Regiospecific No-Carrier-Added Radiobromination and Radioiodination of Aryltrimethyl Group IVb Organometallics [1]

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A series of *para*-substituted aryltrimethyl-silicon, -germanium, and -tin compounds were treated at room temperature with no-carrier-added (n.c.a.) ^{77}Br and ^{131}I to compare their utility as substrates for regiospecific aromatic halogenation. Dichloramine-T was used as an *in situ* oxidant in acidic, polar, or non-polar reaction solvents. N.c.a. aromatic halodemetallation was regiospecific for all substrates, radiochemical yields were generally higher for ^{131}I than ^{77}Br, and halogenation yields increased as Si < Ge < Sn. Arguments are presented for a substitution mechanism involving a σ-complex intermediate with bond formation as the yield-determining step. Although high yields were obtained for the n.c.a. aromatic halogenodestannylations irrespective of aromatic substituent or solvent, significant chlorination occurred as a side-reaction. N.c.a. aromatic halogenodegermylation produced high radiochemical yields with insignificant chlorination, but the radiohalogenation yields were sensitive to ring deactivation and solvent effects. N.c.a. aromatic halogenodesilylation gave high yields only in activated aromatic systems. The relative benefits of each demetallation reaction for regiospecific n.c.a. radiolabelling or preparative halogenation of aromatic rings are outlined.

The increasing sophistication of nuclear medicine techniques has presented challenges to the synthetic chemist involved in the preparation of imaging agents labelled with such radionuclides as ^{75}Br (β^+, $t_{1/2}$ = 1.6 h), ^{77}Br (239, 521 keV γ, $t_{1/2}$ = 56 h), or ^{123}I (159 keV γ, $t_{1/2}$ = 13.2 h) (for reviews see references 2—4). Aside from structural constraints which require that the radiohalide be introduced at a specific molecular site,[5] the radiolabelling technique should be rapid and result in the radiohalogenated product with high radiochemical yield and high specific activity.

One of the approaches to this synthetic problem is to use metallated arenes as substrates for regiospecific electrophilic aromatic halogenation. Several organometallic reagents have been employed in this manner (for a review see reference 6), and reports concerning the application of the aryltrialkyl group IVb metals have recently appeared. Bromodesilylation[7] and iododestannylation[8–10] have been used for radiopharmaceutical production, and systematic studies of no-carrier-added (n.c.a.) electrophilic aromatic halogenodesilylation,[11,12] halogenodegermylation,[13] and bromodestannylation[14,15] have been performed. Unfortunately, conclusions concerning the relative advantages or disadvantages of group IVb organometallic compounds as halogenation substrates are not possible from these studies owing to the differences in reaction conditions which were employed.

This work consists of a systematic comparison of the reactivity of *in situ* oxidized radiobromine (^{77}Br) and radioiodine (^{131}I) with simple aryltrialkyl compounds of silicon, germanium, and tin. The organic-soluble *N,N*-dichloramine-T (DCT)[16] was used as an oxidizing agent, so the reactions could be performed in a homogeneous reaction environment using a variety of solvents. Simple *para*-substituted aryltrimethyl group IVb organometallic compounds were used as halogenation substrates to focus on the reactivity of the aromatic carbon–group IVb metal bond and to minimize side-reactions. Identical reaction conditions were used with each organometallic compound, so that trends in the reactivity of the group IVb elements should not be masked by extraneous factors.

In this paper the preparative aspects of n.c.a. electrophilic aromatic halodemetallation have been emphasized to allow direct application of the results to radiopharmaceutical production. However, since radiohalides act as tracers for macroscopic halide, the results of these aromatic halogenation techniques are also germane to classical synthetic chemistry. Finally, general conclusions concerning the reactivity of these metallated arenes with halogen electrophiles should be of broad interest to organometallic chemists.

Results and Discussion

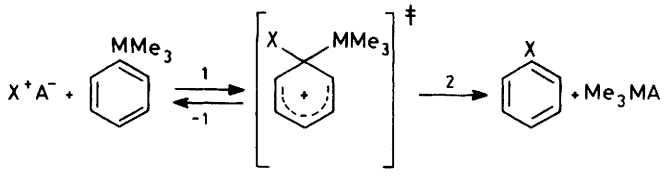
Effect of Metal and Solvent Acidity.—Table 1 shows the radiochemical yields for n.c.a. radiobromination of phenyltrimethyl group IVb metals in methanol and glacial acetic acid. In this table, as well as those later to be discussed, a 30 min reaction period was used because it is convenient for radiopharmaceutical production and synthetic procedures. Moreover, previous investigations using organogermanium[13] and organotin[14,15] substrates have indicated that the halogenodemetallation reactions reach completion in 30 min, and therefore the radiochemical yields which are reported represent thermodynamic equilibrium values.

For both bromine and iodine, the radiochemical yields of aryl halide shown in Table 1 increase in the order Si < Ge < Sn.

