Regiospecific Incorporation of No-Carrier-Added Radiobromine and Radioiodine into Aromatic Rings via Halogenodegermylation

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A series of para-substituted aryltrimethylgermanium compounds have been used as model compounds with [77]Br and ^{131}I to assess the utility of no-carrier-added (n.c.a.) halogenodegermylation as a regiospecific halogenation method. With dichloramine-T as an oxidant, high radiochemical yields were rapidly obtained in both activated and deactivated ring systems using n.c.a. [131]I with a variety of solvents at 25 °C. Use of n.c.a. [77]Br resulted in high yields with activated systems in methanol at 25 °C, and with both activated and deactivated ring systems in the presence of acid or with warming. Halogenation was regiospecific in all cases. High yields, regiospecificity, rapid kinetics, and the low concentration of oxidant required make aromatic n.c.a. halogenodegermylation a useful method for labelling radiopharmaceuticals.

There is increasing interest in radiopharmaceuticals labelled with the halogen radionuclides [75]Br (β^+, $t_{\frac{1}{2}}$ 1.6 h), [77]Br (239, 521 keV γ, $t_{\frac{1}{2}}$ 56 h), [122]I (β^+, $t_{\frac{1}{2}}$ 3.6 min), and [123]I (159 keV γ, $t_{\frac{1}{2}}$ 13.2 h) (for reviews see references 1—5). In the radiohalogenation of many biomolecules, various synthetic requirements have often to be met. Thus, for example, structure–activity relationships may make it essential that the radiohalogen be incorporated at a specific molecular site to assure retention of pharmacological characteristics by the radiolabelled analogue.[6] In addition to this structural constraint, the radiohalogenation reaction should be rapid, not only for use with short-lived positron-emitting radionuclides, but also for convenient labelling with longer-lived radiohalides. Mild halogenation conditions should result in high radiochemical yields with minimal destruction of the substrate molecule; high specific activities are an additional prerequisite for receptor-binding radioligands[7] or pharmacologically potent compounds.

An approach to these problems is to employ halogenodemetallation reactions in which electrophilic radiohalogen species displace a labile metal moiety from an aromatic ring to yield an aryl halide. This technique has been employed using a variety of metals (for a review, see reference 8), and the use of Group IVB elements is particularly attractive due to the ease of synthesis and purification. Systematic studies using model compounds have shown the utility of aryltrimethylsilanes as substrates for regiospecific no-carrier-added (n.c.a.) aromatic halogenation,[9,10] and the successful application of aromatic bromodesilylation to radiopharmaceutical production has been reported.[11] Regiospecific n.c.a. aromatic iododestannylation has been employed for radiopharmaceutical preparation,[12–14] and publications concerning systematic investigations of n.c.a. aromatic bromodestannylation have recently appeared.[15,16] Like silicon and tin, germanium is a Group IVB element; whilst it has an identical electronegativity[17] to the former elements its bond energy,[18] covalent radius,[19] and lability to proton displacement from aromatic rings are intermediate.[20] Based on these favourable chemical properties, it was expected that aryltrimethylgermanium compounds would show useful, and perhaps unique, reactivity toward halogens. This work reports the results of systematic studies of n.c.a. electrophilic halogenodegermylation of simple model compounds with [77]Br and ^{131}I to assess the utility of this labelling method for regiospecific aromatic halogenation.
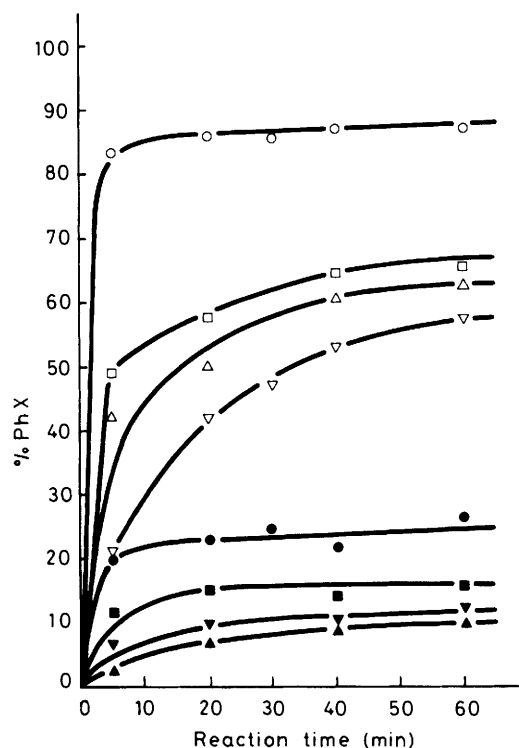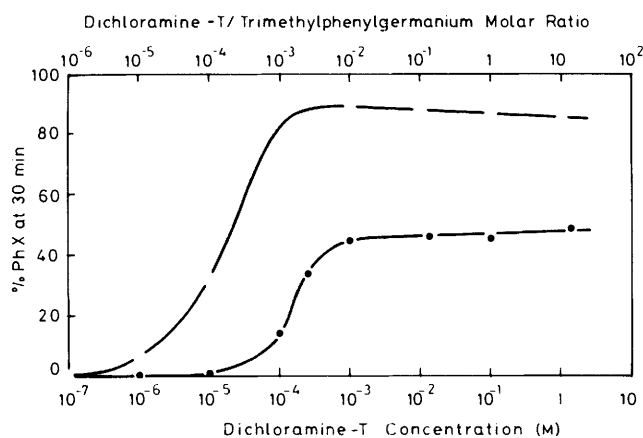

