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γ-Silyl-stabilized tertiary ions? Solvolysis of 4-(trimethylsilyl)-2-chloro-2-methylbutane

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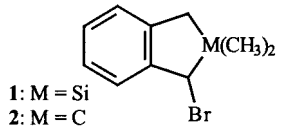
ABSTRACT: Rate constant, isotope-effect, and product studies of the solvolysis of 4-(trimethylsilyl)-2-chloro-2-methylbutane, **11**, and its carbon analog, 2-chloro-2,5,5-trimethylhexane, **10**, in aqueous ethanol and aqueous 2,2,2-trifluoroethanol (TFE) indicate very little participation of the γ-silyl substituent. These results are in sharp contrast to earlier reports on secondary γ-silyl substituted systems, in which the back lobe of the silicon–carbon bond has been shown to overlap with the carbocation p-orbital to form a so-called 'percaudally' stabilized intermediate. While the solvolytic behaviors of **11** and **10** are nearly identical in ethanol, differences in the TFE lead to the conclusion that there is a minor amount of participation by the silyl substituent in that solvent. Interestingly, this observation lends credence to an earlier suggestion that TFE is better than ethanol at stabilizing more highly delocalized ions. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: γ-silyl stabilized tertiary ions; solvolysis; 4-(trimethylsilyl)-2-chloro-2-methylbutane

INTRODUCTION

Silicon is well known to influence reactivity at carbocation centers (for reviews of silyl-substituted carbocations, see Ref. 1). However, the exact nature and magnitude of the silicon effect is highly dependent upon the position of the silicon atom relative to the developing positive charge and the structure and conformation of the reacting substrate.

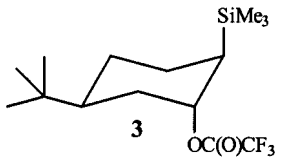
Notwithstanding complications resulting from steric and ground-state effects, results indicate that an α-silyl substituent seems to stabilize carbocations relative to hydrogen, but retards solvolysis rates relative to alkyl substituents. Cartlege and Jones[2] found 2-bromo-2-(trimethylsilyl)propane to solvolyze 38 000 times slower than the carbon analog, 2-bromo-2,3,3-trimethylbutane. Apeloig and co-workers[3,4] found 2-(trimethylsilyl)-2-adamantyl *p*-nitrobenzoate to solvolyze at roughly the same rate as 2-methyl-2-adamantyl *p*-nitrobenzoate, but concluded that the destabilizing influence of the α-silyl effect was masked by a leaving group-dependent electronic geminal interaction which raised the ground-state energy for the silyl-substituted nitrobenzoate. In a study designed to minimize such complexities, Shimizu *et al.*[5] determined solvolytic rates for **1** and its carbon analog **2**, and concluded that the α-silyl substituent was



1: M = Si
2: M = C

roughly 4 kcal mol^{-1} (1 kcal = 4.184 kJ) less effective than an alkyl-substituted system in stabilizing carbocations in solution. The decreased ability of an α-silyl substituent to stabilize positive charge is believed to result from poorer hyperconjugation of Si—C bonds with the carbocation p-orbital.[1,2,6] Although one gas-phase study[7] suggests otherwise, several theoretical calculations have supported this supposition, and suggest that the order of stability for α-substituted carbocations is H < Si < C.[3,8]

In contrast, β-silyl substituents have been shown to stabilize carbocations greatly. Since an early report by Ushakov and Itenberg[9] in 1937, there have been numerous investigations to determine the magnitude and origins of this effect. In a solvolytic study of the conformationally restricted systems **3** and **4**, Lambert *et al.*[10] reported rate accelerations of 2.4×10^{12} and 4.0×10^{4}, respectively, over cyclohexyl trifluoroacetate.



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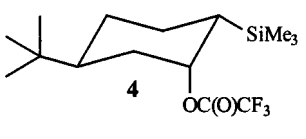

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In addition, it was possible to resolve the influence of the β-silicon into contributions from an inductive effect and a conformationally dependent effect believed to arise either from hyperconjugation or from a true, bridged ion containing a five-coordinate silicon. The conformational effect is, unless forbidden by geometry, believed to provide the majority of the stabilizing influence of the silyl substituent. Although some ambiguity still exists regarding the extent of bridging in the stabilized ion,[8,11] measurement of α-deuterium isotope effects by Fleming,[12] Lambert *et al.*[13] and Shimizu[1a] tend to support hyperconjugation rather than a bridged intermediate.

The ability of a γ-silyl substituent to stabilize carbocations is an interesting phenomenon. In an early paper, unusual reactivity of a γ-silyl system was demonstrated by Sommer *et al.*,[14] who found (3-chloropropyl)trichlorosilane to react with ethanolic KOH within 1 h, whereas *n*-hexyl chloride did not. Indeed, it was later shown that 1,3-elimination of a γ-silyl substituent could be used to synthesize cyclopropanes.[15] Fleming and co-workers[16–19] reported the ability of γ-silyl substituents to control carbocation rearrangements under Lewis acid-catalyzed conditions. During a study of cyclopropane formation from 1,3-deoxystannylation of norbornyl mesylates, Davis and Johnson[20] proposed an alternative mechanism to concerted elimination, which involved a 'percaudally' stabilized intermediate wherein the back lobe of the carbon–tin sigma bond overlapped with the p-orbital of the carbocation to stabilize the positive charge. In an attempt to detect such an intermediate, γ-silyl and γ-stannyl substituted sulfonates were solvolyzed.[21] In aqueous acetic acid, 4-(trimethylsilyl)-2-butyl methanesulfonate was found to solvolyze 7.8 times faster than 2-butyl methanesulfonate, but no methylcyclopropane was found. It was concluded that no γ-silyl stabilized ion existed.

Shiner and Ensinger[22,23] have described a number of γ-silyl-substituted secondary systems whose solvolyses have conclusively been demonstrated to involve percaudally stabilized ions. During the solvolyses of *cis*- and *trans*- 3-(trimethylsilyl)cyclohexyl brosylates (brosylate = 4-bromobenzenesulfonate), the *cis*- (but not the *trans*-) isomer was found to react two orders of magnitude faster than carbon analogs in 97% aqueous 2,2,2-trifluoroethanol (97T). This rate increase, and also the difference in reactivity between the *cis* and *trans* systems, was indicative of a conformationally dependent γ-silicon effect. A β-d_4 isotope effect of nearly unity, the presence of a bicyclohexane 1,3-elimination product and an ethanol–TFE plot[24] markedly different from the other systems provided further evidence of the involvement of percaudally stabilized ion in a 'W' conformation, as shown in Figure 1. Theoretical calculations are also consistent with an orientation-dependent γ-silicon effect.[25]

The γ-silyl effect has also been evidenced in conformationally unrestricted straight-chain systems. 4-

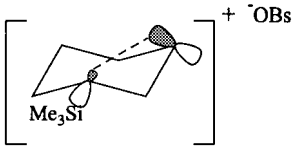
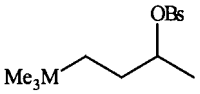


Figure 1. Carbocation stabilized by 'Percaudal' overlap of γ-silyl substituent

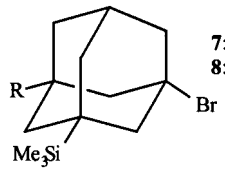
(Trimethylsilyl)-2-butyl brosylate, **5**, was found to react



5: M=Si
6: M=C
OBs = 4-bromobenzenesulfonate (brosylate)