Table 1. No-carrier-added (N.c.a.) halogenodemetallation of Ph-M(Me)$_3$ in methanol and glacial acetic acid.[a]

Solvent	M	Radiochemical yield (%)[b] Ph ^{77}Br	Ph ^{131}I
MeOH	Si	4.1 ± 0.8	1.4 ± 0.3
	Ge	24.8 ± 0.4	85.5 ± 0.3
	Sn	74.0 ± 3.6	93.4 ± 2.9
$MeCO_2H$	Si	5.9 ± 1.1	7.7 ± 2.2
	Ge	45.7 ± 0.6	88.0 ± 1.8
	Sn	79.3 ± 2.4	94.0 ± 1.2

[a] Reaction conditions: 100 μCi dry $^{77}Br^-$ (50 μCi $^{131}I^-$), 10 μl PhM(Me)$_3$, 5 mg dichloramine-T, 1 ml solvent, 25 °C, 30 min. [b] Percentage of total radioactivity in solution; values represent the mean and range of 2—4 experiments.



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Scheme 1.

Table 2. Enthalpy changes for the halogenodemetallation reaction

$$XCl + Ph\text{-}M(Me)_3 \longrightarrow Ph\text{-}X + (Me)_3MCl$$

X	M	$\Delta H°$/kJ mol^{-1} [a]
Br	Si	−62.8
	Ge	−128.0
	Sn	−157.7
I	Si	−20.9
	Ge	−86.2
	Sn	−115.9

[a] Calculated using the bond dissociation energies given in references 18, 20, and 21.

This sequence of yield values supports the mechanism involving a σ-complex intermediate (**I**, Scheme 1) previously suggested for electrophilic aromatic desilylation.[17] While the electronegativities (and therefore the carbon-metal bond polarities) for the three metals are equal (E.N. = 1.90),[18] the calculated[18,19] carbon–metal bond lengths increase in the same order as the aromatic halogenation yields (Si:Ge:Sn = 1.31 Å:1.36 Å:1.54 Å). Thus, electrophilic attack at the *ipso* carbon (step 1, Scheme 1) is favoured from steric considerations as one proceeds down the group IVb column. In addition, the decreasing aromatic carbon–metal bond energies (Si:Ge:Sn = 352 kJ/mol:308 kJ/mol:257 kJ/mol)[20] increasingly favour step 2 over step −1 (and completion of the metal substitution reaction) as M varies from silicon to germanium to tin. The relative aromatic halogenodemetallation yields shown in Table 1 are therefore expected, regardless of whether formation or decomposition of the σ-complex intermediate is the rate-limiting step of the substitution reaction.

Examination of the enthalpy changes involved in the demetallation reactions shown in Table 2 indicates the rank order of halogenation yields in glacial acetic acid which would be expected if bond-breakage (step 2 of Scheme 1) were the rate-limiting step. Note that XCl can be used as the halogenating species in the calculations for this solvent; in solvents of low acidity this cannot be assumed due to the formation of *N*-halogenated intermediates.[22–24] Although it appears that the enthalpy changes in Table 2 correlate well with the yield values shown in Table 1 for glacial acetic acid, the fact that aromatic iododemetallation occurs more readily than bromodemetallation conflicts with the thermodynamic calculations. In addition, if bond-breakage were the yield-determining step of Scheme 1, one would expect on the basis of bond energies and statistical probability that alkyl substitution to form methyl halides would be a significant competitive reaction pathway. For example, the calculated enthalpy changes for the substitution of methyl groups from phenyltrimethyltin to form methyl halides are −168.6 kJ/mol for bromine and −115.9 kJ/mol for iodine. Because both of these $\Delta H°$ values are as exothermic as those shown in Table 2 for aromatic substitution, it can be inferred that step 2 is not the yield-determining step of Scheme 1. It was previously suggested that the σ-complex of electrophilic aromatic substitution of group IVb metals was stabilized by σ-π conjugative electron release from the C–M bond in the rank order Si < Ge < Sn, with bond formation the rate-limiting step.[17] This explanation also seems to apply to the results in Table 1.

The relatively higher yields obtained from iododemetallation relative to bromodemetallation were earlier attributed to the relative ease of the pH-dependent reduction of electrophilic bromine species and to the relative instability of BrCl species.[13] This conclusion is supported by the results in Table 1. Based on the relative rates for aromatic protodemetallation (Si:Ge:Sn = 1:36:3.5 × 10^5)[25] and on the high n.c.a. halogenation yields obtained in glacial acetic acid in the presence of competitive protodestannylation, the rates for electrophilic aromatic halodestannylation are expected to be very rapid. Competitive reduction of oxidized bromine species can therefore be expected to play a minor role in the reaction scheme, and the yields of bromobenzene or iodobenzene are not increased by the shift from a neutral (methanol) to a mildly acidic (acetic acid) reaction environment. By contrast, the slower kinetics of bromodegermylation makes competitive reduction a significant side-reaction, as indicated by the higher aromatic halogenation yields obtained when using glacial acetic acid as a reaction medium. The kinetics of aromatic desilylation are apparently so slow that halogenation yields remain low in glacial acetic acid, although increased bromination and iodination can be seen in the more acidic reaction solvent.

Effect of Water. Investigating the effect of water on n.c.a. electrophilic aromatic halodemetallation gives mechanistic insight as well as practical information on these halogenation reactions. Increasing the concentration of water in the reaction solvent increases the probability of competitive redox reactions of electrophilic halogenation species involved in the demetallation reaction, and these influences can thereby be studied. From the practical viewpoint, high radiochemical yields obtained in the presence of water are technical advantages in preparing radiopharmaceuticals with short-lived ^{75}Br ($t_{1/2}$ = 1.6 h), since the time required for drying the radionuclide solution is eliminated. Avoidance of the necessity of drying aqueous radioiodide solutions is also useful, owing to the volatile nature of iodide and its tendency to oxidize when heated.

