Mechanisms of S_E2 Reactions: Emphasis on Organotin Compounds

JON M. FUKUTO and F. R. JENSEN*

Department of Chemistry, University of California, Berkeley, California 94720

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In contrast to nucleophilic substitution reactions at aliphatic carbon centers that have been studied in great detail, electrophilic aliphatic substitution reactions have been relatively unexplored (except for studies at "carbanionic" centers[1]). It is accepted that bimolecular nucleophilic substitution at carbon involves backside attack resulting in an overall inversion of configuration at carbon (Figure 1). However, no such general statement can be made concerning bimolecular electrophilic aliphatic substitution. The mechanistic intricacies of S_E2 reactions have just begun to be realized and appear to be more complicated and varied than S_N2 cleavages.

The simplest and most logical transition-state geometries for S_E2 reactions are shown in Figure 2.

Transition-state 2a, the S_E2 open retention, has the electrophilic atom attacking the metal–alkyl bond front side without prior or simultaneous coordination of the anionic atom. Transition-state 2b, the S_E2 cyclic retention, has a "four-centered" geometry with the anionic atom Y coordinating the electropositive metal. Both of these pathways would yield products with retention of configuration at the R group. Transition-state 2c, the S_E2 inversion, has the electrophile attacking on the backside of the carbon atom in a geometrically analagous fashion to the S_N2 reaction. Substantial charge separation exists and inversion stereochemistry at carbon would result.

The most extensive body of work involving substantiated S_E2 processes, based on both kinetic and stereochemical studies, deals with electrophilic cleavages of organomercurials.[2] It has been established that retention of configuration is the normal course of electrophilic cleavage of the carbon–mercury bond.[3] The proclivity of organomercury compounds to react exclusively via retention mechanisms can most likely be attributed to the Lewis acidity of organomercurials: They have available low-lying vacant orbitals that can complex the incoming electrophile either prior to or simultaneous with the actual cleavage (Figure 2b). In any event, retention stereochemistry would be the consequence, in agreement with experiment.

These results with mercurials have been generalized in texts and reviews, leading to the conclusion that the normal stereochemical course of electrophilic substitution is retention of configuration on carbon.

Frederick Jensen was born in Yerington, NV. After spending a short stint in the United States Navy he attended the University of Nevada and then Purdue University, where he obtained a Ph.D. degree in Chemistry in 1955. Since then he has been on the staff of the University of California, Berkeley, where he is now Professor of Chemistry.

Jon M. Fukuto was born in Riverside, CA, in 1956. He received his B.A. degree in 1978 from the University of California, San Diego. He is currently working with Professor F. J. Jensen at the University of California, Berkeley. He will soon be moving to UCLA for postdoctoral work in Pharmacology.

Early mechanistic work performed with various alkylithium substrates revealed that mixed stereochemistry is possible.[4–7] The results with lithium alkyls must, however, be approached with caution since a strong possibility exists that they do not react via concerted S_E2 processes. Alkyllithiums are known to react via clusters, especially for reactions performed in pentane or ether, and there is a strong possibility that electron-transfer mechanisms exist.

Stereochemical studies involving Grignard reagents have also been performed. Walborsky and co-workers used 1-methyl-2,2-diphenylcyclopropylmagnesium bromide as a stereochemical probe and found reactions with CO_2, I_2, and Br_2 to give products with retention of configuration.[8] Also, Jensen and Nakamaye found that reaction of *endo*-norbornyl Grignard reagent with either $HgBr_2$ or CO_2 gives products with retention of configuration.[9]

Organoboranes demonstrate variable stereochemistry in electrophilic substitutions. Brown and Lane observed that tri-*exo*-2-norbornylborane reacts with bromine in the dark to yield pure *exo*-2-bromonorbornane. However, the same substrate reacts with bromine in the presence of sodium methoxide to give predominantly *endo*-2-bromonorbornane.[10]

The bromodemetalation of an optically active dialkylthallium bromide by tribromide ion has been investigated.[11] *sec*-Butylneopentylthallium bromide was prepared and allowed to react with tribromide ion in dimethylformamide (DMF). The resulting *sec*-butyl bromide was found to be of rotation opposite to that of the starting thallium compound, indicating that the halogen cleavage occurs with inversion.[11] The results are best explained by considering that the reaction occurs via attack of Br_2 on coordinatively saturated $R^*R'TlBr_2^-$ to yield directly $R'TlBr_2$ and inverted R*Br.

Cleavages of several transition-metal–alkyl bonds by electrophiles have been investigated. Whitesides and co-workers synthesized *erythro*-$(CH_3)_3CCHDCHDFe$-

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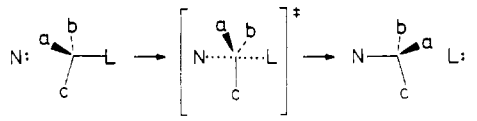

Figure 1. S_N2 reaction, showing transition state.