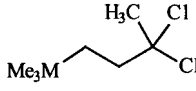
120 times faster in 97T than the carbon analog 5,5-dimethyl-2-hexyl brosylate, **6**.[26] Reduced β-d_3 and α-*d* isotope effects and unusually small or inverse β-d_2 isotope effects were also seen, as well as the formation of significant amounts of methylcyclopropane. Consequently, the proposed mechanism for this reaction also involved silicon-promoted carbon participation. Additionally, since the products were found to be racemic, it was suggested that, unlike the cyclohexyl system wherein participation occurs exclusively through a W conformation, the γ-silyl substituent can stabilize the transition state for the straight-chain system by either a W or an endo-sickle conformation. Several later studies of stereospecifically labeled straight-chain γ-silyl-substituted secondary brosylates lent further support to this conclusion.[27,28]

While there is ample evidence for participation involving a γ-silyl substituent for secondary systems, surprisingly little work has been done on the corresponding tertiary systems. Fleming and co-workers[16–19] reported Lewis acid-catalyzed rearrangements for γ-silyl-substituted tertiary alcohols. Grob and co-workers[29,30] measured solvolysis rates for the substituted adamantyl bromides **7** and **8** in 80% (v/v) aqueous



7: R = H
8: R Me$_3$Si

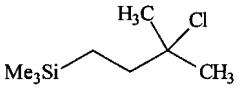
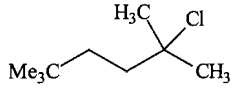
ethanol (80E) and found only modest rate accelerations of 8.6-and 33-fold, respectively. Grob and Waldner[31,32] also studied the ethanolysis of the tertiary stannyl chloride, **9**, and its carbon analog, 2-chloro-2,5,5-



9: M = Sn
10: M = C
11: M = Si

trimethylhexane, **10**. Product studies of **9** indicated the

Table 1. Rate constants for solvolyses of tertiary chlorides at 25 °C

Compound	Solvent			
	97T ($k \times 10^{-5}$ s)	97T (k_{rel})	80E ($k \times 10^{5}$ s)	80E (k_{rel})
 **11**	130.9 (0.2)	2.35	1.185 (0.003)	1.13
 **10**	55.75 (0.02)	1.00	1.050 (≈0)	1.00
 **12**	13.19[a]	0.237	0.9338[b]	0.889

[a] Ref. 34.
[b] Ref. 35.

exclusive formation of dimethylcyclopropane; this compound was seen to react 12–14 times faster in 80E (calculated from rate constants reported at 50 and 60 °C) than the carbon analog. By comparison of Grunwald–Winstein *m* values,[33] it was concluded that this reaction was not concerted, but involved a carbocation intermediate.

Accordingly, we decided to study the solvolysis of 4-(trimethylsilyl)-2-chloro-2-methylbutane, **11**. The study of this system was expected to provide further insight into the nature of the stabilizing influence of a γ-silyl substituent, and to determine its effect, if any upon a tertiary system. Measurements of rate constants, kinetic isotope effects and product studies were made on this system and on the carbon analog, **10**.

RESULTS

The conductometric rate constants for the solvolysis of **11** and several carbon analogs[34,35] in aqueous ethanol and 2,2,2-trifluoroethanol at 25 °C are given in Table 1. In cases where multiple determinations of a rate constant were performed, values in parentheses indicate average deviations. To aid in making comparison, relative rate constants are also indicated.

β-Deuterium kinetic isotope effects for **10** and **11** are given in Table 2. For comparison, the isotope effects for a number of other tertiary chlorides are also included.[35,36]

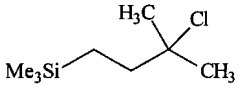
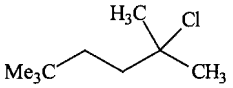
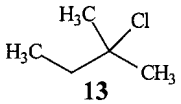
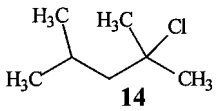
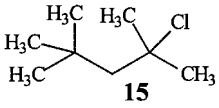
In order to determine reaction products, **11** was allowed to solvolyze for at least 10 half-lives at 25 °C in deuterated 80E (80% ethanol-d_6–20% D_2O by volume) and deuterated 97T (97% 2,2,2-triflurorethanol-d_3–3% D_2O by weight). The identities and relative proportions of the products were determined by ^{1}H NMR and are given in Table 3. In addition to the expected elimination and substitution products, a small amount of the 1,2-elimination product, **20**, was also observed in 97T. This compound results from a hydride shift to form a β-silyl-stabilized carbocation, followed by elimination of the trimethylsilyl group. Such a rearrangement has been previously observed by Fleming and co-workers.[18,19]

DISCUSSION

At first glance, stabilization of the carbocation by percaudal participation of the γ-silyl substituent appears to be absent. The results appear to confirm expectations that a tertiary carbocation intermediate exhibits a smaller electron demand on a silyl substituent. For example, Li and Stone[37] have previously demonstrated in the gas phase that the magnitude of the β-silyl effect decreases by 10 kcal mol^{-1} with each replacement of a β-hydrogen by a methyl group. Consequently, it seems likely that the γ-effect would also be much reduced for the tertiary as opposed to the secondary system.

In contrast to the secondary γ-silyl brosylate, **5**, which reacted 129 times faster[26] than the carbon analog, **6**, in 97T and 2.7 times faster in 80E, the tertiary chloride **11** solvolyzed only 2.35 times as fast as its carbon analog in 97T; the rate constants are essentially identical in 80E. It is interesting that, of the two solvents, the only acceleration detected for the silyl compound is seen in

Table 2. Isotope effects for solvolyses of tertiary chlorides at 25 °C[a]

Compound	Parameter	Solvent	
		97T	80E
 **11**	$\beta\ d_6\ (k_H/k_{2-\text{methyl}-d_{3-1,1,1-d3}})^{1/2}$	1.610	1.727
	$\beta\ d_3\ (k_H/k_{2-\text{methyl}-d_{3-1,1,1-d3}})$	1.269	1.314
	$\beta\ d_2\ (k_H/k_{3,3-d_2})$	1.159	1.320
 **10**	$\beta\ d_6\ (k_H/k_{2-\text{methyl}-d_{3-1,1,1-d3}})^{1/2}$	1.761	1.741
	$\beta\ d3\ (k_H/k_{2-\text{methyl}-d_{3-1,1,1-d3}})$	1.327	1.320
	$\beta\ d_2\ (k_H/k_{3,3-d_2})$	1.452[b]	1.409[b]
 **12**	$\beta\ d_3\ (k_H/k_{\beta\ -d_9})^{1/3}$	1.378[c]	1.349[c]
 **13**	$\beta\ d_3\ (k_H/k_{1,1,1-d_3})$	—	1.34[d]
	$\beta\ d_2\ (k_H/k_{3,3-d_2})$	—	1.40[d]
 **14**	$\beta\ d_3\ (k_H/k_{1,1,1-d_3})$	—	1.34[d]
	$\beta\ d_2\ (k_H/k_{3,3-d_2})$	—	1.47[d]
 **15**	$\beta\ d_3\ (k_H/k_{1,1,1-d_3})$	—	1.40[d]
	$\beta\ d_2\ (k_H/k_{3,3-d_2})$	—	1.08[d]

[a] Except where noted, the isotopically labeled compounds used were at least 97% deuterated.
[b] Compound was approximately 90% deuterated.
[c] Ref. 35.
[d] Ref. 36.

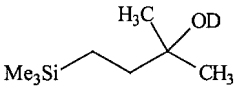
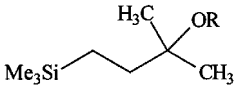
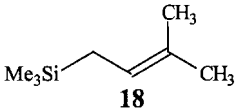
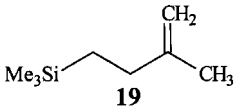
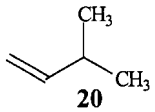
97T. This observation is in accord with data for secondary systems which also show (but to a much greater extent) larger rate enhancements in TFE than in ethanol.[22,23,26,28] Thus, while rate studies seem to indicate greatly diminished participation of the γ-silyl substituent, the possibility of some stabilization in 97T still exists.