Figure 1 shows the effect of water on the yields of aryl halide obtained from n.c.a. aromatic bromo- and iodo-destannylation

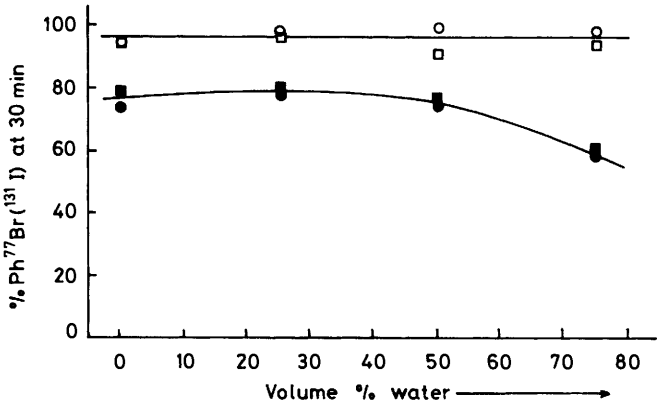


Figure 1. Effect of water on the n.c.a. halogenodestannylation of phenyltrimethyltin in methanol and glacial acetic acid: ^{77}Br, filled symbols; ^{131}I, empty symbols. ○ and ●, methanol; □ and ■, glacial acetic acid.

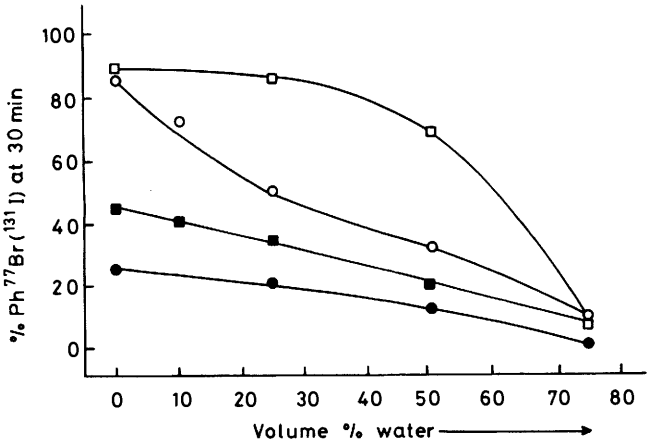


Figure 2. Effect of water on the n.c.a. halogenodegermylation of phenyltrimethylgermanium in methanol and glacial acetic acid: ^{77}Br, filled symbols; ^{131}I, empty symbols. ○ and ●, methanol; □ and ■, glacial acetic acid.

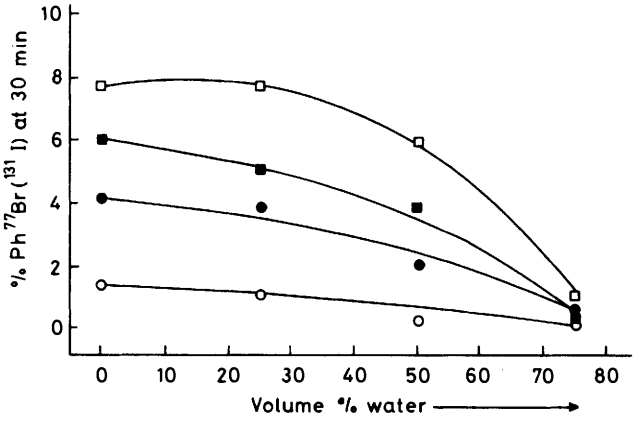


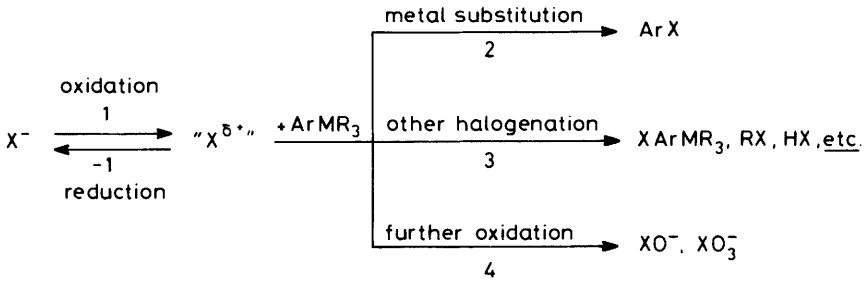
Figure 3. Effect of water on the n.c.a. halogenodesilylation of phenyltrimethylsilicon in methanol and glacial acetic acid: ^{77}Br, filled symbols; ^{131}I, empty symbols. ○ and ●, methanol; □ and ■, glacial acetic acid.

of phenyltrimethyltin in glacial acetic acid and methanol. As discussed above, the kinetics of destannylation are so rapid that there is no difference in substitution yields in acetic acid or methanol, and the iodination and bromination yields are represented by single curves for both solvent types. Aromatic iododestannylation is independent of water content, as is aromatic bromodestannylation up to *ca.* 50 vol% water. When the reaction solvent consists of greater than 50% water, there is a slight decrease in the yield of bromobenzene. This may be attributed to competitive reduction of electrophilic bromination species by the higher concentrations of water.