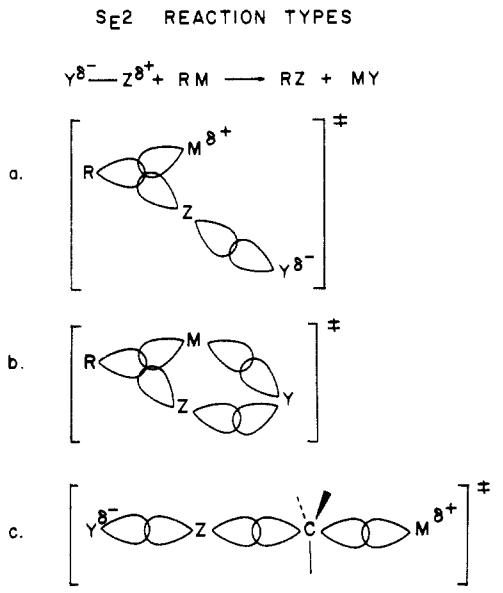

Figure 2. Transition-state geometries for S_E2 cleavages where M is an electrofugal group (usually a metal atom), R is an alkyl group, and Z is the electrophilic site in reagent YZ. (a) S_E2 open retention. (b) S_E2 cyclic retention. (c) S_E2 inversion.

$(CO)_2Cp$ for use as a stereochemical probe for electrophilic processes.[12] Parallel work was carried out with alkylcobaloximes by Jensen and co-workers.[13] In both cases reaction with bromine leads to inverted alkyl bromides. It has been shown, however, that those systems do not react entirely via S_E2 pathways,[14-16] but can react also by other mechanisms involving initial oxidation of the metal atom. Thus, transition-metal–alkyl compounds do not always lend themselves to the study of S_E2 processes owing to troublesome, potentially competing alternative reaction pathways.

Early stereochemical studies with the kinetically established S_E2 reactions of tetraorganotins by Gielen and co-workers indicated that, as with organomercurials, S_E2 cleavages of the carbon–tin bond occurred with retention stereochemistry.[17] The stereochemical probe used in this study was, however, a cyclopropyl derivative; in view of the known barrier to inversion of cyclopropane rings, it is not surprising that retention was observed.

The above cited systems in which retention of configuration at carbon was observed seemed to be biased to retention pathways either by the availability of low-lying vacant orbitals on the leaving group promoting a four-centered mechanism (Figure 2b), or geometrical constraint on the carbon. An attempt was therefore made to select a system in which retention or inversion could be favored by altering the structure of the substrate and/or reaction conditions.

Only retention stereochemistry had been observed in substantiated S_E2 processes at the time the work described hereafter was initiated. In design of a system that favors inversion stereochemistry, certain factors expected to promote S_E2 inversion were considered. It must contain: (1) a leaving group which is relatively stable when bearing a positive charge (or the equivalent); (2) a leaving group with no low-lying vacant orbitals; (3) steric hindrance to front-side substitution and little hindrance to inversion; (4) a polar solvent (when necessary) to stabilize developing, far-removed positive and negative charges. Certain organotin compounds, selected by trial and error, were found to satisfy the above criteria.

Results with Tetraalkyltins

Organotin compounds were chosen as ideal substrates because they fulfill all the criteria mentioned and have, furthermore, a carbon–metal bond adequately polarized so that reactions with electrophiles are rapid. Also, a wide variety of tetraorganotin halides are easily synthesized. The tetravalency of the tin atom allows more variety with respect to steric and electronic properties than the previously discussed divalent mercury compounds. Tetraalkyltin compounds also do not have low-lying vacant orbitals for complexation of electrophiles,[18] thus allowing the possibility of either front-side or backside attack on the carbon–metal bond. (To our knowledge simple tetraalkyltin compounds have never been shown to demonstrate any Lewis acid character). Moreover, tetravalent tin compounds contain a tin atom in its highest oxidation state, therefore precluding any oxidative processes as were established for transition-metal alkyls.[14-16]

Kinetics. The kinetics of the halodemetalation of tetraalkyltins has been investigated previously. Early work by Gielen and Nasielski demonstrated that the cleavage of a wide variety of carbon–tin bonds by halogen is overall second order in polar solvents, first order in the tin compound and first order in halogen.[19]

Following the lead of Gielen and Nasielski, Jensen and Davis investigated the kinetics of several reactions of compounds $(Np)_3SnR$ (Np = neopentyl; R = methyl, ethyl, isopropyl, 2-butyl, neopentyl)[20] with bromine in methanol (eq 1).

$$(Np)_3SnR + Br_2 \xrightarrow[NaBr]{MeOH} RBr + (Np)_3SnBr \quad (1)$$

Kinetic complications can arise from the dissociation (eq 2) of the product, trineopentyltin bromide,[21] to

$$(Np)_3SnBr \rightleftharpoons (Np)_3Sn^+ + Br^- \quad (2)$$

produce bromide ion, which could, in turn, complex with bromine to form tribromide ion (eq 3). This ki-

$$Br_2 + Br^- \overset{K}{\rightleftharpoons} Br_3^- \quad (3)$$

$$K = 177 \text{ at } 25\ ^\circ C^{24}$$

netic complication can be removed by the addition of swamping bromide ion in the form of sodium bromide.

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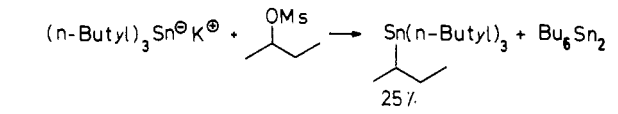

Figure 3. Ms = $MeSO_2$.

The reaction was found to be second order. The rate constant, k_2, was invariant for a change in organotin concentration by about a factor of 165 and a factor of 8 in bromine concentration.