Indeed, the $\beta-d_2$ and $\beta-d_3$ isotope effects for **11** in 97T, which are significantly smaller than those seen for **10**, lend further support to the possibility of the existence of a percaudally stabilized ion in that solvent. The W or endo-sickle conformation required for percaudal participation of a γ-silyl substituent has been shown to lead to greatly reduced or even inverse $\beta-d_2$ isotope effects in secondary straight-chain and cyclohexyl systems.[22,23,26,28] In such instances, the dihedral angle between the C—D bonds and the developing p-orbital of the reacting carbon center is such as to allow for very little hyperconjugation (for a discussion of the conformational dependence of the β-deuterium isotope effect, see Refs[36,38]), and often only the inductive effect (which leads to inverse isotope effects) is observed. Since a stabilized intermediate in the solvolysis of **11** would be expected to proceed through a similar conformation (Fig. 1), the β -d_2 isotope effect for this system would also be expected to be small. Indeed, in 97T, the β -d_2 effect for **11** of 1.159, although not as small as for the secondary systems, is considerably smaller than that of 1.452 for **10**.

It might be argued that the reduced β-deuterium isotope effect is the result of a particular conformer being sterically favored. This has been observed for 2-chloro-2,4,4-trimethylpentane, **15** (β -d_2 isotope effect 1.08).[36] However, conformational restriction due to steric repulsion between adjacent alkyl groups would not be expected to be as important for **11**. Indeed, the carbon analog **10**, which would in fact be expected to be more congested, exhibits a typical β -d_2 isotope effect of 1.452. Furthermore, the β -d_3 isotope effect for **11** in 97T (in which the β-methyl group is freely rotating and unaffected by conformational restrictions) is also seen to be reduced relative to the β -d_3 effect for **10**. The fact that the isotope effects are reduced to a greater extent in 97T than 80E also rules out the steric explanation.

The isotope effects also appear to reflect differing

Table 3. Solvolysis products of 4-(trimethylsilyl)-2-chloro-2-methylbutane

Product[a]	Solvent	
	Deuterated 97T	Deuterated 80E
 **16a**	14.6	39.6
 **17a** R = OCD_2CF_3 **17b** R = OCD_2CD_3	50.1	26.0
Total substitution products	64.7	65.6
 **18**	21.0	20.7
 **19**	12.7	13.6
 **20**	1.7	0
Total elimination products	35.4	34.3

[a] Expressed as mol% of total mixture.

amounts of competing rate-determining elimination, depending upon the extent of participation of the silicon. An examination of the products from the solvolysis of **11** supports this observation. The relative amounts of elimination in 97T and in 80E are remarkably similar. This is in sharp contrast with results obtained for *tert*-butyl chloride,[34,36] which shows considerably larger amounts of elimination and also a larger β -d_3 isotope effect in TFE as compared with ethanol. The results for the *tert*-butyl system have been attributed to partial rate-determining elimination from the tight ion-pair in TFE, with the larger β-deuterium isotope effect arising from the contribution of a primary isotope effect.[36] Indeed, results similar to those obtained for *tert*-butyl chloride are seen for **10**, whose β -d_3 isotope effect remains essentially identical in the two solvents, but whose β-d_2 isotope effect is larger in 97T.

In spite of the evidence of participation provided by the similarity in the amounts of elimination products in both solvents, the absence of significant amounts of 1,1-dimethylcyclopropane seems to preclude the possibility of an intermediate carbocation stabilized by strong silicon-promoted carbon participation. For secondary γ-silyl-substituted systems, significant amounts of cyclic 1,3-elimination products derived from loss of the trimethylsilyl group have been observed.[22,23,26–28] Strong percaudal participation in the solvolysis of **11** should therefore be accompanied by the formation of 1,1-dimethylcyclopropane. It is therefore possible that, while the degree of positive charge delocalization at silicon is insufficient to favor attack of a solvent molecule at silicon to cause 1,3-elimination, the conformation required by participation apparently tends to disfavor rate-determining β -CH_2 elimination in 97T.

Using the results of this study and by drawing an analogy with solvolytic studies of *tert*-butyl chloride,[34,36,39] we have postulated a reasonable mechanistic picture for the solvolyses of **10** and **11**, as shown in Fig. 2. The rate-determining step for all of the systems is probably the formation of the solvent-separated ion pair. However, whereas competing rate-determining elimination appears to be occurring for **10** in 97T, this does not seem to be the case for **11**, whose β -d_2 isotope effect is much smaller in that solvent. Indeed, the ion formed during the solvolysis of **11** may gain some additional stability from participation (albeit slight) of the γ-silyl substituent. In 80E, although a very small extent of participation may be indicated by the slightly smaller β -d_2 isotope effect of **11** (1.32 versus 1.40), both compounds probably react by similar mechanisms. In neither system is evidence of competing rate-determining elimination conclusive.

CONCLUSION

The results of this study indicate a much smaller extent of percaudal participation by a γ-silyl substituent during the solvolysis of a tertiary substrate than for a secondary substrate. Considering the inherent stability of tertiary carbocations, it is not surprising that there is a reduced demand on the ability of the silyl substituent to delocalize the positive charge.

An interesting comparison can be made between our results and Grob and co-workers' earlier study[29,30] involving ethanolysis of the γ-silyl substituted adamantyl system **7**. The rate acceleration of 8.6-fold found in 80E is larger than our value of 1.13-fold (essentially none). This observation is in good agreement with the expectation that percaudal participation of the silyl substituent would be much less for the open-chain system than the adamantyl system in which silyl substituent is held in the conformation required for maximum participation.

Additionally, while we did not observe appreciable rate acceleration for the open-chain silyl system **11** in 80E, Waldner and Grob[31] reported a rate acceleration of 12–14-fold for the corresponding stannyl analog **9**, and also the formation of 1,1-dimethylcyclopropane. These results concur with the expectation that percaudal participation is more important for a γ-stannyl as opposed to a γ-silyl system, because of the greater electron-