Figure 1. Aromatic n.c.a. halogenodegermylation yields from trimethylphenylgermanium as a function of time in various solvents. X = [77]Br or [131]I. [77]Br, filled symbols; ^{131}I, empty symbols. ○ and ●, Methanol: □ and ■, methylene chloride; △ and ▲, acetonitrile; ▽ and ▼, isopropyl alcohol

Results and Discussion

Effect of Solvent.—The effect of the reaction medium on the progress of n.c.a. bromo- and iodo-degermylation reactions using dichloramine-T[21] as an oxidizing agent with trimethylphenylgermanium at 25 °C is shown in Figure 1. These results show that with either radiobromine or radioiodine, n.c.a. halogenodegermylation occurs rapidly, the maximum product yield being attained within 10 min in most substrates. The

Table 1. Effect of temperature on the n.c.a. bromodegermylation of trimethylphenylgermanium in methanol

Temp. (°C)	Radiochemical yield at 30 min
25	24.8 ± 0.4
50	38.6 ± 0.6
75	44.2 ± 1.2
100	45.1 ± 2.5

Figure 2. Effect of dichloramine-T concentration on the n.c.a. halogenodegermylation of 0.1M-trimethylphenylgermanium in methanol. $X = {}^{77}Br$ or ${}^{131}I$. $\bigcirc$, ${}^{131}I$ (25 °C); $\bullet$, ${}^{77}Br$ (70 °C)

maximum product yield which is achieved, however, is strongly affected by the type of reaction solvent employed. This is illustrated by the wide spread of equilibrium values shown in Figure 1. Although no simple relationship between solvent characteristics and radiochemical yield was seen, it is notable that for both n.c.a. ${}^{77}Br$ and ${}^{131}I$, yields are higher for reactions in a hydrogen-bonding, high-dielectric constant solvent (methanol) compared with solvents which lack high dielectric constant (isopropyl alcohol), hydrogen-bonding capability (acetonitrile), or both (methylene chloride). This solvent effect may be due to a decrease in the energy of the transition states of the σ-complex intermediate hypothesized for halogenodemetallation reactions.[22,23]

Noteworthy in Figure 1 is the disparity between radiochemical yields with n.c.a. ${}^{77}Br$ and n.c.a. ${}^{131}I$. Although the radiobromination yields are relatively low using n.c.a. ${}^{77}Br^{-}$, they are still much higher than that obtained by direct n.c.a. electrophilic bromination of benzene.[24] Moreover, the bromodegermylation yields can be increased by heating the reaction mixture, as shown in Table 1. Radiochemical yields of *ca.* 45% were obtained after a reaction time of 30 min at 75 °C, which is of practical use since many compounds of radiopharmaceutical interest are resistant to such mild heating.