The observed rate constant k_2(obsd) for the bromodemetalation shows an inverse dependance on bromide ion concentration. This inverse dependance is due to equilibrium 3 between bromine and tribromide; increased bromide ion concentration removes electrophilic bromine by converting it to the unreactive tribromide.

The rate law which best fits the observations is presented in eq 4.

$$\text{observed rate} = k_2(\text{obsd})[R_3SnR'][Br_2]_t = k_2[R_3SnR'][Br_2] \quad (4)$$

$$[Br_2]_t = [Br_2] + [Br_3^-] \quad (5)$$

Equation 4 can be put into the form:

$$(1/k_2) + (K/k_2)[Br^-] = 1/k_2(\text{obsd}) \quad (6)$$

A plot of $1/k_2$(obsd) vs. [Br^-] was a straight line even at a very high bromide ion concentration; thus the reaction is indeed second order and bromide ion does not enter into the reaction.

Synthesis. With the kinetic results in hand, a study of the stereochemistry of the halogen cleavage was undertaken. There are three major ways to form carbon–tin bonds: addition of tin hydrides to olefins, alkylation of tin halides by lithium or Grignard reagents, and substitution reactions of alkyl halides or alkyl sulfonate esters with tin anions. Of the three methods, only the last is easily amenable to the formation of a chiral carbon bound to tin.

For the synthesis of a tetraorganotin compound with one optically active alkyl group, the most efficient use of the optically active precursor would be to incorporate it in the final step. This route was attempted in the synthesis of tri-*n*-butyl-*sec*-butyltin, but low yields of the desired compound were obtained (Figure 3). Hexabutylditin was the main product. These results reflect, at least in part, an E2 elimination competing with the desired S_N2 pathway. Inasmuch as trialkyltin hydrides can react, catalyzed by trialkyltin anions, to yield the hexaalkylditin and H_2, the origin of the ditin product is evident.[22]

In the analogous reactions with alkyl bromides, higher physical yields were obtained, as compared to the methanesulfonate ester substrate, but with much lower optical yields. This can be attributed to a competing electron transfer process.

Triphenyltin anions were found to react almost entirely via an S_N2 pathway.[20,23] Phenyl groups are known to be cleaved by halogen preferentially to normal aliphatic ligands on tin.[24] These two facts have been exploited in the design of the reaction sequence of Scheme I for the synthesis of optically active tetraalkyltins.

Scheme I. Synthesis of Optically Active Tetraalkyltin Compounds

$$Ph_3SnCl + 2M \xrightarrow[THF/NH_3]{-78\ ^\circ C} Ph_3Sn^-M^+ + MCl$$

$$Ph_3Sn^-M^+ + R^*OMs \xrightarrow[THF/NH_3]{-33\ ^\circ C} Ph_3SnR^* \text{ (inversion)}$$

$$Ph_3SnR^* + 2Br_2 \xrightarrow[MeOH/CCl_4]{} R^*SnPhBr_2$$

$$R^*SnPhBr_2 + 2R'MgBr \xrightarrow[Et_2O]{} R^*SnPhR'_2$$

$$R^*SnPhR'_2 + Br_2 \xrightarrow[MeOH/CCl_4]{} R^*SnR'_2Br$$

$$R^*SnR'_2Br + R''MgBr \xrightarrow[Et_2O]{} R^*SnR'_2R''$$

Stereochemical Studies of the S_E2 Cleavage of Trineopentyl-*sec*-butyltin. The earliest stereochemical work by Gielen and co-workers indicated that, as with organomercurials, S_E2 cleavages of carbon–tin bonds occurred with retention.[17] The stereochemical probe used in this study was, however, a cyclopropyl derivative, and as mentioned earlier, the geometric constraints of cyclopropane rings would bias the stereochemistry. In order to achieve inversion stereochemistry a specific system was designed which would essentially force the reaction to occur via an inversion mechanism.[20] Trineopentyl-*sec*-butyltin was synthesized. Neopentyl groups are cleaved very slowly from tin,[25] and an examination of space-filling models shows severe steric congestion to front-side attack because of the bulk of the three neopentyl substituents.

In the inversion transition state (Figure 2c, M = R_3Sn) substantial charge buildup is realized. Due to the large electron-donating properties of the neopentyl group, the incipient trineopentyltin cation is expected to be relatively stable. Also, use of a solvent that could adequately stabilize the charges, such as methanol, would encourage the inversion transition state. Methanol, a protic solvent, is capable of stabilizing the bromide ion through hydrogen bonding, and since it has available electron pairs on oxygen, it could solvate the tin cation.

Bromide ion was added to the methanol for reasons described earlier in the discussion on kinetics. The addition of bromide ion also serves two other purposes: first, it slows down the oxidation of the solvent by tying up the oxidant, molecular bromine, as tribromide ion; second, since the concentration of free bromine is low, the likelihood of radical reactions is lessened.