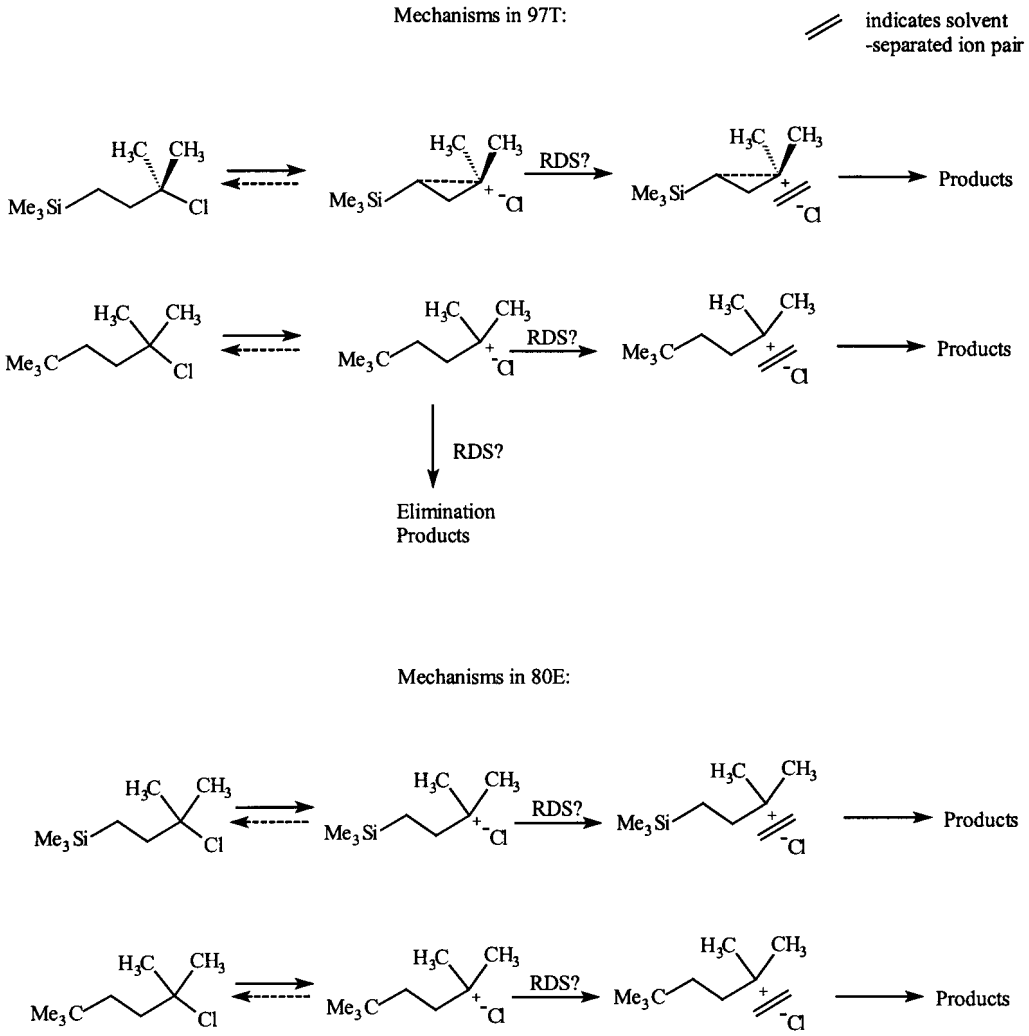


Figure 2. Proposed mechanisms for solvolysis of 4-trimethylsilyl-2-chloro-2-methylbutane and 2,5,5-trimethyl-2-chloropentane

donating ability of tin. While deuterium kinetic isotope effects for **9** have not been measured, it is likely that they would provide evidence for a mechanism involving percaudal participation in the open-chain stannyl system. Moreover, if measured, the rate acceleration in 97T might be expected to be much greater than that in 80E.

In ethanolic solvents, the apparent near total lack of participation of the γ-silyl substituent during the solvolysis of **11** implies that the percaudally stabilized ion is not appreciably more stable than the open tertiary ion. However, in TFE, there is some bias toward a percaudally delocalized ion. Interestingly, this observation is in good accord with an earlier suggestion of Stoelting and Shiner[40] that TFE is relatively more effective than ethanol at stabilizing larger, more delocalized carbocations. Indeed, in view of this evidence, it appears that the γ-silyl effect is greatly reduced for tertiary systems, but can manifest itself to some extent under the appropriate circumstances.

EXPERIMENTAL

General

NMR spectra were recorded on a 300 MHz Varian XL-300, a 500 MHz Bruker AM-500 or a 500 MHz Varian ^{Unity}INOVA 500 spectrometer. IR spectra were taken on a Mattson Instruments 4020 Galaxy Series Fourier transform IR spectrometer. Analytical gas chromatography (GC) was carried out using a Hewlett-Packard Model 5890 gas chromatograph, equipped with a 50 m × 0.2 mm i.d. (0.33 μm film thickness) HP-5 column and a flame ionization detector. Preparative GC was performed using a Varian Aerograph Series 2700 gas chromatograph, equipped with a 6 ft × 1/4 in column of 20% OV101 on Chromosorb P (60–80 mesh) and a thermal conductivity detector. Mass spectra were recorded on a Kratos MS80 RFAQQ instrument. GC–mass spectra were obtained on a Hewlett-Packard GC/MSD 5971 instrument, equipped

with a 60 m × 0.25 mm i.d. SPB-5 column. Melting-points and boiling-points are uncorrected. Boiling-points for molecular distillations were not directly determined since the still did not have provisions for a thermometer.

Materials

Nitrogen. In order to ensure removal of carbon dioxide and water, all nitrogen used for transferring and distilling conductivity solvents was purified by passage through a 3 ft glass column packed with 4 Å molecular sieves.

Conductivity solvents. Conductivity water and conductivity ethanol were prepared as described by Murr[41] and Tilley.[42] Conductivity 2,2,2-trifluoroethanol was prepared as described by Shiner *et al.*[34] and Tilley.[42]

Kinetics

All rate constants for this work were determined conductometrically at 25 °C using a bipolar pulsed conductance (BIPCON) instrument, based on the design of Caserta *et al.*[43] with the modifications of Ensinger[44] and Tilley.[42] The constant-temperature oil-bath employed for kinetic measurements was designed by Murr,[41] with computer-regulated temperature control later added using modifications of Ensman,[45] Withnell,[46] Wilgis[47] and Tilley.[42] The conductance cells used were made in this laboratory, based on the design of Murr,[41] using modifications by Rapp,[48] Tomasik,[49] Wilgis[47] and Tilley.[42] Data calibration and acquisition were performed on a JCC Systems computer containing an Intel 33 MHz 386 processor with a 387 math co-processor chip, using software described by Tilley,[42] which is based on earlier programs of Ensinger,[44] Wilgis,[47] Tomasik,[49] Sporleder[50] and Stoelting.[51] Calibration was done with the aid of a Dial-An-Ohm resistor box (General Resistance, North Branford, CT, USA). After acquisition, the raw data were then converted into resistance–time data using a program written by Tilley[42] and analyzed using a non-linear, doubly weighted least-squares program originally written by Murr,[41] with modifications by Buddenbaum,[52] Vogel,[53] Pinnick,[54] Bowersox,[55] Tomasik,[49] Wilgis,[47] Stoelting,[56] Ensinger[57] and Tilley.[42]

NMR product studies of 4-(trimethylsilyl)-2-chloro-2-methylbutane, 11

Product study in deuterated 97T. In an NMR tube with a Pyrex extension was placed 2,2,2-trifluoroethanol-d_3 (Cambridge Isotope Laboratories), 706.5 µl, 970 mg, and D_2O, 30 µl. To this was added 4-(trimethylsilyl)-2-chloro-2-methylbutane, **11**, 10 µl, 0.049 mmol [density 0.869 g ml^{-1} (Ref. 58)], and 2,6-lutidine, 6.5 µl, 0.056 mmol. The tube was sealed and the mixture was allowed to react at 25 °C for at least 10 half-lives. Relative amounts of the products were determined from integrated peak areas of the 500 MHz ^{1}H NMR spectrum; the error using this technique is estimated to be 2–3%. Peaks unique to each product are as follows: **16a**, 1.475 ppm (m, CH_2, 3-carbon, β- to Si); **17a**, 1.502 (m, CH_2, 3-carbon, β- to Si); **18**, 1.393 (d, CH_2, 4-carbon, α- to Si, J = 8.5 Hz), 1.56 (s with fine splitting, allylic CH_3), 1.68 (s with fine splitting, allylic CH_3), 5.213 (triplet of septets, vinyl H, J = 8.5 Hz, 1.4 Hz); **19**, 0.656 (m, CH_2, 4-carbon, α- to Si), 1.72 (s, allylic CH_3), 2.027 (m, CH_2, 3-carbon, β- to Si), 4.66 (m, vinyl H), 4.72 (m, vinyl H); **20**, 0.976 (d, 2CH_3's), 2.25 (m, CH), 4.85 (overlapped d of d, *E*-terminal vinyl H, J_{cis} = 10.4 Hz), 4.96 (overlapped d of d of d; looks like d of t, *Z*-terminal vinyl H, J_{trans} = 17.3 Hz, J_{gem} = 1.7 Hz, J_{allylic} = 1.7 Hz), 5.83 (overlapped d of d of d, internal vinyl H). (Alcohol **16a** and ether **17a** were distinguished by spiking the reaction mixture with known **16**. The multiplets used to determine the **16a**/**17a** ratio were of similar shape but partially overlapped. An estimate of the relative amounts of **16a** and **17a** was obtained by measuring and comparing the relative heights of the outermost peak of each multiplet.)