Effect of Dichloramine-T Concentration.—The relationship between the concentration of dichloramine-T oxidizing agent and the radiochemical yield of labelled bromobenzene or iodobenzene resulting from the n.c.a. halogenodegermylation of trimethylphenylgermanium in methanol is illustrated in Figure 2. Also shown in this figure are the relative dichloramine-T/ trimethylphenylgermanium molarities. High radioiodination yields were obtained with dichloramine-T concentrations as low as 10^{-4}M, and reasonable radiobromination yields with 10^{-3}M.

This corresponds to a dichloramine-T molarity which is only 0.1% of that of the organogermanium substrate for n.c.a. iodination; n.c.a. radiobromination requires a dichloramine-T/substrate molar ratio of only 1%. Owing to the low concentrations of oxidizing agent which are required, aromatic n.c.a. halogenodegermylation may be useful as a method for radiohalogenating oxidation-sensitive substrates.

Effect of pH; Differences between Bromination and Iodination.—Figure 3 illustrates the effect of pH on the n.c.a. halogenodegermylation yields from trimethylphenylgermanium in a reaction solvent consisting of methanol–water (3:1). Results are shown for ${}^{77}Br$ and ${}^{131}I$, using both dichloramine-T and chloramine-T as oxidizing agents. These curves demonstrate several important differences between radiobromination and radioiodination as well as differences arising from the use of dichloramine-T *versus* chloramine-T as an oxidant.

Considering the radiochemical yields which are obtained using dichloramine-T as an oxidizing agent, it is seen that for both ${}^{77}Br$ and ${}^{131}I$, n.c.a. halogenodegermylation proceeds well at low solvent pH, but as the pH is increased, there is a progressively lower radiochemical yield. This decrease in yield occurs faster for radiobromine than for radioiodine, the reaction with bromine essentially being quenched at pH 8, while high radiochemical yields for iodination are obtained even at pH 11. It has been suggested that radioiodination at low solvent pH values involves reactive ${}^{131}ICl$ species,[21,24] while in more basic media, N-iodo sulphonamides have been hypothesized as the reactive species.[21,24,25] Thus, the dichloramine-T iodo-degermylation yield curve in Figure 3 can be attributed to a composite of products resulting from the reaction of trimethylphenylgermanium with (i) ${}^{131}ICl$ to give the very high yields at low pH, with (ii) N-${}^{131}I$ sulphonamides to result in the relatively constant yields from pH 2—10, and (iii) at very basic values, quenching of the iododegermylation reaction due to the increased importance of the iodide–iodate couple at high pH.[26]