When trineopentyl-*sec*-butyltin is bromodemetalated in methanol with added bromide ion, stereospecific inversion at carbon is observed. This result is the first example of an S_E2 reaction occurring with inversion stereochemistry. Thus the viability of the S_E2 inversion transition state has been demonstrated.[26]

The stereochemistry of the bromodemetalation of trineopentyl-*sec*-butyltin was also investigated in carbon tetrachloride. This solvent would not be expected to

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Table I
Stereochemistry[a] of the Bromodemetalation of $R_3Sn(sec\text{-}Bu)$

conditions	observed stereochemistry, %			
	R_3Sn = $i\text{-}Pr_3Sn$[b]	$i\text{-}Pr_2NpSn$[b]	$i\text{-}PrNp_2Sn$[b]	Np_3Sn[b,d]
CCl_4[e]	70 ret	74 ret	76 ret	89 ret
CH_3OH	22 ret	1 ret	35 inv	40-65 inv
CH_3OH, 0.2 M NaBr	12 ret			~100 inv[f]
CH_3OH, 0.4 M NaBr	9 ret	4 ret		
CH_3OH, 0.91 M $NaClO_4$	10 ret			
CH_3CN	9 inv	60 inv	~100 inv	~100 inv

[a] Defined as optical purity of 2-bromobutane/optical purity of organotin: 15.8° used as maximum rotation of starting *sec*-butyltriphenyltin[22] and 34.2° for *sec*-butyl bromide.[27] ret = retention: inv = inversion. [b] R_3Sn: Np = neopentyl: *i*-Pr = isopropyl. [c] [organotin] = 0.22-0.25 M: reactions performed in dark, in air atmosphere, with dropwise addition of Br_2 over 1-5 h. Reactions not taken to completion. [d] Results from ref 18. [e] With appropriate inhibitor.[18] [f] [NaBr] = 0.122 M.

be able to solvate a transition state with charge buildup such as in the inversion mechanism (Figure 2c, M = R_3Sn). In initial studies in carbon tetrachloride, only a small net retention was realized.[25] It became evident that the low optical yields were a result of competing radical processes.

Bromine is a good radical trap for alkyl radicals and tetraalkyltins are good radical traps for bromine atom. Therefore a radical trap which could interrupt these processes was sought. The radical inhibitor bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl) sulfide was found to adequately inhibit the radical process. The actual form of the radical trap is unknown since the sulfide does react with bromine to produce as yet unknown products. To our delight, when trineopentyl-*sec*-butyltin is bromodemetalated in carbon tetrachloride in the presence of the radical inhibitor retention stereochemistry as high as 92% is found.[26] (The remaining 8% is probably due to a still bothersome radical process since the inversion pathway, which involves charge separation, would be energetically inaccessible in carbon tetrachloride.)

This complete reversal of stereochemistry upon solvent change can be easily rationalized when the competing inversion and retention transition states are examined. The inversion pathway requires a substantial separation of charge. This charge buildup is compensated by solvation in methanol, but in a nonpolar solvent such as carbon tetrachloride the energetics of this process would be prohibitively high. In the cyclic-retention mechanism a partial positive charge is generated on the tin atom by further polarization of the carbon–tin bond induced by the incoming electrophile, thus allowing complexation by the anionic leaving group. The cyclic-retention transition state (Figure 2b) requires little charge separation and should be relatively independent of solvent. An open-retention mechanism could also be relatively independent of solvent. The energetics of these processes would therefore be similar in both carbon tetrachloride and methanol. Since the energy of the inversion pathway is certainly raised and the energy of the retention pathway relatively unaffected, retention is the stereochemical consequence of reactions performed in carbon tetrachloride.

The kinetic, stereochemical, and relative rate data for systems with trineopentyltin as the leaving group, in reactions with bromine with added bromide ion, demonstrate that both retention and inversion mechanisms are possible.

Leaving Group Effects. As previously noted, trineopentyltin was deliberately chosen as leaving group in order to favor the inversion stereochemistry. It has been argued that the trineopentyltin leaving group is so sterically congested that an abnormal stereochemical course takes place and that retention is still the general stereochemical outcome of halodemetalation reactions of tetraorganotins.[27] In partial response to this and to further elucidate factors governing S_E2 reactions of the carbon–tin bond, the steric bulk of the electrofugal tin group was varied, utilizing the four organotins, *sec*-$Bu(Np)_n(i\text{-}Pr)_{3-n}Sn$ (Np = neopentyl). Each of these compounds was bromodemetalated in carbon tetrachloride, methanol, with and without added bromide ion, and acetonitrile.[28] The results are shown in Table I.

Within a set of reaction conditions, increased neopentyl for isopropyl substitution increases the net inversion stereochemistry. This phenomenon could be a reflection of the sheer steric bulk of neopentyl compared to isopropyl; the neopentyl ligand more effectively shields the electrophile from the front side of carbon.

An alternative explanation for the propensity of neopentyl substitution to yield inverted products could be the relief of steric strain in the ground state. As with solvolysis reactions,[29] severe steric congestion can accelerate a reaction that involves a tetrahedral to trigonal procession along a reaction coordinate. Strain experienced in the tetrahedral form would be mitigated by a trigonal geometry. Therefore, as the steric compression of the molecule in the ground state increases via neopentyl for isopropyl substitution, the need for steric relief increases.

Another possible explanation is that, due to the higher electron-donating character of the neopentyl group compared to isopropyl, the incipient tin cation, formed in the inversion mechanism, becomes more stable with increased neopentyl for isopropyl substitution.