Product study in deuterated 80E. The above procedure was repeated by adding 10 µl, 0.049 mmol of **11** and 6.5 µl, 0.056 mmol of 2,6-lutidine to a tube containing ethanol-d_6 (Cambridge Isotope Laboratories), 800 µl, and D_2O, 200 µl. Peaks unique to each product are as follows: **16a**, 0.496 ppm (m, CH_2, 4-carbon, α- to Si), 1.136 (s, geminal CH_3s); **17b**, 0.450 (m, CH_2, 4-carbon, α- to Si); **18**, 1.342 (d, CH_2, 4-carbon, α- to Si, J = 8.5 Hz), 1.5 (s with fine splitting, allylic CH_3), 1.646 (s with fine splitting, allylic CH_3), 5.103 (triplet of septets, vinyl H); **19**, 0.6113 (m, CH_2, 4-carbon, α- to Si), 1.679 (s with fine splitting, allylic CH_3), 1.962 (m, CH_2, 2-carbon, β- to Si), 4.615 (m, vinyl H), 4.648 (m, vinyl H).

Synthetic Procedures

Synthesis of γ-silyl-substituted chlorides. *(Trimethylsilyl)methyl iodide,* ***21****.* This was synthesized as described by Whitmore and Sommer.[59] Under nitrogen, approximately 1500 ml of acetone were purified by refluxing for 6 h over CaO and $KMnO_4$, followed by fractionation through a 40 cm Vigreaux column (b.p. 56 °C; lit.[60] b.p. 56.2 °C).

To sodium iodide, 215.1 g, 1.435 mol, dissolved in approximately 1200 ml of acetone, was added (trimethylsilyl)methyl chloride, 101.3 g, 0.8258 mol, all at once, using an additional 200 ml of acetone for rinsing. The mixture was stirred under nitrogen at reflux for 24 h. Almost immediately, a white precipitate of NaCl formed that thickened over time, eventually hindering agitation.

The cooled solution was filtered through a medium-

porosity, 600 ml fritted funnel, rinsing with 200 ml of wash acetone. Acetone was then removed by fractionation through a 40 cm Vigreaux column. After cooling, pentane (50 ml) and water (250 ml) were poured down the Vigreaux column into the pot. The mixture was transferred into a separating funnel, using 150 ml of water and 250 ml of pentane, shaken and separated. The aqueous layer was extracted with pentane (6×50 mL).

The combined organic layers were washed with 10% aqueous sodium thiosulfate (3×100 ml) to remove free iodine, and then with water (2×100 ml). The pentane solution was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation in a room-temperature bath.

The residue was then distilled (10 cm Vigreaux column, b.p. 137–140 °C; lit.[59] b.p. 139.5 °C) to give 137.8 g of **21** (78%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.147 (s), 2.00 (s); ^{13}C NMR ($CDCl_3$, 75 MHz), δ −12.06, 1.59.

Ethyl 3-(trimethylsilyl)propionate, ***22***. Compound **22** was synthesized using a procedure by Sommer and Marans.[58] Under nitrogen, sodium metal, 6.51 g, 0.2831 mol, was dissolved in 100 ml of commercial anhydrous ethanol, completion requiring applied heat (reflux).

Next, purified ethyl acetoacetate,[60] 33.5 g, 0.2574 mol, was added at reflux during 15 min. Then **21**, 50.0 g, 0.234 mol, was added over 15 min.

After 36 h at moderately fast reflux, the cooled mixture was stirred with 6.76 g, 0.049 mol, of sodium hydrogensulfate monohydrate, for 10 min (insolubles, pH basic), heated (clarified) and gently refluxed for 30–40 min (brownish precipitate cloudiness, pH 5–6). The mixture was cooled, transferred and agitated with 500 ml of diethyl ether and ultimately filtered on a fine-porosity frit to remove precipitated salts (NaI, $NaHSO_4$, Na_2SO_4). Most of the ether was removed by distillation. The concentrate was transferred to a 250 ml round-bottomed flask. The remaining ethanol and ethyl acetate were mainly removed by distillation through a 40 cm Vigreaux column, whereupon NaI precipitation occurred. The cooled residue was transferred with 400 ml of pentane, causing further precipitation of NaI. The filtrate was washed with water (3×100 ml), dried ($CaSO_4$) and filtered through a pentane-slurried 4 cm bed of alumina gel (Fisher, basic, Brockman I) in a medium-porosity, 350 ml fritted funnel, rinsing the bed with 200 ml additional pentane. Pentane was mainly removed by distillation through a 40 cm Vigreaux column, the last traces by blowing with a gentle nitrogen stream, giving 20.39 g of **22** (50%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ −0.035 (s, 9H), 0.799 (m, 2H), 1.21 (t, 3H), 2.23 (m, 2H), 4.08 (q, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ −2.05, 11.60, 14.16, 28.85, 60.18, 175.01.

Methyl 2-(trimethylsilylmethyl)acetoacetate, ***23***[19, 61, 62]. This was prepared by a procedure based on those of Sommer and Marans[58] and Fleming and Godhill.[62] DMF was purified by stirring over KOH pellets for 15 min, followed by distillation from CaO. Methyl acetoacetate was purified by distillation at reduced pressure (b.p. 69 °C at 13 mmHg). To a suspension of 0.80 g, 0.10 mol, of LiH in 100 ml of DMF were added dropwise, with stirring, 11.6 g, 0.10 mol of methyl acetoacetate during 10 min. Hydrogen evolved slowly, requiring stirring for an additional 3 h. ^{1}H NMR of an aliquot (500 MHz, neat) showed quantitative formation of the lithium enolate. Next, **21**, 21.4 g, 0.10 mol, was added dropwise over 10 min. The mixture was stirred for 20 h at room temperature, 48 h at 60 °C and 24 h at 100 °C to ensure total reaction.

The cooled reaction mixture was poured into 1 l of water, with additional rinses of 200 and 300 ml. The combined pentane extracts (5×200 ml) were washed with water (3×500 ml), dried ($MgSO_4$) and solvent was removed by rotary evaporation. A distillation fraction (113–122 °C at 20 mmHg) was found by NMR ($CDCl_3$, 500 MHz) to contain mostly the desired product. This, when re-distilled (10 cm Vigreaux column; lit.[61] b.p. 60 °C at 2.0 mmHg) was sufficiently pure by NMR for use in the next reaction. A total of 8.76 g of **23** were synthesized (43%). NMR indicated both a keto and an enol form. ^{1}H NMR ($CDCl_3$, 500MHz, keto form), δ −0.009 (s, 9H), 1.028 (m, 1H), 1.150 (m, 1H), 2.207 (s, 3H), 3.425 (m, 1H), 3.714 (s, 3H); ^{1}H NMR ($CDCl_3$, 500MHz, enol form), δ −0.033 (s, 9H), 1.530 (s, 2H), 1.942 (s, 3H), 3.715 (s, presumably 3H; very close to larger peak of keto form), 12.5 (s); ^{13}C NMR ($CDCl_3$, 125 MHz, keto form), δ 1.420, 15.21, 27.58, 52.05, 55.30, 171.17, 202.28; ^{13}C NMR ($CDCl_3$, 125 MHz, enol form), δ −1.13, 14.52, 19.11, 51.14, 97.10, 169.64, 173.60; IR (neat), 1744.9 cm^{-1} (s, C=O str for ester C=O of keto form), 1719.3 cm^{-1} (s, C=O str for ketone C=O of keto form), 1648 (m, C=O str for conjugated C=O of enol form), 1613.7 (m, C=C str of enol form); MS (CI, NH_3), *m/z* 203.1 ($M+1$, 1.3%), 202.1 (M^+, 2.1%), 187 (43.4%), 170 (6.0%), 160 (12.8%), 159 (24.5%), 155 (27.3%), 143 (24.2%), 127 (18.9%), 113 (27.6%), 89 (58.7%), 75 (20.5%), 73 (100.0%), 59 (17.8%), 55 (66.3%), 45 (12.8%), 43 (29.3%).