The yields of bromobenzene and iodobenzene obtained *via* n.c.a. aromatic halogenodegermylation under the identical solvent conditions as above are illustrated in Figure 2. In contrast to halogenodestannylation, addition of water to the reaction solvent rapidly decreases the aromatic halogenodegermylation yield. This is reasonable based on the relatively slower kinetics for substitution of germanium from aromatic rings,[25] which makes possible alternative reaction pathways, such as oxidation of water by electrophilic halogen species.[13] The redox potential for water oxidation is reduced at lower pH values, which explains the relatively high concentrations of water which are tolerated when glacial acetic acid is used as the reaction solvent. This acid suppression of water oxidation is stronger for iodine than for bromine owing to the relatively low reduction potential of the former, which makes redox reactions with water less favoured.[13] N.c.a. iododegermylation yields of 70% are achieved with up to 50 vol% water in acetic acid, whereas n.c.a. bromodegermylation yields of 40% can be achieved with 10 vol% water in acetic acid.

Similar effects are also seen for n.c.a. electrophilic aromatic halogenodesilylation in aqueous acetic acid and methanol (Figure 3). In this case, the kinetics are even slower than for aromatic halogenodegermylation, and low yields of aryl halide are obtained. However, the effect of acid enhancement of yields *via* suppression of competitive reduction of electrophilic halogen species by solvent water is clearly illustrated.

General Reaction Considerations Concerning Electrophilic Aromatic Halogenodemetallation. Drawing upon the above results, the reactivity of *in situ* oxidized halogen electrophiles with aryltrimethyl-silicon, -germanium, and -tin can be represented by the idealized Scheme 2. *In situ* oxidation of bromide and iodide to form the electrophilic halogenation species '$X^{\delta+}$' (step 1) occurs in competition with solvent reduction (step −1). As suggested earlier, step −1 can be suppressed by lowering the solvent pH.[13] The electrophilic halogenation species can react further *via* aromatic metal substitution (path 2), halogenation of alternative sites of the organometallic substrate (path 3), or undergo further oxidation (path 4). In this investigation, reaction pathway 3 has been minimized by the use of simple *para*-substituted aryltrimethyl group IVb compounds lacking reactive functional groups. Pathway 4 can be effectively retarded only by the occurrence of relatively rapid kinetics in competitive metal substitution pathway 2. The rate for reaction pathway 2 is influenced by three chemical parameters: the metal atom being substituted, the aromatic substituent located *para* to the metal moiety, and the solvent. As explained above, the choice of metal has a strong effect because of differences in steric hindrance to attack and hyperconjugative stabilization of the σ-complex involved.[17] Electron-donating substituents *para* to the aromatic carbon-



Scheme 2.

Table 3. Radiochemical yields for regiospecific n.c.a. halogenodestannylation of *para*-substituted phenyltrimethyltin compounds[a]

$$p\text{-G-C}_6\text{H}_4\text{-Sn(Me)}_3 \longrightarrow p\text{-G-C}_6\text{H}_4\text{-}^{77}\text{Br}(^{131}\text{I})$$

Solvent	G	Radiochemical yield (%)[b] ^{77}Br	^{131}I
$MeCO_2H$	OMe	80.1 ± 2.2	92.9 ± 3.0
	Me	79.5 ± 1.0	96.9 ± 2.4
	F	81.0 ± 1.1	95.9 ± 1.5
	H	79.3 ± 2.4	94.0 ± 1.2
	Br	76.3 ± 2.1	89.6 ± 1.7
	CF_3	78.4 ± 1.6	92.5 ± 1.4
MeOH	OMe	86.8 ± 0.3	95.3 ± 1.4
	Me	75.0 ± 0.9	95.2 ± 4.5
	F	72.2 ± 1.0	97.3 ± 0.2
	H	74.0 ± 3.6	93.4 ± 2.9
	Br	71.0 ± 2.2	78.1 ± 2.1
	CF_3	79.3 ± 1.4	76.0 ± 1.5
CCl_4	OMe	92.8 ± 0.9	89.0 ± 2.6
	Me	94.1 ± 1.5	81.0 ± 3.0
	F	88.7 ± 1.7	94.1 ± 0.7
	H	85.1 ± 2.4	92.4 ± 1.1
	Br	78.1 ± 3.5	79.8 ± 1.0
	CF_3	82.7 ± 1.9	85.5 ± 2.6

[a] Reaction conditions: 100 μCi dry $^{77}Br^-$ or 50 μCi dry $^{131}I^-$, 10 μl $GC_6H_4SnMe_3$, 5 mg dichloramine-T, 1 ml solvent, 25 °C, reaction time 30 min. [b] As Table 1.