The observed change in net stereochemistry reflects a change in the relative rates of the inversion and retention processes. Both of these mechanisms are occurring in solution and varying either substitution on tin or the solvent (and, as we shall see later, varying the electrophile) can change the relative rates of the two pathways. In these reactions there is no evidence to suggest that a decrease in net stereochemistry is a reflection of a racemization process.

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Table II
Stereochemistry[a] of the Bromodemetalation of $R_3Sn(sec\text{-}Bu)$

solvent	observed stereochemistry, % R_3Sn = $i\text{-}Pr_3Sn$[b]	$i\text{-}Pr_2NpSn$[b]
methanol	9.3 ret	3.5 ret
ethanol	32.8 ret	4.8 ret
n-propyl alcohol	25.1 ret	8 ret
acetonitrile	14.5 inv	65.7 inv
dimethylformamide	3.8 inv	48.6 inv
benzonitrile	12.2 ret	4.4 ret
1,2-dichloroethane	7.7 ret	24.4 ret
chlorobenzene	27.6 ret	33.1 ret
tetrahydrofuran	23.7 ret	51.7 ret
carbon tetrachloride	56.6 ret	73.8 ret

[a] Defined as optical purity of 2-bromobutane/optical purity of organotin; 15.8° used as maximum rotation of starting *sec*-butyltriphenyltin[22] and 34.2° for *sec*-butyl bromide.[27] [b] R_3Sn: Np = neopentyl; *i*-Pr = isopropyl; ret = retention; inv = inversion.

The results with $R_3Sn = (i\text{-}Pr)_3Sn$ and $(i\text{-}Pr)_2NpSn$ in methanol and acetonitrile are of special interest because the stereochemistry of the bromodemetalation is not overly biased toward either retention or inversion by alkyl substitution on tin. The rate of the inversion process for these systems is very nearly equal to the rate of the retention process (especially for $R_3Sn = (i\text{-}Pr)_3Sn$). These compounds therefore provide excellent model systems for studying other factors that could affect the stereochemistry of S_E2 reactions.

Solvent Effects. A large solvent effect on the stereochemistry of the bromodestannylation reactions is evident in the results in Table II. Gielen and Frosty also observed a large medium effect in that certain tetraalkyltins could be brominated in chlorobenzene with inversion in the presence of "naked" fluoride ion and with retention in the absence of the fluoride salt.[30]

Using two tetraalkyltins, triisopropyl-*sec*-butyltin and diisopropylneopentyl-*sec*-butyltin, as stereochemical probe, a more extensive study of solvent effects was undertaken. The two tetraalkyltins were bromodemetalated in 10 solvents. The results are compiled in Table II.

As expected, nonpolar solvents favor a retention mechanism in which no charge buildup is necessary. More polar solvents allow the competing inversion mechanism to become more prevalent; in fact, in acetonitrile and dimethylformamide inversion is the predominant reaction pathway.

Results with Mixed Halogen Electrophiles. Reactions between bromine and secondary carbon–tin bonds occur with retention or inversion depending on solvent or substitution on tin. Only bromine has been reported as the electrophile in the stereochemical studies presented thus far. The effect the electrophile exerts on the eventual mechanism of reaction has therefore been investigated.

The halodemetalations of triisopropyl-*sec*-butyltin and diisopropylneopentyl-*sec*-butyltin were performed in methanol and acetonitrile with iodine, iodine monochloride, and iodine monobromide as electrophiles. The results are summarized in Table III.

Table III
Stereochemistry[a] of the Halodemetalation of $R_3Sn(sec\text{-}Bu)$

solvent	electrophile	observed stereochemistry, % R_3Sn = $i\text{-}Pr_3Sn$[b]	$i\text{-}Pr_2NpSn$[b]
methanol	I_2	15.2 ret	11 ret
methanol	IBr	30.7 ret	73 ret
methanol	ICl	43.1 ret	40.6 ret
methanol	Br_2[c]	9.2 ret	3.5 inv
acetonitrile	I_2	5 inv	13.2 inv
acetonitrile	IBr	40.7 inv	100 inv
acetonitrile	ICl	62.5 inv	100 inv
acetonitrile	Br_2[c]	14.5 inv	65.7 inv

[a] Defined as optical purity of 2-iodobutane/optical purity of organotin; 38.5% used as maximum rotation of *sec*-butyl iodide[31] and 15.8° for *sec*-butyltriphenyltin.[22] [b] R_3Sn: Np = neopentyl; *i*-Pr = isopropyl; ret = retention; inv = inversion. [c] From Fukuto, J. M.; Jensen, F. R., in press.

The kinetics of the iododemetalation of tetraalkyltins has been previously investigated. In both methanol and dimethyl sulfoxide the rate expression was found to be purely second order, first order in organotin and first order in iodine.[19,32] The kinetic order of reactions between mixed halogen electrophiles and tetraalkyltins in polar solvents has yet to be determined. Because only second-order kinetics have been observed in polar solvents for both bromine and iodine, for the sake of discussion, it is reasonable to assume that iodine monochloride and iodine monobromide behave accordingly in polar solvents.

The alkyl halide formed was found to be, in all cases, almost entirely the iodide. This suggests that the reactions between the mixed halogens and tetraalkyltins occur by polar mechanisms; the nature of the product is governed by the polarity of the iodine–bromine or iodine–chlorine bond and the carbon–tin bond. In previous studies reactions of organotins with iodine monochloride or iodine monobromide also yielded only alkyl iodides.[33]

The data reveal that in all cases iodine yields products with greater net retention than bromine. This result can be at least partially explained by the ability of iodine to form bonds at longer distances compared to bromine.