The above effects also apply to the bromodegermylation yields obtained using n.c.a. ${}^{77}Br^{-}$ and dichloramine-T, but besides the variation in the type of halogenation species induced by alteration in solvent acidity, there are in addition underlying electrochemical changes which are dependent on hydrogen ion concentration. Because electrophilic halogenation, regardless of the final halogenating species, initially involves the oxidation of halide to halogen, it is informative to consider the fate of bromine and iodine in aqueous solution. The dependence of the potential of the water–oxygen couple on [H⁺] means that the oxidation of water by Br• and I• (and hence the stability of these aqueous halogen species) also varies with solvent acidity. The thermodynamic data for the pertinent redox reactions in acidic, neutral, and basic aqueous media are summarized in Table 2 (shown in terms of molecular halogen for stoicheiometric convenience). In 1M H⁺, both Br• and I• are stable toward reduction. At pH 7, I• remains stable toward reduction whereas the reduction of Br• to form bromide is now thermodynamically favoured. This is an important electrochemical difference between these two halogens which has dramatic effects on the electrophilic halogenation yields obtained with radiobromine and radioiodine, since it affects the formation of the ultimate radiohalogenating species. For the case of aromatic n.c.a. halogenodegermylation, these effects are seen in Figure 3, where the bromodegermylation yields using dichloramine-T are much more sensitive to [OH⁻] than are the yields from the corresponding iododegermylation reaction. High yields with ${}^{77}Br$ are found only in acid pH, whereas radioiodination can proceed in mildly basic media. As the results in Table 2 indicate, in very basic media reduction of both Br• and I• is to be expected from thermodynamic considerations. This reductive pathway involving oxidation of hydroxyl ion
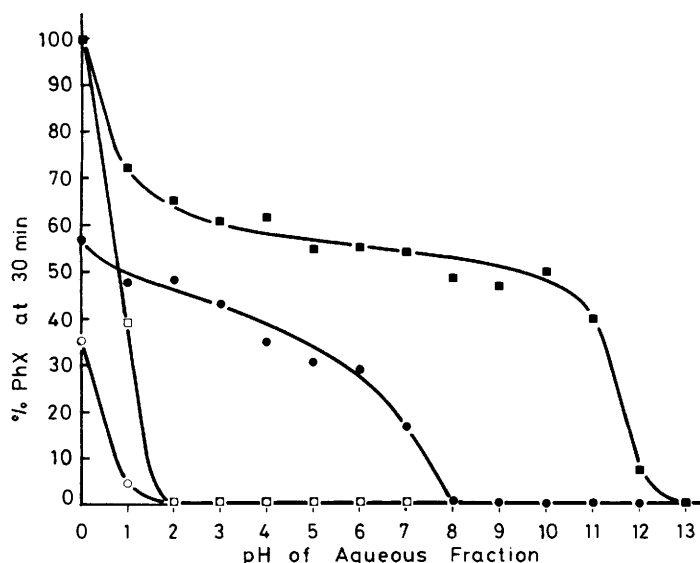
Figure 3. Aromatic n.c.a. halogenodegermylation yields as a function of aqueous fraction pH in methanol–water 3:1. Filled symbols refer to the use of 0.1M-dichloramine-T as oxidant, empty symbols are for 0.1M-chloramine-T. X = [77]Br or [131]I. ● and ○, [77]Br; ■ and □, [131]I

Table 2. Oxidation–reduction reactions involving bromine or iodine in acidic, neutral, and basic media

		E°/V [a]	
pH	Redox reaction	X = Br	X = I
0	$2X_2 + 2H_2O = O_2 + 4H^+ + 4X^-$	−0.164	−0.694
7	$2X_2 + 2H_2O = O_2 + 4H^+ + 4X^-$	0.250	−0.280
14	$2X_2 + 4OH^- = O_2 + 2H_2O + 4X^-$	0.664	0.134

[a] Calculated using the standard reduction potentials given in ref. 27.

Table 3. Effect of water on the n.c.a. halogenodegermylation of trimethylphenylgermanium in glacial acetic acid at 25 °C

	Radiochemical yield at 30 min	
Volume (%) H_2O in $MeCO_2H$	% Ph [77]Br	% Ph [131]I
0	45.7 ± 0.6	78.6 ± 1.9
10	39.9 ± 0.9	80.1 ± 0.7
25	34.3 ± 1.9	74.3 ± 1.2
50	20.1 ± 0.2	66.3 ± 2.9
75	8.6 ± 0.9	32.8 ± 3.4

undoubtedly leads to the low yields shown in Figure 3 for n.c.a. halogenodegermylation at high pH.