Table 4. Radiochemical yields for regiospecific n.c.a. halogenodegermylation of *para*-substituted phenyltrimethylgermanium compounds[a]

$$p\text{-G-C}_6\text{H}_4\text{-Ge(Me)}_3 \longrightarrow p\text{-G-C}_6\text{H}_4\text{-}^{77}\text{Br}(^{131}\text{I})$$

Solvent	G	Radiochemical yield (%)[b] ^{77}Br	^{131}I
$MeCO_2H$	OCH_3	67.6 ± 1.8	86.7 ± 2.6
	CH_3	54.1 ± 0.4	85.2 ± 0.3
	F	51.1 ± 1.5	88.3 ± 1.1
	H	45.7 ± 0.6	78.6 ± 0.5
	Br	20.3 ± 0.1	59.1 ± 1.8
	CF_3	< 10%	13.3 ± 0.6
MeOH	OCH_3	53.4 ± 2.1	95.4 ± 0.8
	CH_3	38.8 ± 1.4	86.6 ± 2.2
	F	35.3 ± 0.8	85.6 ± 0.1
	H	24.8 ± 0.4	85.5 ± 0.3
	Br	< 10%	35.4 ± 0.2
	CF_3	< 10%	15.6 ± 0.3
CCl_4	OCH_3	59.7 ± 1.9	76.6 ± 3.1
	CH_3	28.3 ± 2.0	63.2 ± 2.1
	F	21.2 ± 1.3	53.0 ± 3.6
	H	12.2 ± 0.7	42.0 ± 1.9
	Br	< 10%	12.2 ± 1.4

[a] Reaction conditions: 100 μCi dry $^{77}Br^-$ or 50 μCi dry $^{131}I^-$, 10 μl $GC_6H_4GeMe_3$, 5 mg dichloramine-T, 1 ml solvent, 25 °C, reaction time 30 min. [b] As Table 1.

Table 5. Radiochemical yields for regiospecific n.c.a. halogenodesilylation of *para*-substituted phenyltrimethylsilicon compounds[a]

$$p\text{-G-C}_6\text{H}_4\text{-Si(Me)}_3 \longrightarrow p\text{-G-C}_6\text{H}_4\text{-}^{77}\text{Br}(^{131}\text{I})$$

Solvent	G	Radiochemical yield (%)[b] ^{77}Br	^{131}I
$MeCO_2H$	OMe	60.2 ± 3.4	75.3 ± 3.7
	Me	29.8 ± 0.9	14.9 ± 4.0
	F	18.6 ± 1.7	< 10%
MeOH	OMe	66.5 ± 3.1	83.2 ± 4.1
	Me	27.8 ± 2.0	< 10%
	F	18.0 ± 1.6	< 10%
CCl_4	OMe	51.8 ± 3.2	16.7 ± 0.7

[a] Reaction conditions: 100 μCi dry $^{77}Br^-$ or 50 μCi dry $^{131}I^-$, 10 μl $GC_6H_4SiMe_3$, 50 mg dichloramine-T, 1 ml solvent, 25 °C, reaction time 30 min. [b] As Table 1.

metal bond can lower the energy of the transition state for this intermediate (Scheme 1) and thereby enhance reaction rates. Similarly, because the intermediate σ-complex is a charge-separated structure, the energy of its transition state can be decreased by the use of polar solvents.

Regiospecific N.c.a. Halogenodemetallation of Substituted Aryltrimethyl Group IVb Compounds. The influence of metal, aromatic substituent, and solvent on n.c.a. electrophilic aromatic halogenodemetallation of *para*-substituted phenyltrimethyl-tin, -germanium, and silicon is reported in Tables 3—5. For all three metals, organometallic compounds containing phenyl rings substituted with groups G = OMe, Me, F, H, Br, and CF_3 were used as halogenation substrates to show the effect of electron donation and withdrawal on the metal substitution yields with n.c.a. ^{77}Br and ^{131}I. For brevity and to underline the practical utility of the demetallation reactions for radiolabelling or preparative halogenation, only yields which exceeded 10% are reported. In all substrates tested, n.c.a. electrophilic aromatic halo-destannylation, -degermylation, and -desilylation proceeded in a regiospecific manner with greater than 97% of the aromatic halogenation occurring at the *para* position (*cf.* reference 13). Therefore, for conciseness only the *para*-substitution yields are reported in Tables 3—5. The n.c.a. radiobromination and radioiodination reactions were performed in glacial acetic acid, methanol, and carbon tetrachloride to illustrate the effects of an acidic, polar, and non-polar solvent on the progress of electrophilic aromatic halogenodemetallation.

As Table 3 indicates, the aromatic substitution of tin by electrophilic bromine and iodine species occurs so readily that there is very little influence of aromatic substituent or solvent on the outcome of the reaction. For both ^{77}Br and ^{131}I, halogenation yields exceed 70% in all three solvent types with aromatic systems both activated and deactivated toward electrophiles. This ready cleavage of aryl carbon–tin bonds by electrophilic halogen species makes aromatic halogenodestannylation impervious to external chemical effects, both intra- and extra-molecular, and therefore a useful preparative aromatic halogenation technique.