We have seen that the substituents on tin are vitally important in determining stereochemistry.[28] Increased neopentyl for isopropyl substitution on tin results in products with greater net inversion, owing at least in part to unfavorable steric interactions between the incoming electrophile and the bulky alkyl ligands in the retention transition state. Anything which could reduce steric interactions of this sort would lower the energy of the retention pathway. The iodine–tin bond length is longer than the bromine–tin bond by about 0.23 Å: The Sn–I bond in Me_3Sn–I is 2.72 Å and the Br–Sn bond length in Me_3SnBr is 2.49 Å.[24] Also the C–I bond is about 0.2 Å longer than the corresponding C–Br bond.[24]

The results for the mixed halogen electrophiles in methanol show that they consistently give more retention than the corresponding reaction with I_2. The only

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(31) M. Gielen and J. Nasielski, *Bull. Soc. Chim. Belg.*, 71, 661 (1962).
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(33) R. L. Chambers, L. F. McGahey, and F. R. Jensen, in press.

Table IV
Stereochemistry of the Bromodemetalation of 1-(Trialkylstannyl)butane-*1-d* Compounds

alkyl	conditions[a]	stereochemistry[d]
neopentyl	CH_3OH, NaBr[b]	~94% inversion
isopropyl	CH_3OH	~45% inversion[e]
isopropyl	CH_3OH, 4.6 equiv $NaClO_4$	~54% inversion[e,f]
isopropyl	CCl_4, inhibitor[c]	racemization
pentyl	CH_3OH	~47% inversion[e]
pentyl	CCl_4, inhibitor[c]	~21% retention

[a] Reactions conducted in dark, at room temperature, air atmosphere, bromine added dropwise to the reaction mixture, organotin concentration 0.2–0.25 M. [b] Alkyl halide removed as methanol azeotrope as formed. [c] Bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl) sulfide; see ref 28 and 18. [d] Stereochemistry as inversion or retention defined in text; numerical value = (optical purity 1-bromobutane-*1-d*)/(optical purity of 1-(trialkylstannyl)butane-*1-d*). [e] These numerical values should be considered to be approximately equal, given the uncertainty in the enantiomeric purity of the starting compound. [f] We have previously shown that an increase in the ionic strength of the reaction solvent may favor inversion; see ref 28.

difference in the three systems is the anionic leaving group since the electrophilic atom is in all cases iodine.

In the S_E2 cyclic-retention mechanism, the tin atom is stabilized by coordination of the anionic leaving group of the dinuclear electrophile. Apparently chloride and bromide are better suited for this type of coordination than is iodide, due to either their smaller size or greater electronegativity.

In acetonitrile, the mixed halogen electrophiles give more inversion than iodine. This result is the opposite of what was found in methanol. Acetonitrile would appear to be better suited for tin cation stabilization than methanol, as would be important in the S_E2 inversion transition state. (Reactions performed in acetonitrile always give products with greater inversion than those in methanol.) Since the trialkyltin cation is adequately stabilized in acetonitrile, presumably internal stabilization by the anionic leaving group is not as important as in methanol.

Primary Carbon Centers. Most of the stereochemical evidence presented thus far has concerned reactions at secondary carbon centers. An investigation of the stereochemistry of bromodemetalations at primary carbon–tin bonds was therefore undertaken. Gielen and Frosty earlier investigated the stereochemistry of the bromination of *erythro*-$(CH_3)_3CCHDCHDSnR_3$ compounds (R = methyl, isopropyl, neohexyl) in chlorobenzene.[29] They observed retention of configuration in all cases. However if potassium fluoride and 18-crown-6 are added, the bromination of the neohexyl derivative occurs with predominant inversion.

In a more comprehensive study (*R*)-(−)-1-(trialkylstannyl)butane-*1-d* (alkyl = neopentyl, pentyl, and isopropyl) was treated with bromine in methanol and carbon tetrachloride.[34] The results are shown in Table IV.

Inasmuch as trineopentyl-*sec*-butyltin is bromodemetalated in methanol with added bromide ion with complete inversion of configuration, it is not surprising that (butyl-*1-d*)trineopentyltin is brominated with 94% inversion in methanol. However triisopropyl-*sec*-butyltin reacts with 22% retention in methanol while (butyl-*1-d*)triisopropyltin is cleaved with 45% inversion! This result demonstrates that the steric bulk of the group being substituted can affect the stereochemistry radically. Apparently S_E2 reactions at primary centers favor inversion mechanisms in methanol much more than they do at secondary centers. Even the all-primary organotin, which was specifically chosen to minimize steric conjestion to frontside attack, is bromodemetalated with inversion of configuration.

The S_N2 process is known to proceed faster at primary centers than at secondary centers due to the steric requirements of an inversion transition state. The S_E2 inversion process investigated here is analagous to the S_N2 process in terms of transition-state geometry. Purely on steric grounds it is therefore not surprising that the S_E2 process at primary centers occurs with predominant inversion. Even with an unhindered frontside approach the electrophile still prefers backside attack.