Comparison of the curves shown in Figure 3 when dichloramine-T is used as an oxidant for [77]Br⁻ or [131]I⁻, with the results when chloramine-T is used, illustrates an important pH effect which is induced solely by the oxidizing agent. Although the pK_a of the conjugate acid N-chlorotoluene-p-sulphonamide is 4.55,[28] chloramine-T is the N-sodium salt of this acid, which upon dissociation and subsequent disproportionation reactions gives an increase in the basicity of the solution.[28,29] N,N-Dichloramine-T lacks the sodium cation, so dissolution does not generate NaOH but, rather, gives a rise in the acidity of the solution. The effect of the basicity of chloramine-T is seen in Figure 3, where low yields with both [77]Br and ^{131}I are obtained unless the solvent is sufficiently acid to neutralize the reaction mixture. Although this effect is exaggerated in Figure 3 owing to the relatively high concentration of oxidant (0.1M) and low aqueous fraction (25%), it nevertheless illustrates how chloramine-T may disturb the pH of the microenvironment of a labelling reaction, and that the use of dichloramine-T may avoid this problem.

Using either dichloramine-T or chloramine-T, radiochemical yields for bromodegermylation are lower than for iodo-degermylation. While this may reflect the relative difficulty of oxidizing bromide ($E^\circ = 1.09$ V) relative to iodide ($E^\circ = 0.54$ V),[27] [77]Br yields are also relatively low in the highly oxidative 1M H⁺ (pH = O) environment. In acid pH, [77]BrCl and [131]ICl are the hypothetical reactive species,[21,24] and the relatively low rate of radiobromination may indicate that the kinetics of n.c.a.

bromodegermylation are slow relative to the disproportionation of [77]BrCl. The disproportionation constant for ICl is only 1.8×10^{-3},[19] compared with 0.34 for BrCl,[19] so the kinetics of iododegermylation may not play as important a role in determining the iodination yields. A detailed study of the kinetics of the bromo- and iodo-demetallation of trimethylaryl Group IVB metals will be described in a separate paper.

Use of Acetic Acid: Effect of Water.—Because low pH promotes aromatic n.c.a. bromo- and iodo-degermylation, a study of the suitability of acetic acid as a solvent was carried out, since this weak acid (pK_a 4.75) should be of use with many acid-stable biomolecules. As shown in Table 3, high radiochemical yields are obtained within 30 min using n.c.a. [77]Br and n.c.a. [131]I with trimethylphenylgermanium in glacial acetic acid. The catalytic effect of the acid on aromatic n.c.a. bromo-degermylation is seen by contrasting the yields in Table 3 with those of Table 1. The radiobromination yields in acetic acid at 25 °C are much higher than those in methanol at the same temperature, and roughly equal to those in methanol at 100 °C. Radioiodination yields using ^{131}I in acetic acid are also high. For both n.c.a. halogenodegermylation reactions, a high content (*ca.* 50% by volume) of water in the reaction solvent is tolerated, and this has practical advantages when working with short-lived [75]Br or [122]I, because the time otherwise required for drying the radiohalide prior to radiosynthesis is saved.

Effects of Substituents on Aromatic Halogenodegermylation.—Table 4 shows the results of aromatic n.c.a. bromodegermyl-

Table 4. Radiochemical yields and relative isomeric distributions for the n.c.a. bromodegermylation of 4-substituted phenyltrimethylgermanium compounds[a]

$$p\text{-}XC_6H_4GeMe_3 \xrightarrow[\text{DCT}]{\text{n.c.a. }^{77}\text{Br}^-} XC_6H_4{}^{77}Br$$

