	$(Me_3Si)_3SiH$	1	:	1.3		
 **5**		**5a** $R_1 = H, R_2 = Cl$		**5b** $R_1 = Cl, R_2 = H$	–	–
	Bu_3SnH	1.3	:	1		
	$(Me_3Si)_3SiH$	1	:	4.6		
 **6**		**6a** $R_1 = H, R_2 = Cl$		**6b** $R_1 = Cl, R_2 = H$	1.6[c]	6.1[c]
	Bu_3SnH	5.2	:	1		
	$(Me_3Si)_3SiH$	1.4	:	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 Bu_3SnH and $(Me_3Si)_3SiH$



$$CH_3^{\bullet} + HSi(SiH_3)_3 \longrightarrow [H_3C\cdots H{-}Si(SiH_3)_3]^{\bullet\ddagger} \longrightarrow H_4C + (H_3Si)_3Si^{\bullet} \quad (1)$$

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 CH_4), 1.683 Å (1.484 Å in $(H_3Si)_3SiH$), and 3.202 Å, respectively.

Examination of molecular models (and the results of force-field 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

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[1] For a recent review, see: Neumann, W. P. *Synthesis* **1987**, 665.

[2] (a) Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1987**, *109*, 5267. (b) 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.

[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 d_6-benzene in a vacuum-sealed 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*.

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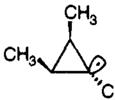
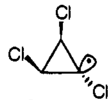
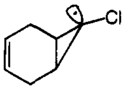
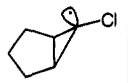
Table 2. Calculated Energy Differences (ΔE), Equilibrium Constants (K_{eq}), Energies of Activation ($\Delta E^{\ddagger}$), and Inversion Rates (k_i) for Various Cyclopropyl Radicals and Chlorocyclohexyl Radical at 6-31G*

radical[a]	ΔE [b] kcal/mol	K_{eq} [c] (80° C)	% [d]	$\Delta E^{\ddagger}$ [e] kcal/mol	k_i [f] s^{-1}
cyclopropyl	0.0	0.0	50	3.9	8.7×10^{9} [g]
α-chloro-cyclopropyl	0.0	0.0	50	7.9	1.1×10^{7}
 **R-1-trans**	0.3	1.5	60	7.6	1.7×10^{7}
 **R-2-trans**	0.5	2.0	67	4.5	3.1×10^{9}
 **R-3-trans**	1.0	4.2	81	7.6	1.7×10^{7}
 **R-4-trans**	1.3	6.4	87	7.7	1.4×10^{7}
	1.5	8.5	90	2.5	9.1×10^{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. [e] Calculated inversion barriers starting from the more stable structure. [f] At 25 °C. Calculated from $\Delta E^{\ddagger}$ and the Eyring equation. [g] The experimental value (ESR) of $10^{11} < k_i \leq 10^{12}$ 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 $(Me_3Si)_3SiH$ than with the more flexible Bu_3SnH. Consequently, $(Me_3Si)_3SiH$ shows a higher selectivity than Bu_3SnH 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 Bu_3SnH 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** $\rightleftharpoons$ **R-trans** equilibrium. Consequently product ratios were used to determine unknown equilibrium constants of isomeric radicals,[3] i.e., eq 2.

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

Our finding that Bu_3SnH and $(Me_3Si)_3SiH$ 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, $\Delta E^{\ddagger}$ and the corresponding inversion rates, k_i, for several radicals (Table 2). Comparison of the calculated k_i values (all $> 1.4 \times 10^{7}$ s^{-1}) with experimentally known rates of H abstraction[8] (e.g., 1.85×10^{6} and 2.55×10^{5} M^{-1} s^{-1} for the reaction of tertiary alkyl radicals with Bu_3SnH and $(Me_3Si)_3SiH$, respectively, at 25 °C[9]) supports the assumption[3] 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-4-cis**, and thus their equilibrium constants, K_{eq}, at 80 °C are 4.2 and 6.4, respectively (Table 2). As the observed product ratios **[3a]**/**[3b]** (0.38 with Bu_3SnH and 0.14 with $(Me_3Si)_3SiH$ (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 $(Me_3Si)_3SiH$ than for Bu_3SnH 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 Bu_3SnH, but it is $7.1 \times 4.2 = 29.8$ for $(Me_3Si)_3SiH$.

A similar analysis clarifies why the reduction of **4** by Bu_3SnH 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 Bu_3SnH 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-4-trans** relative to **R-4-cis** ($K_{eq} = 6.4$). With $(Me_3Si)_3SiH$, 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 $(Me_3Si)_3SiH$) 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 Bu_3SnH and of 6.1 (8.5/1.4) for $(Me_3Si)_3SiH$.

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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(8) (a) Chatgilialoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* **1991**, *56*, 6399. (b) Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, 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 Bu_3SnH or $(Me_3Si)_3SiH$ by α-chlorocyclopropyl radicals are not available. However, supporting this conclusion is the fact that reduction with Ph_3SnH 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 Ph_3SnH transfers H to radicals ca. 17 times faster than Bu_3SnH (Carlsson, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1968**, *90*, 1055) and ca. 170 times faster than $(Me_3Si)_3SiH$,[8a] it is expected that α-chlorocyclopropyl radicals isomerize faster than they abstract H from Bu_3SnH or $(Me_3Si)_3SiH$.

(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_3SnH.[8a]