The relatively greater steric hindrance and smaller hyperconjugative stabilization of the transition state by germanium make its substitution kinetics slower and more susceptible to chemical manipulation, such as aromatic substituent and solvent effects. This is seen in Table 4, which reports the aromatic halogenodegermylation yields using n.c.a. ^{77}Br and ^{131}I. The aromatic iodination yields exceed those of bromination, probably owing to competitive reduction pathways.[13] N.c.a. electrophilic aromatic bromodegermylation is enhanced by reaction in an acidic environment, *via* suppression of competitive reduction, and is decreased by reaction in a nonpolar environment owing to lack of stabilization of the

reaction intermediate. Electron-donating substituents increase the aromatic halogenation yields obtained with n.c.a. ^{77}Br and ^{131}I in all solvents *via* a decrease in the energy of the transition state for intermediate **I** (Scheme 1). From the practical standpoint, electrophilic aromatic halogenodegermylation results in either high or reasonable yields of aryl halide depending on the degree of electronic activation or deactivation of the aromatic ring and on the reaction solvent which is employed. These effects are stronger on aromatic bromodegermylation than on aromatic iododegermylation.

The trend toward greater inertness is even more pronounced for electrophilic aromatic halogenodesilylation, as expected from the relatively small aromatic carbon–silicon bond length and σ-π conjugative electron release. As Table 4 indicates, high n.c.a. halogenation yields were obtained only in aromatic systems activated toward electrophiles by strongly electron-donating substituents (G = OMe). Lower aromatic substitution yields were also obtained in aromatic systems moderately activated toward electrophiles when the reaction was performed in acidic or polar solvents, but in no case was n.c.a. aromatic bromodesilylation or iododesilylation observed in non-activated or deactivated aromatic rings.

Chlorination Side-Reaction by Dichloramine-T. The use of *N*-chloroamines as oxidizing agents can also give rise to chlorinated side-products. For preparative synthetic applications this usually does not present a serious problem, because bromination and iodination occur faster than chlorination, and stoicheiometric excesses of bromide or iodide can be used. However, for radiopharmaceutical production using n.c.a. radiohalide, the concentration of chlorine in the reaction mixture is magnitudes of order greater than that of the radiohalide and chlorination can occur. This can give rise to unwanted chlorinated by-products which are difficult to separate chromatographically.

The lability of the aromatic carbon–tin bond in this case is a liability. As Figure 4 illustrates, chlorination of phenyltrimethyltin by 1 equiv. of dichloramine-T occurs as a side-reaction in acidic, polar, and non-polar solvents. For a reaction period of 30 min, chlorobenzene was obtained with a yield of 71, 52, and 14% in methanol, glacial acetic acid, and carbon tetrachloride, respectively. By contrast, the yield for chlorodegermylation of phenyltrimethylgermanium was only 3.4% after reaction for 30 min in glacial acetic acid. The yield for aromatic chlorodegermylation in methanol or carbon tetrachloride, or for aromatic chlorodesilylation in all three solvents, was less than 1% after 30 min. As Figure 4 demonstrates, chlorinated products could not be avoided when using dichloramine-T with phenyltrimethyltin for shorter reaction periods, since significant chlorination yields were obtained even after a reaction time of 1 min.

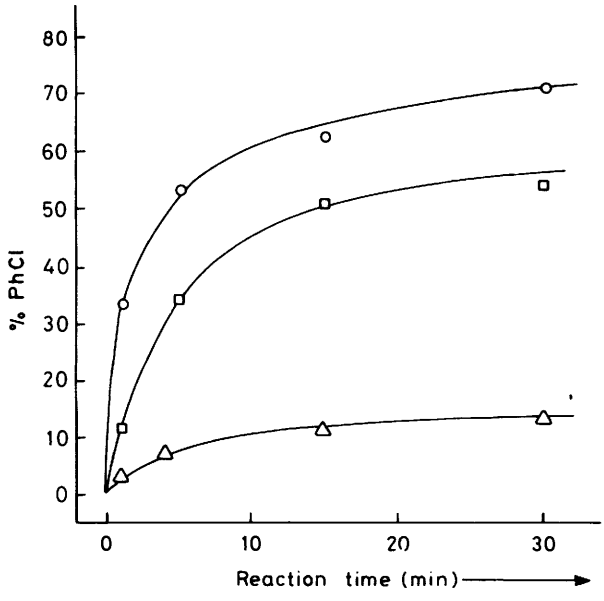


Figure 4. Chlorodestannylation of phenyltrimethyltin by dichloramine-T in various solvents: ○, methanol; □, glacial acetic acid; △, carbon tetrachloride.

Conclusions.—This work has compared the reactivity of aryltrimethyl group IVb organometallics with n.c.a. radiobromide and radioiodide oxidized *in situ* using *N,N*-dichloroamine-T. For both n.c.a. electrophilic aromatic bromodemetallation and iodometallation, the aromatic halogenation yields were found to increase in the order Si < Ge < Sn. Arguments were presented to support the hypothesis[17] that aromatic halogenodemetallation proceeds *via* a σ-complex with bond formation as the rate-limiting step.

From the relatively higher aromatic demetallation yields obtained for radioiodine relative to radiobromine, and the effect of water on the yields of aryl halide obtained, it was concluded that the rate of aromatic halogeno demetallation decreases in the sequence Sn > Ge > Si. The influences of metal, aromatic substituent, and solvent acidity and polarity on the rate of aromatic halogenodemetallation were outlined.