Solvent (temperature)	X	Total organic Yield (%)	Total aromatic substitution Yield (%)	Relative isomeric distribution (%)[b]		
				p	m	o
MeOH	OMe	73.5 ± 0.4	67.4 ± 0.3	99.5	0.1	<0.4
(70 °C)	Me	77.6 ± 1.0	55.9 ± 1.1	99.4	<0.3	<0.3
	F	72.4 ± 0.2	52.8 ± 2.8	99.9	0.0	0.1
	H	70.3 ± 0.6	40.0 ± 2.1			
	Br	70.2 ± 0.4	19.8 ± 0.6	98.6	<0.9	0.5
	CF₃	65.9 ± 0.8	7.0 ± 0.6	99.7	0.3	0.0
	NO₂	62.6 ± 2.5	6.3 ± 0.4	99.4	0.0	<0.6
MeCO₂H	OMe	92.8 ± 0.2	67.6 ± 1.8	99.7	0.0	<0.3
(25 °C)	Me	86.8 ± 0.7	54.1 ± 0.4	99.4	<0.3	<0.3
	F	89.9 ± 0.6	51.1 ± 1.5	99.5	0.0	0.5
	H	84.9 ± 0.6	45.7 ± 0.6			
	Br	88.7 ± 1.1	20.3 ± 0.1	98.3	<1.2	0.5
	CF₃	77.2 ± 1.2	7.3 ± 0.6	99.0	0.0	1.0
	NO₂	40.7 ± 2.0	6.0 ± 1.0	99.5	0.1	<0.4
MeOH	OMe	86.9 ± 0.6	53.4 ± 2.1	99.5	0.1	<0.4
(25 °C)	Me	76.0 ± 0.6	38.8 ± 1.4	99.4	<0.3	<0.3
	F	84.2 ± 0.3	35.3 ± 0.8	99.5	0.1	0.4
	H	81.6 ± 0.5	24.8 ± 0.4			

[a] Reaction conditions: dry ^{77}Br (50—100 µCi), $XC_6H_4GeMe_3$ (20 µl), DCT (28 mg), solvent (1 ml), reaction time 30 min. Values reported are the mean from 2—4 experiments. [b] % o + % m + % p = 100%.

Table 5. Radiochemical yields and relative isomeric distributions for the n.c.a. iododegermylation of 4-substituted phenyltrimethylgermanium compounds[a]

$$p\text{-}XC_6H_4GeMe_3 \xrightarrow[\text{DCT}]{\text{n.c.a. }^{131}\text{I}^-} XC_6H_4{}^{131}I$$

Solvent (temperature)	X	Total organic Yield (%)	Total aromatic substitution Yield (%)	Relative isomeric distribution (%)[b]		
				p	m	o
MeOH	OMe	99.5 ± 0.1	95.4 ± 0.8	99.2	0.1	<0.7
(25 °C)	Me	95.4 ± 0.2	86.6 ± 2.2	99.5	<0.3	<0.2
	F	97.8 ± 2.1	85.6 ± 0.1	99.5	<0.4	0.1
	H	95.2 ± 1.0	85.5 ± 0.3			
	Br	72.4 ± 3.2	35.4 ± 0.2	98.2	<1.2	<0.6
	CF₃	44.6 ± 3.1	15.6 ± 0.3	99.8	0.2	0.0
	NO₂	4.1 ± 0.2	0.5 ± 0.1	99.9	0.0	0.1
MeCO₂H	OMe	98.5 ± 0.1	86.7 ± 2.6	99.3	0.2	<0.5
(25 °C)	Me	97.8 ± 0.3	85.2 ± 0.3	99.1	<0.5	<0.4
	F	94.7 ± 0.4	88.3 ± 1.1	99.6	<0.4	0.0
	H	89.9 ± 0.6	78.6 ± 0.5			
	Br	95.6 ± 0.5	59.1 ± 1.8	98.6	<0.9	<0.5
	CF₃	38.6 ± 3.2	13.3 ± 0.6	99.9	0.1	0.0
	NO₂	3.1 ± 0.1	0.4 ± 0.1	99.9	0.0	0.1
CCl₄	OMe	93.2 ± 0.8	76.6 ± 3.1	99.8	0.0	0.2
(25 °C)	Me	84.9 ± 4.4	63.2 ± 2.1	99.3	<0.4	<0.3
	F	61.3 ± 4.5	53.0 ± 3.6	99.7	<0.3	0.0
	H	61.2 ± 0.8	42.0 ± 1.9			
	Br	49.1 ± 0.6	12.2 ± 1.4	98.7	<0.8	<0.5
	CF₃	8.1 ± 0.0	1.8 ± 0.2	99.9	0.1	0.0
	NO₂	1.0 ± 0.1	0.2 ± 0.1	99.9	0.0	0.1