Methanol-d, ***24***[63,64]. Methanol-*d* was synthesized according to the procedure described by Streitwieser et al.[64] Dimethyl sulfate was purified by distillation at reduced pressure (b.p. 81–83 °C at 15 mmHg). Dimethyl carbonate, treated with 4 Å molecular sieves for 4 days, was fractionally distilled through a 50 cm vacuum-jacketed glass column packed with glass helices (b.p. 91 °C;C).

To dimethyl carbonate, 414 g, 4.60 mol, and D_2O, 102.6 g, 5.12 mol, in a 1 l one-necked round-bottomed flask, dimethyl sulfate, 16 g, 0.13 mol, was added; a stir bar was inserted and a 60 cm reflux column affixed, protected by Drierite (Hammond). After a 120 h reflux, ^{1}H NMR (neat, 500 MHz) showed only 0.3 mol% of dimethyl carbonate remaining. After cooling, the reflux column was replaced by a 50 cm vacuum-jacketed

column packed with glass helices. Methanol-*d* was collected at a reflux ratio of 10:1 (b.p. 60.5 °C at 742.6 mmHg). ^{1}H NMR indicated approximately 99% deuteration. A 234.7 g amount of **24** was obtained (77%): ^{1}H NMR (500MHz, neat), δ 3.35 (relative to added tetramethylsilane).

Methyl 3-(trimethylsilyl)propionate-2,2-d$_2$, ***25***[19,65]. Compound **25** was prepared by reverse Claisen condensation of **23** in methanol-*d*, analogous to Sommer and Marans' preparation of **22**.[58] To 60 ml of anhydrous diethyl ether were added 2.2 g of a 60% dispersion of NaH in mineral oil, 0.055 mol NaH. An additional 15 ml of diethyl ether were used to facilitate transfer of the NaH into the flask. To the suspension of NaH in diethyl ether was added **23**, 8.54 g, 0.042 mol, over a period of 15 min, such that hydrogen evolution was not too rapid.

Methanol-*d*, 5 ml, was then added over 5 min, such that HD evolution was not too rapid, forming a thick, unstirrable paste. Additional methanol-*d*, 55 ml, added all at once with stirring, led to dissolution to give a slightly cloudy, pale yellow solution. This mixture was heated, distilled through a Vigreaux column to a b.p. of 61 °C;C and refluxed (condenser replacing column) under nitrogen for another 45 h.

The cooled mixture was neutralized to pH 6–7 with 2.4 ml of glacial acetic acid-*d* (Aldrich) and poured into 250 ml of water, with an additional 50 ml of water for rinsing. This solution was extracted with pentane (4×50 ml). The combined organic layers were washed with water (2×60 ml) and dried ($CaSO_4$). Pentane was mainly distilled through a 10 cm Vigreaux column. The residue was then distilled to give 4.53 g of colorless liquid. A ^{1}H NMR spectrum showed the desired compound, but integration of residual protons at the 2-position showed only approximately 92% deuteration, necessitating further exchange.

The incompletely deuterated **25**, 4.52 g, 0.028 mol, was added to a solution of metallic sodium, 0.19 g, 0.0083 mol, pre-reacted in 30 ml of methanol-*d*. After a 48 h reflux, this was cooled, neutralized with 0.6 ml of glacial acetic acid-*d*, and treated with 150 ml of water. This was extracted with pentane (4×50 ml); the combined organic layers were washed with water (2×50 ml) and dried ($MgSO_4$). Solvent was distilled (10 cm Vigreaux column). The residue was then distilled on a molecular still (58 mmHg, bath 90–100 °C; lit.[19] b.p. undeuterated 68 °C at 18 mmHg.) The ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) now indicated 97% deuteration. GC indicated 93% purity, adequate for the next step. A total of 3.48 g of **25** was obtained (51%): ^{1}H NMR ($CDCl_3$, 500MHz), δ −0.017 (s, 9H), 0.810 (s, 2H), 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ −2.16, 11.27, 28.07 (multiplet), 51.35, 175.41; IR (neat), 3466 cm^{-1} (m, overtone of C=O str), 2965 (s), 2896 (s), 2222 (m, C–D str), 2130 (m, C–D str), 1739 (s, C=O str), 1435 (s), 1280 (vs), 1204 (vs), 1107 (s), 842 (vs).

4-(Trimethylsilyl)-2-methyl-2-butanol, ***16***[58]. Under nitrogen, to 30 ml, 0.09 mol, of 3 M methylmagnesium bromide in diethyl ether (Aldrich) was added, with stirring, at a rate to maintain moderate reflux, a solution of **22**, 5.0 g, 0.0287 mol, pre-dissolved in 30 ml of anhydrous diethyl ether from a freshly opened can. After addition the mixture was stirred overnight at reflux. At room temperature after gradual addition of 20 ml of water with agitation, the flask contents were transferred to 150 ml of water in a separating funnel, with the aid of 200 ml more water. While maintaining pH 6–7 by added glacial acetic acid, the aqueous layer was extracted with diethyl ether (1×100, 2×75 ml). The combined ether layers were washed with saturated sodium hydrogencarbonate (2×50 ml) and water (2×50 ml) and dried ($CaCl_2$). Diethyl ether was removed by rotary evaporation (35 °C bath). Molecular distillation at 4 mmHg (bath 50 °C) (lit.[58] b.p. 48 °C at 4 mmHg) gave 3.17 g of **16** (69% yield): ^{1}H NMR ($CDCl_3$, 500 MHz), δ −0.018 (s, 9H), 0.485 (m, 2H), 1.18 (s, 6H), 1.38 (s, OH, variable shift), 1.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ −1.92, 10.48, 28.54, 37.79, 71.56.

4-(Trimethylsilyl)-2-methyl-d$_3$-2-butanol-1,1,1-d$_3$, ***16b***. Into 85 ml of 1 M methylmagnesium-d_3 iodide in diethyl ether (Aldrich), 0.85 mol, stirred under nitrogen were added 5.00 g, 0.287 mol of **22** at a gradual rate such as to maintain moderate reflux. After an additional 90 min of stirred reflux, the cooled solution was treated gradually with 30 ml of saturated NH_4Cl. The ether layer was decanted and three additional extractions were performed (1×100, 2×25 ml). The combined organic layers were washed with 5% aqueous NH_4Cl (3×50 ml) and water (2×50 ml) and dried over Na_2SO_4. Most of the diethyl ether was removed by distillation through a 10 cm Vigreaux column (warm water-bath) and the remainder by rotary evaporation (room temperature bath). The residue was purified by molecular distillation (8 mmHg). Integration of residual methyl protons in the ^{1}H NMR spectrum showed deuterium incorporation in the desired positions to be at least 99%. A total of 3.51 g of **16b** were obtained (74%): ^{1}H NMR ($CDCl_3$, 500 MHz), δ −0.045 (s, 9H), 0.457 (m, 2H), 1.38 (m, 2H), 1.61 (broad singlet, variable, OH); ^{13}C NMR ($CDCl_3$, 125 MHz), δ −1.95, 10.40, 27.50 (septet), 37.64, 71.20.