These effects were illustrated by the regiospecific electrophilic halogenodemetallation reactions of substituted aryltrimethyl group IVb organometallics with n.c.a. ^{77}Br and ^{131}I in acidic, polar, and non-polar solvents. Organotin compounds gave high aromatic halogenation yields regardless of halogen, solvent, or degree of electronic activation. Organogermanium compounds were found to be chemically more interesting, since aromatic halogenodegermylation results in high aromatic halogenation yields yet is sensitive to the type of halogen electrophile, aromatic substituents, and solvent acidity and polarity. Organosilicon compounds were relatively inert, requiring aromatic ring activation as well as acidic polar reaction media to give high aromatic halogenation yields.

From the context of practical applications of electrophilic aromatic halogenodemetallation to regiospecific halogenation in synthetic or radiosynthetic schemes, it can be concluded that halogenodestannylation reactions show the greatest versatility with respect to reaction conditions. However, the high reactivity of aromatic carbon–tin bonds presents problems such as instability of halogenation substrates and chlorination side-products when preparing radiopharmaceuticals. No-carrier-added aromatic halogenodegermylation is preferable to halogenodestannylation when using *N*-chloramines as oxidants owing to the low yield of aryl chloride produced. Use of the aromatic halogenodegermylation reaction results in very high iodination yields, and moderately high bromination yields, even in deactivated aromatic systems. Aryltrimethylsilicon precursors are more inert to halogenodemetallation, and consequently require more forcing reaction conditions. However, for activated aromatic systems aromatic halogenodesilylation gives useful halogenation yields, and arylsilanes share with arylgermanium compounds the advantages of greater chemical stability, resistance to chlorination, and lower toxicity than aryltrimethyltin compounds.

Experimental

Reagents.—*ortho-*,*meta-*, and *para*-Isomers of the arenes shown in Tables 3—5 were purchased in 98—99% purity from

EGA Chemie (Steinheim, FRG) for use as reference compounds in the g.c. analysis of reaction products. *para*-Substituted aryltrimethylsilicon, -germanium, and -tin compounds were synthesized *via* the Grignard compound of the corresponding *para*-brominated arene, purified by fractionation and chemically characterized.[26] Chloramine-T was purchased from E. Merck (Darmstadt) in analytical quality, and was used for the synthesis of dichloramine-T.[27] All solvents used in this investigation were of analytical grade and were obtained from E. Merck (Darmstadt).

Radioisotopes.—The ^{77}Br used in these experiments was produced *via* the $^{75}As(\alpha,2n)^{75}Br$ reaction using the Jülich CV-28 compact cyclotron, removed from the target material using a dry distillation technique, and dissolved as n.c.a. radiobromide in triply distilled water.[28,29] The ^{131}I used in these investigations was purchased from Amersham-Buchler (Braunschweig, FRG) with a specific activity of 5—15 Ci/mg NaI (33—100 Ci/mmol) in phosphate-buffered (pH 6.9—7.5) physiological saline solution.

Radiohalogenation Experiments.—All radiohalogenation procedures were carried out in tightly sealed 2 ml glass reaction vessels containing a magnetic stir bar. Prior to beginning each reaction, 50—100 μCi (20 μl) $^{77}Br^-$ solution or 25—50 μCi (5 μl) $^{131}I^-$ solution was dried completely in the reaction vessel.

The general labelling sequence used for the n.c.a. halodemetallation reactions was to place the aryltrimethyl group IVb compound (10 μl) into the reaction vessel and add the reaction solvent (1 ml), followed by dichloramine-T (5 mg) while stirring. For the data reported in Figures 1—3, the aqueous solutions of acetic acid and methanol were prepared immediately before addition to the reaction vessel.

Following a pre-determined reaction time, each reaction was quenched by pouring the vessel contents into 10% aqueous sodium hydrogen sulphite (5 ml). The organic products were extracted into chloroform solution of the respective halogenated standards (1 μl/ml; 5 ml), and the organic layer was removed and dried ($CaCl_2$). Aliquots of each phase were removed and the radioactivity content was measured in a well type γ-scintillation counter to allow calculation of the % organic yield.

Analysis of the Radiohalogenated Reaction Products.—The organic reaction products in the chloroform phase (100 μl) were analysed by radio-gas chromatography using a discontinuous technique in which the eluted products were individually adsorbed on charcoal-filled tubes.[30] The isomeric brominated and iodinated analogues of α,α,α,-trifluorotoluene, bromobenzene, and benzene were separated using a 4 × 4 m column of 6% Bentone-38 and 20% silicon oil DC-200 on Chromosorb W-AW-DMCS (60—80 mesh),[31] while the isomers of brominated and iodinated anisole, toluene, and fluorobenzene were separated using a 4 × 4 m column of Igepal CO-880 on Chromosorb W-AW-DMCS (60—80 mesh).[32] The individual gas chromatographic fractions adsorbed on charcoal were counted with a well-type γ-scintillation counter. The radioactivity of the individual products was directly compared with that of the total radioactivity found in aliquots of the inorganic and organic phases, and the radiochemical yield of each product was calculated in terms of the percentage of total radioactivity in the reaction solvent. All experimental yields reported in this work represented the mean from 2—4 experiments.