[a] Reaction conditions: dry ^{131}I$^-$ (25—50 µCi), $XC_6H_4GeMe_3$ (20 µl), DCT (28 mg), solvent (1 ml), reaction time 30 min. Values reported are the mean from 2—4 experiments. [b] % o + % m + % p = 100%.

ation of *para*-substituted aryltrimethylgermanium compounds. In both methanol at 70 °C and glacial acetic acid at 25 °C, useful radiochemical yields were obtained with aromatic systems as deactivated as *p*-bromophenyl. Electron-donating substituents increase, while electron-withdrawing substituents decrease, the radiochemical yield of bromodegermylation. The

para-F substituent probably increases yields relative to H due to its hyperconjugative character; its electron-inductive effect would be expected to decrease yields. Useful radiochemical yields can also be obtained at room temperature from the n.c.a. bromodegermylation of aromatic systems activated toward electrophiles. This is shown in Table 4 by the results in

methanol at 25 °C for compounds bearing an electron-donating substituent. Regiospecific displacement (<98%) of the trimethylgermanium moiety occurred in all substrates tested, even in the strongly *ortho*-activating *p*-methoxyphenyl analogues.

Similar effects were also seen with aromatic n.c.a. iododegermylation, although generally higher radiochemical yields were obtained, as shown in Table 5. Useful radiochemical yields were afforded at 25 °C from substrates which are both activated and deactivated toward electrophiles, and reaction in solvents as different as methanol, acetic acid, and carbon tetrachloride is possible with n.c.a. [131]I. As with [77]Br, iodo-degermylation proceeds in a regiospecific manner.

Conclusions

This work has shown that electrophilic aromatic n.c.a. halo-genodegermylation is useful for the rapid and regiospecific introduction of high specific activity radiobromine and radioiodine into aromatic rings. Aromatic radiobromination yields are generally lower than those for radioiodine, which can be attributed to the relative instability of BrCl intermediates and the relatively high oxidation potential of bromide. The latter characteristic leads to a greater pH-sensitivity in radiobromination because of the appearance of water oxidation as a thermodynamically favoured reaction pathway. However, high radiochemical yields are achieved using [77]Br oxidized *in situ* with aromatic systems activated towards electrophiles, or with deactivated aromatic rings using acidified or mildly heated reaction media. Due to the low oxidation potential and pH-insensitivity of radioiodide, aromatic n.c.a. iododegermylation occurs with high radiochemical yield in a variety of solvents without acidification or heating. Aromatic halogenodegermy-lation proceeds in a regiospecific manner, and thus offers distinct advantages over direct electrophilic n.c.a. halogenation, which under comparable reaction conditions requires ring activation and results in a mixture of products.[21,24,30,31]

Although this study was done using relatively long-lived [77]Br and ^{131}I for convenience, the results indicate that aromatic n.c.a. halogenodegermylation can also be used to prepare high specific activity radiopharmaceuticals labelled with [75]Br, [122]I, or [123]I. By careful choice of reaction solvent, high radiochemical yields can be obtained within a 5 min period. This, together with the regiospecific nature of halogenodegermylation, makes this technique useful for the synthesis of halogenated radio-pharmaceuticals with stringent structure–activity requirements. This is particularly true since this method needs only a low relative concentration of oxidizing agent, so that oxidative damage to complicated substrate molecules can be minimized.