4-(Trimethylsilyl)-2-methyl-2-butanol-3,3-d$_2$, ***16c***. This was synthesized from **25** using the same procedure as for **16b** except that 3 M methylmagnesium bromide was used instead of 1 M methylmagnesium-d_3 iodide. In this work-up, after removing most of the diethyl ether through a 10 cm Vigreaux column, the residue was directly distilled on a molecular still (4 mmHg, bath 70–85 °C), affording 2.31 g of **16c**. ^{1}H NMR ($CDCl_3$, 500 MHz) indicated impure alcohol; GC showed 96% purity. After preparative GC, 1.84 g of 99.99% pure **16c** was obtained (54%); integration of the residual methylene protons in the ^{1}H

NMR spectrum showed the extent of deuteration in the desired positions to be at least 97%. ^{1}H NMR ($CDCl_3$, 500 MHz), δ −0.023 (s, 9H), 0.463 (s, 2H), 1.175 (s, 6H), 1.46 (broad s, variable, OH); ^{13}C NMR ($CDCl_3$, 125 MHz), δ −1.91, 10.26, 28.48, 36.98 (quintet), 71.45; IR (neat), 3374 cm^{-1} (s, broad), 2967 (s), 2908 (s), 2183 (m), 2128 (w), 2081 (w), 1364 (m), 1249 (s), 1184 (s), 863 (s), 835 (s).

4-(Trimethylsilyl)-2-chloro-2-methylbutane, ***11***. This was prepared according to the method described by Sommer and Marans.[58] In a separating funnel, 1.8 g, 0.011 mol, of **16** was shaken for 15 min with 30 ml of concentrated HCl. Pentane extracts (4 × 25 ml) were washed with 5% $NaHCO_3$ (3 × 30 ml) and water (2 × 40 ml) and dried ($CaCl_2$). Solvent rotary evaporation followed by molecular distillation at 55 mmHg (lit. b.p.[58] 90 °C at 55 mm Hg) gave 0.80 g of **11** (40%): ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.002 (s, 9H), 0.647 (m, 2H), 1.550 (s, 6H), 1.705 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ −1.91, 11.76, 31.67, 40.49, 72.82; gated-decoupled ^{13}C NMR ($CDCl_3$, 125 MHz), δ −1.90 (q, J = 119 Hz), 11.75 (t, J = 119 Hz), 31.66 (q, J = 128 Hz), 40.48 (t, J = 125 Hz), 72.85 (s); GC–MS, *m/z* 165 (^{37}Cl M^+-CH_3, 1.3%), 163 (^{35}Cl M^+-CH_3, 3.8%), 95 (27.8%), 93 (78.2%), 73 (100%), 70 (70.8%), 55 (36.6%).

4-(Trimethylsilyl)-2-chloro-2-methyl-d_3-butane-1,1,1-d_3, ***11a***. Compound **11a** was synthesized from **16b** using the same procedure as for **11**, except that most of the pentane was distilled out through a 10 cm Vigreaux column with an ice–water-cooled condenser, and the last traces by rotary evaporation from a small flask at ambient temperature. The residue was purified on a molecular still (56 mmHg). Integration of residual methyl protons in the ^{1}H NMR spectrum showed deuterium incorporation in the desired positions to be approximately 99%. A total of 2.5 g of **11a** was obtained (75%): ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.00 (s, 9H), 0.642 (m, 2H), 1.697 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ −1.90, 11.73, 30.72 (septet, J = 19 Hz), 40.36, 72.39.

4-(Trimethylsilyl)-2-chloro-2-methylbutane-3,3-d_2, ***11b***. Compound 11b was synthesized from **16c** using the same procedure as for **11a**. Integration of the residual methylene protons in the ^{1}H NMR showed deuterium incorporation in the desired positions to be not less than 97%. The yield was 1.12 g (55%). ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.002 (s, 9H), 0.629 (s, 2H), 1.548 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ −1.897, 11.56, 31.61, 39.73 (quintet), 72.66.

Synthesis of carbon analogs. *1-Chloro-3,3-dimethylbutane,* ***26***. The synthesis followed Schmerling's procedure.[66] Into a three-necked, 100 ml round-bottomed flask equipped with a thermometer and a bubbler-monitored gas inlet (nebulator), and a bubbler-monitored outlet, with the inlet monitor connected to a lecture bottle of ethylene, were placed 50 ml of pentane and 28.1 g, 0.303 mol, of *tert*-butyl chloride. While stirring, the flask was cooled to −60 °C in a dry-ice–acetone bath and 2.81 g, 0.021 mol, of aluminum chloride were added.

Ethylene was then bubbled through the mixture and the dry-ice–acetone bath was removed. At −20 °C, vigorous absorption of ethylene was indicated by cessation of gas flow from the outlet bubbler, which required increasing the gas flow to prevent suck-back. A simultaneous rapid temperature rise required prompt restoration of dry-ice bath cooling. Cooling to about −30 to −40 °C (slow absorption) and allowing to warm to −10 °C (rapid absorption) were cycled until ethylene absorption ceased, as seen by equal gas flow in the inlet and outlet bubblers.

At −40 °C, the pentane solution was decanted from the solids, using an additional 50 ml of pentane to rinse. The pentane solution was then washed with water (2 × 50 ml), saturated $NaHCO_3$, again with water (2 × 50 ml) and dried over K_2CO_3.

Pentane was removed through a 14 cm vacuum-jacketed column packed with glass helices. The remaining liquid was fractionally distilled; the large fraction (b.p. 115–119 °C; lit.[66] b.p. 115 °C) comprising 27.62 g of **26** (76%): ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.929 (s, 9H), 1.73, (m, 2H), 3.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ 29.28, 30.80, 41.59, 46.95.

4,4-Dimethylpentanoic acid, ***27***[67,68]. Under nitrogen, to 8 g, 0.33 mol, of oven-dried Mg turnings and 50 ml of anhydrous diethyl ether was added a portion of a solution of 21.0 g, 0.174 mol, of **26** in 150 ml of anhydrous diethyl ether. After brief heating with a heat gun had initiated reaction, the remaining chloride solution was added to maintain reflux. Thereafter, a 55 °C bath was applied to continue reflux another 1.5 h.

The cooled solution was poured into 101.5 g of dry-ice pellets. The resulting thick slurry required additional diethyl ether to facilitate stirring. When most of the dry-ice had evaporated, 250 ml of 1 M HCl were added, and stirring was continued until the dry-ice was gone. The ether layer was separated, combined with additional ether extracts (2 × 100 ml), dried ($CaSO_4$), and the ether removed by rotary evaporation.

The residue, dissolved in 250 ml of 5% aqueous NaOH, was washed with diethyl ether (4 × 100 ml), discarding the ether layers. The aqueous layer was acidified by gradual addition of concentrated HCl; the product separated as an oil. The mixture was then extracted with CH_2Cl_2 (3 × 100 ml). The combined CH_2Cl_2 layers were washed with water and dried. Rotary evaporation on a warm water-bath gave 16.1 g of crude product, which was vacuum distilled (b.p. 104–108 °C at 13–14 mmHg; lit.[68] b.p. 105 °C at 13 mmHg) to give 13.22 g of **27** (58%): ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.907 (s, 9H), 1.56 (m, 2H), 2.32 (m, 2H), 11.32 (very broad singlet, OH).