The results in carbon tetrachloride show either racemization or retention (21% retention for the tripentyl derivative). Racemization cannot necessarily be taken to mean equal rates of reaction for the inversion and retention pathways. Competing radical pathways are often the preferred mode of reaction for organometallic compounds.[18] Complete or partial racemization most likely occurs via a radical process since it would be difficult to fathom an inversion pathway with separation of charge being energetically accessible in a nonpolar solvent such as carbon tetrachloride.

In any event it is obvious that not only are solvent and substitution on tin important in determining stereochemistry, but the alkyl groups on the reacting carbon exert a substantial influence as well. Inasmuch as primary centers prefer an inversion mechanism in methanol even in the absence of front-side congestion by ligands on tin, one may conclude that there is no preferred stereochemistry for S_E2 reactions on tetraalkyltins.

Results with Trialkyltin Bromides

Kinetics. In conjunction with the work on reactions of tetraalkyltins with bromine, trialkyltin bromides were also studied. The products of the bromodemetalation of tetraalkyltins are alkyl bromides and trialkyltin bromides. In order to assure that the stereochemical and kinetic results for the bromodemetalation of tetraalkyltins do not have included in them a contribution from bromodemetalation of the trialkyltin bromide, the overall rates of the two processes were determined. The rate constant for the cleavage of trineopentyl-*sec*-butyltin by bromine in methanol with added bromide ion is 4.4×10^{-2} M^{-1} s^{-1} while the corresponding rate constant for trineopentyltin bromide is 8.7×10^{-4} M^{-1} s^{-1}. Gielen and Nasielski published similar values, on the order of 10^{-4} M^{-1} s^{-1}, for the bromodemetalation of various trialkyltin bromides in acetic acid at 20 °C.[34] The rates for the cleavage of trialkyltin bromides are thus approximately 50 times slower than for tetraalkyltins. The rates of cleavage are dramatically reduced by substituting bromine for alkyl on tin. This is not unexpected since R_2BrSn^+ would be a poorer leaving group than R_3Sn^+ due to the greater electron-withdrawing property of bromine.

(34) M. Gielen and J. Naseilski, *Bull. Soc. Chim. Belg.*, 71, 601 (1962).

(35) R. L. Chambers, L. F. McGahey, and F. R. Jensen, in press.

Table V
Bromodemetalation of
(*R*)-(-)-2-(Bromodineopentylstannyl)butane as a
Function of Sodium Bromide Concentration in Methanol

conditions[a]	time, h	stereochemistry
1 equiv of NaBr	115	66% retention[b]
	259	63% retention
+0.75 equiv of Np_2SnBr_2	426	76% retention
2 equiv of NaBr	142	45% retention
+0.75 equiv of Np_2SnBr_2	310	54% retention
3 equiv of NaBr	140	33% retention
+0.75 equiv of Np_2SnBr_2	282	43% retention

[a] Equiv = equivalents, based on organotin; ionic strength maintained with $NaClO_4$; alkyl halide removed azeotropically as formed; [organotin] 0.28 M, reactions conducted in dark, 45 °C; Np_2SnBr_2 = dineopentyltin dibromide. [b] Stereochemistry = (optical purity 2-bromobutane)/(optical purity *sec*-butyltriphenyltin × 100%) (see ref 28).

The kinetics for the bromination of $(Np)_2SnR(Br)$ compounds (R = methyl, ethyl, propyl, isopropyl, *sec*-butyl, isobutyl, and neopentyl) in methanol with added bromide ion[36] can be interpreted by the two term rate expression of eq 7.

$$\text{rate} = k_2[Np_2SnR(Br)][Br_2] + k_3[Np_2SnR(Br)][Br_2][Br^-] \quad (7)$$

The kinetic behavior of the primary substrates, R = methyl, ethyl, propyl, is best described by the bromide ion-dependent term. The secondary substrates show mixed kinetic behavior and trineopentyltin bromide behaves according to the second-order, bromide ion independent term.

The bromide ion dependent, third-order term is envisioned to occur via bromine attack on a trialkyltin bromide–bromide ion complex (eq 8 and 9). (Tri-

$$Np_2SnRBr + Br^- \rightleftharpoons [Np_2SnR(Br)_2]^- \quad (8)$$

$$[Np_2SnR(Br)_2]^- + Br_2 \rightarrow RBr + [Np_2SnBr_2] + Br^- \quad (9)$$

alkyltin halides have been found to exhibit Lewis acidity unlike tetraalkyltin compounds.)[36] The primary alkyltin substrates seem to prefer this mode of reaction since steric hindrance to bromide ion complexation is minimal, whereas the trineopentyltin bromide molecule is too sterically congested for bromide ion complexation and therefore reacts via the second-order, bromide ion-independent term. The secondary systems are intermediate between the two and therefore exhibit mixed kinetic behavior.

Stereochemistry. In order to determine the stereochemistry associated with each term the following experiments were performed. Optically active (butyl-*1-d*)dineopentyltin bromide was treated with bromine in methanol with added sodium bromide. The resulting 1-bromobutane-*1-d* was formed with 68% net inversion. Since the kinetics for the primary substrates are dominated by a bromide ion dependent, third-order term, this process is assigned inversion stereochemistry. *sec*-Butyldineopentyltin bromide was treated with bromine in methanol with no added bromide ion and,

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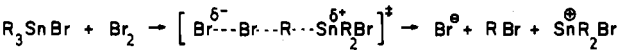

Figure 4.