Chlorination Experiments.—The above reaction procedure was used, with the exception that the radiohalide component was omitted. Dichloroamine-T (10 mg), the phenyltrimethyl group IVb compound (5μl), and solvent (1 ml) were allowed to react for a pre-determined period. The vessel contents were then removed and the reaction quenched by extraction [10% $NaHSO_3$ (5 ml); $CHCl_3$ (5 ml)]. Aliquots (100 μl) of the organic phase were analysed by gas chromatography (4 × 4 m Igepal CO-880 on Chromosorb W-AW-DMCS 60—80 mesh). The stoicheiometric yields of chlorobenzene were then calculated for each experiment on the basis of the gas chromatograph's thermoconductivity detector response using a calibrated mass-TCD response curve.

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References

1 Presented in part at the Fifth International Symposium on Radiopharmaceutical Chemistry, Tokyo, July 9—13, 1984. See *J. Labelled Comp. Radiopharm.*, 1984, **21**, 1076.
2 S. M. Qaim and G. Stöcklin, *Radiochim. Acta*, 1983, **34**, 25.
3 G. Stöcklin and G. Kloster, in 'Computer Emission Tomography,' eds. P. J. Ell and B. L. Holman, Oxford University Press, Oxford, 1982, p. 299.
4 R. H. Seevers and R. E. Counsell, *Chem. Rev.*, 1982, **82**, 575.
5 'Radiopharmaceuticals: Structure-Activity Relationships,' ed. R. P. Spencer, Grune and Stratton, New York, 1980.
6 H. H. Coenen, S. M. Moerlein, and G. Stöcklin, *Radiochim. Acta*, 1983, **34**, 47.
7 D. S. Wilbur and Z. V. Svitra, *J. Labelled Comp. Radiopharm.*, 1984, **27**, 415.
8 D. E. Seitz, G. L. Tonnesen, S. Hellman, R. N. Hanson, and S. J. Adelstein, *J. Organomet. Chem.*, 1980, 186, C33.
9 G. L. Tonnesen, R. N. Hanson, and D. E. Seitz, *Int. J. Appl. Radiat. Isot.*, 1981, **32**, 171.
10 R. N. Hanson, J. B. Blumberg, Z. M. Poddubiuk, M. A. Davis, and B. L. Holman, *Int. J. Appl. Radiat. Isot.*, 1981, **32**, 429.
11 D. S. Wilbur, K. W. Anderson, W. E. Stone, and H. A. O'Brien, *J. Labelled Comp. Radiopharm.*, 1982, **19**, 1171.
12 D. S. Wilbur, W. E. Stone, and K. W. Anderson, *J. Org. Chem.*, 1983, **48**, 1542.
13 S. M. Moerlein, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1687.
14 M. J. Adam, T. J. Ruth, B. D. Pate, and L. D. Hall, *J. Chem. Soc., Chem. Commun.*, 1982, 625.
15 R. S. Coleman, R. H. Seevers, and A. M. Friedman, *J. Chem. Soc., Chem. Commun.*, 1982, 1276.
16 H. H. Coenen, G. Petzold, and G. Stöcklin, *J. Labelled Comp. Radiopharm.*, 1982, **19**, 1580.
17 C. Eaborn, *J. Organomet. Chem.*, 1975, **100**, 43.
18 'Lang's Handbook of Chemistry,' ed. J. A. Dean, McGraw-Hill, 12th edn., New York, 1979.
19 V. Shomaker and D. P. Stevenson, *J. Am. Chem. Soc.*, 1941, **63**, 37.
20 G. Pilcher and H. A. Skinner, in 'The Chemistry of the Metal-Carbon Bond,' eds. F. R. Hartley and S. Patai, John Wiley and Sons, New York, 1982, p. 43.
21 J. A. Kerr, in 'Handbook of Chemistry and Physics,' eds. R. C. Weast, M. J. Astle, and W. H. Beyer, C.R.C. Press, Boca Raton, Fla., 64th edn., 1983, p. F-176.
22 R. C. Montelaro and R. R. Rueckert, *Arch. Biochem. Biophys.*, 1977, **178**, 555.
23 R. C. Montelaro and R. R. Rueckert, *J. Gen. Virol.*, 1975, **29**, 127.
24 G. Petzold, JÜL-Report 1810, 'Untersuchungen zur elektrophilen Radiobromierung und -iodierung aromatischer Verbindungen mit N-Halogenverbindungen ohne Trägerzusatz,' Kernforschungsanlage Jülich, FRG, 1982.
25 C. Eaborn and K. C. Pande, *J. Chem. Soc.*, 1960, 1566.
26 S. M. Moerlein, unpublished results.

27 F. Munth, in 'Methoden der Organischen Chemie (Houben-Weyl),' ed. E. Müller, Thieme Verlag, Stuttgart, 4th edn., 1955, vol. 9, ch. 19.
28 G. Blessing, R. Weinreich, S. M. Qaim, and G. Stöcklin, *Int. J. Appl. Radiat. Isot.*, 1982, **33**, 333.
29 G. Blessing and S. M. Qaim, *Int. J. Appl. Radiat. Isot.*, 1984, **35**, 927.
30 G. Stöcklin and W. Tornau, *Radiochim. Acta*, 1966, **6**, 86.
31 E. J. Knust and M. Schüller, *J. Chromatogr.*, 1975, **114**, 207.
32 L. Vasáros, H.-J. Machulla, and W. Tornau, *J. Chromatogr.*, 1971, **62**, 458.

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