Ethyl 4,4-dimethylpentanoate, ***28***. A 13.22 g, 0.10 mol, amount of **27** was refluxed with a catalytic amount of sulfuric acid in 370 ml of ethanol for 18 h. The mixture was neutralized with aqueous $NaHCO_3$ and most of the ethanol distilled. The residue, in pentane, was washed with aqueous $NaHCO_3$, then water, and dried (K_2CO_3). Pentane was mainly distilled at ambient pressure, and the residue under vacuum (b.p. 105–109 °C at 105 mmHg; lit.[69] b.p. 60–62 °C at 8.0 mmHg) to give 9.44 g of **28** (64%): ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.87 (s, 9H), 1.23 (t, 3H), 1.52 (m, 2H), 2.25 (m, 2H), 4.10 (q, 2H).

Ethyl 4,4-dimethylpentanoate-2,2-d_2, ***28a***. This was prepared by repeated base-catalyzed exchange of 9.44 g of the undeuterated ester, **28**, with ethanol-*d*–ethoxide. Ethanol-*d* was removed after each exchange thus: the mixture was neutralized with glacial acetic acid-*d* (Aldrich). Most of the spent ethanol-*d* was removed by distillation. The residue, in pentane, was washed with water, dried ($MgSO_4$) and the solvent distilled. After 2–3 exchanges, the deuterated ester was purified by vacuum distillation (b.p. *ca* 72 °C at 20 mmHg) to give 5.40 g of **28a** (56%). ^{1}H NMR analysis of the residual methylene protons showed deuterium incorporation to have taken place to approximately 97%. ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.869 (s, 9H), 1.231 (t, 3H), 1.509 (s, 2H), 4.09 (q, 2H).

2,5,5-Trimethyl-2-hexanol, ***29***. This was synthesized according to Grob and Waldner.[32] To the ethereal Grignard reagent prepared from 3.0 g, 0.123 mol, of oven-dried magnesium turnings and **26**, 10.0 g, 0.083 mol, was added dry acetone (purified as described for the synthesis of **21**), 5.89 g, 0.101 mol, dropwise so as to maintain the ether at moderate reflux. After addition of acetone, 2 M NH_4Cl was added dropwise until the pH of the aqueous layer was neutral. The separated ether layer was combined with ether extracts (3×50 ml); the combined layers were washed with water (3×50 ml) and dried (Na_2SO_4). The ether was removed by rotary evaporation and the residue distilled at 12.5 mmHg (b.p. 62–64 °C; lit.[32] b.p. 61.5–62 °C at 10 mmHg) to give 4.91 g of **29** (41% yield). Preparative GC of the crude product, 1.78 g, afforded pure alcohol **29**: ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.859 (s, 9H), 1.181 (s, 6H, partially overlapped with multiplet at δ 1.20), 1.20 (m, 2H, partially overlapped with singlet at δ 1.181), 1.412 (m, 2H), 1.464 (s, broad, variable, OH); ^{13}C NMR ($CDCl_3$, 125 MHz), δ 29.12, 29.29, 29.88, 38.09, 38.49, 70.99.

2-Methyl-d_3-5,5-dimethyl1-2-hexanol-1,1,1-d_3, ***29a***. Compound **29a** was synthesized by the same procedure as for **29**, using acetone-d_6 (99.9% D; Cambridge Isotope Laboratories) instead of acetone. A 7.54 g amount of **29a** was obtained (60%), of which 1.43 g was purified by preparative GC. Residual methyl protons could not be seen in the ^{1}H NMR spectrum; it was assumed that deuterium incorporation was greater than 99%. ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.854 (s, 9H), 1.194 (m, 2H), 1.395 (m, 2H), 1.496 (s, broad, variable, OH); ^{13}C NMR ($CDCl_3$, 125 MHz), δ 28.13 (septet), 29.29, 29.87, 38.04, 38.38, 70.68.

2,5,5-Trimethyl-2-hexanol-3,3-d_2, ***29b***. Compound **29b** was prepared by addition of 3 M methylmagnesuim bromide (Aldrich) to **28a**, as in the synthesis of **16**. Residual methylene protons could not be detected in the ^{1}H NMR spectrum; it was assumed that deuterium incorporation was at least 97%, that which was determined for **28a**. ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.865 (s, 9H), 1.184 (s, 6H), 1.197 (s, 2H), 1.342 (s, broad, variable, OH).

2-Chloro-2,5,5-trimethylhexane, ***10***. This was synthesized by a procedure of Grob and Waldner.[32] Compound **29**, 1.7 g, 0.117 mol, was shaken in a separating funnel for 15 min with 33 ml of concentrated HCl. This mixture was extracted with pentane (3×75 ml). The combined organic layers were washed with 5% $NaHCO_3$ (4×50 ml) and water (3×50 ml) and dried ($CaCl_2$). Pentane was removed by rotary evaporation at ambient temperature and the residue was distilled at 13 mmHg in a molecular still (lit.[32] b.p. 46.5–47.5°C at 11 mmHg) to give 0.45 g of **10** (24%): ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.894 (s, 9H), 1.355 (m, 2H), 1.567 (s, 6H), 1.706 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ 29.30, 29.89, 32.39, 38.79, 40.90, 71.52.

2-Chloro-2-methyl-d_3-5,5-dimethylhexane-1,1,1-d_3, ***10a***. Compound **10a** was prepared from **29a** according to the procedure used (above) for **10**. Residual protons for the deuterated methyl groups could not be seen in the ^{1}H NMR spectrum; it was assumed that deuterium incorporation was greater than 99%. A total of 0.64 g of **10a** were obtained (60%): ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.892 (s, 9H), 1.353 (m, 2H), 1.699 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ 29.30, 29.89, 31.43 (septet), 38.75, 40.75, 71.03.

2-Chloro-2,5,5-trimethylhexane-3,3-d_2, ***10b***. Compound **10b** was prepared using a modification of the procedure described by Shiner and Verbanic.[70] Between 1 and 0.5 ml of **29b** was placed in a 1 dram (4 ml) screw-topped vial. A Pasteur pipette connected to a lecture bottle of hydrogen chloride gas by means of Tygon tubing was clamped into place above the vial so that the tip of the pipette was almost touching the bottom of the vial. Hydrogen chloride gas was gently bubbled into the 2,5,5-trimethyl-2-hexanol-3,3-d_2. After 5 min, the vial became hot to the touch. After another 5 min, the liquid in the vial developed a pinkish color and became cloudy. After a total of 15 min, two layers were seen to form. The bubbling was discontinued and the mixture was dissolved

in pentane, washed with water and aqueous sodium hydrogen carbonate and again with water. The pentane solution was then dried (K_2CO_3), and the solvent was removed by rotary evaporation at ambient temperature. The residue was then vacuum distilled on a molecular still (lit.[32] b.p. 46.5–47.5 °C at 11 mmHg) to give the product. ^{1}H NMR analysis of residual methylene protons showed deuterium incorporation to be approximately 90%; presumably some depletion occurred as a result of addition of HCl to some elimination product. ^{1}H NMR ($CDCl_3$, 500 MHz), δ 0.892 (s, 9H), 1.341 (s, 2H), 1.561 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ 29.30, 29.89, 32.32, 38.62, 40.5 (multiplet ^{13}C′s for CD_2 and CDH compounds), 71.37. (Some small peaks believed to correspond to the CDH compound were also seen in the ^{13}C NMR spectrum at δ 32.384, 38.706 and 71.5.)

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