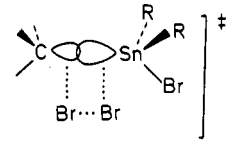

Figure 5. Retention mechanism for trialkyltin halides.

in the presence of an appropriate free radical inhibitor, 2-bromobutane was formed with 75% retention of configuration. Therefore the bromide ion independent, second-order term is tentatively assigned retention stereochemistry.

If the second-order term is associated with a retention mechanism and the third-order, bromide ion dependent term with an inversion mechanism, it would be expected that an increase in bromide ion concentration would increase the relative rate of the inversion pathway. This hypothesis was tested by observing the stereochemistry of the bromination of optically active *sec*-butyldineopentyltin bromide in methanol as a function of bromide ion concentration. The results are presented in Table V.

Increased bromide ion concentration did decrease the amount of retention stereochemistry. Presumably this is a result of increasing the relative rate of the inversion pathway, but this cannot be stated with absolute certainty since net inversion stereochemistry is never realized. (The results can be interpreted in terms of a *decrease* in the rate of the retention pathway with competitive radical reactions decreasing the optical yields.)

Due to the sluggish nature of these reactions, dineopentyltin dibromide was added to simulate the later stages of the reaction. The net retention increases with added Np_2SnBr_2. This result is not surprising. Since the dibromide is a stronger Lewis acid than the monobromide, the bromide ion is tied up with it rather than the monobromo starting material. Thus, the rate of the bromide ion dependent, inversion pathway is decreased.

Intuitively the assignment of inversion for the third-order term and retention for the second-order term is not unreasonable. In the absence of bromide ion, one of the immediate products of the inversion mechanism is the dialkyltin bromide cation (Figure 4). Due to the inductive effect of the bromine atom this species would be unstable. The retention pathway would yield neutral products and should be energetically more accessible (Figure 5). In the presence of bromide ion, the tin substrate could react via an organotin–bromide ion complex, allowing the immediate tin product to be neutral.

The extent to which the reaction occurs through the organotin–bromide ion complex would be a function of the equilibrium constant for the complexation. Steric congestion on tin would decrease the equilibrium constant and cause the reaction to proceed predominantly through the retention pathway. This is undoubtedly the case for the trineopentyltin bromide reactions. The primary carbon substrates would exhibit less steric hindrance to complexation and therefore react almost exclusively through the organotin–bromide ion complex.

Also, with tetraalkyltins, it was earlier found that primary centers have a definite preference to react via an inversion pathway. Secondary substrates can react by either mechanism but apparently favor retention pathways.

Concluding Remarks

Based primarily on the work on S_E2 reactions at carbon–mercury bonds,[2] it became generally accepted, even in textbooks, that at noncarbanionic centers S_E2 reactions occur via retention of configuration at carbon.

In an attempt to acertain whether these conclusions may be generalized, a nonbiased system which would encourage inversion and discourage retention of configuration on carbon was developed.

Systems which are heavily biased for retention are expected to occur via four-centered transition states that require the availability of low-lying, vacant orbitals on the metal center. Tetraalkyltin compounds, which to our knowledge show no Lewis acid character, were therefore selected. Bulky, electron-donating groups on tin were expected to favor the inversion pathway as would polar solvents. Substitution at the reacting carbon also was expected to play a significant role; secondary centers might react equally well via retention or inversion mechanisms in polar solvents, whereas primary centers were expected to prefer inversion. The electrophile might also play an important role in the eventual stereochemistry of the S_E2 process. All of these expectations were found to hold.

Further studies in which the electronic and steric properties of the tin leaving group were varied, indicated that the energy difference between the retention and inversion pathways is small and can be easily manipulated. As the steric "bulk" of the tin leaving group is increased, the reaction proceeds increasingly through the inversion mechanism, presumably due to either shielding to frontside attack, required in retention pathways, or back-strain in the trialkyltin leaving group.

Trialkyltin bromides react much slower with bromine (with added bromide ion in methanol) than do tetraalkyltin compounds. Also, in contrast to tetraalkyltin compounds that exhibit second-order kinetics (rate = $k_2[Br_2][R_4Sn]$), they react by mixed second- and third-order kinetics; the third-order term contains the concentration of bromide ion. The third-order term dominates with primary alkyl compounds and occurs with inversion of configuration on carbon. The second-order term dominates with compounds such as trineopentyltin bromide and likely occurs with retention of configuration. With secondary systems both terms are important. The third-order term becomes more important with increased bromide ion concentration, and accordingly the amount of inversion increases.

As expected, solvent plays an important role in the mechanism of halogen cleavage of tetraalkyltins. Nonpolar solvents favor retention mechanisms where no separation of charge is necessary. In polar solvents the inversion mechanism can compete with and, at times, predominates over retention pathways.

The nature of the electrophile also plays a significant role in the stereochemistry of S_E2 reactions. These effects are fairly complicated and no generalizations can be easily made.

In any event, it is clear that the "overall" mechanism of S_E2 processes can be manipulated in a fairly predictable way, provided no inherent mechanistic bias is present. Organotins represent a group of compounds which demonstrate this; changes in substrate, electrophile, and media can dramatically change the preferred mechanism of cleavage since there is no general, single reaction pathway.

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