The use of aryltrimethylgermanium compounds as precursors for the n.c.a. radiohalogenation of aromatic rings is complementary to the use of the corresponding organosilicon and organotin substrates. Like aryltrialkylstannane precursors, but unlike the corresponding silicon analogues, aryltrimethyl-germanium compounds can be used for both rapid n.c.a. radio-bromination and radioiodination of aromatic systems. While organosilicon substrates are susceptible to rapid bromodemetal-lation,[9-11] the slow reaction kinetics for aromatic n.c.a. iododesilylation[9] preclude its use with [122]I. On the other hand, the chemical stability[20,*] and low toxicity[32] of organoger-manium compounds are advantages which are shared with organosilicon analogues. These characteristics lend themselves to ease of synthetic handling as well as adaptation to 'kit'-type

labelling procedures, in which batch production of precursors for routine use at facilities with an in-house cyclotron or at remote sites lacking a cyclotron or synthetic chemistry equipment is made possible. In this regard, organogermanium compounds have advantages over organosilicon compounds (which are not as suitable for labelling with radioiodine), as well as over organotin compounds, which are highly toxic[33] and are chemically less stable.[20,*]

Experimental

Reagents.—The *ortho*-, *meta*-, and *para*-halogenated arenes shown in Tables 4 and 5 were purchased in 98—99% purity from EGA Chemie (Steinheim, FRG) for use as reference compounds in the g.l.c. analysis of reaction products. *para*-Substituted aryltrimethylgermanium compounds were synthesized *via* the Grignard compound of the corresponding *para*-brominated arene, purified by fractionation, and chemically characterized.[34] Chloramine-T was purchased from E. Merck (Darmstadt, FRG) in analytical quality, and was used for the synthesis of dichloramine-T.[35] All solvents used in this study 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(α,2n) [77]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.[36] 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.

Radiolabelling Experiments.—All radiohalogenation pro-cedures were carried out in tightly sealed 2 ml glass reaction vessels containing magnetic stirrers. Prior to each reaction the [77]Br$^-$ solution (50—100 μCi, 20 μl) or the [131]I$^-$ solution (25—50 μCi, 5 μl) was dried completely in the reaction vessel.

The general labelling sequence used for the n.c.a. halo-genodegermylation reactions was to place the trimethylaryl-germanium compound (10^{-4} mol) into the vessel, and add the reaction solvent (1 ml), followed by addition of dichloramine-T or chloramine-T (10^{-4} mol) while the whole was stirred. For the experiments reported in Table 3, the aqueous solutions of acetic acid were prepared immediately before addition to the reaction vessel. For the experiments reported in Figure 3, the pH of the aqueous fraction was adjusted using HCl or NaOH solutions and measured with a calibrated pH meter; the solution was then diluted with three parts of methanol and immediately used as a solvent for the radiohalogenation procedure. The experimental procedure for the data shown in Figure 2 deviates from the general sequence in that the dichloramine-T was added (for concentrations $\leqslant 10^{-2}$M) as a 100 μl methanol solution rather than as a solid.

Following a pre-determined reaction time, each reaction was quenched by transferring the vessel contents to aqueous sodium sulphite (10%; 5 ml). The organic products were extracted into a chloroform solution (5 ml) of the respective halogenated standards (1 μl/ml), and the organic layer was removed and dried with calcium chloride. 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 Reaction Products.—The organic reaction products in 100 μl of the chloroform phase were analysed by radio-gas chromatography using a discontinuous technique in which the eluted products were individually adsorbed on

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* After 12 months at 2 °C, the *para*-substituted trimethylarylgermanium compounds shown in Tables 4 and 5 showed >99% purity upon g.c. analysis. The corresponding trimethylaryltin compounds showed 5—15% decomposition under the same storage conditions.

charcoal-filled tubes.[37] The isomeric brominated and iodinated analogues of α,α,α-trifluorotoluene, bromobenzene, and benzene were separated using a 4 × 4 000 mm column of 6% Bentone-38 and 20% silicon oil DC-200 on Chromosorb W-AW-DMCS (60—80 mesh),[38] while the isomers of brominated and iodinated anisole, toluene, fluorobenzene, and nitrobenzene were separated using a 4 × 4 000 mm column of Igepal CO-880 on Chromosorb W-AW-DMCS (60—80 mesh).[39] 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 solution. All experimental yields reported in this work represent the mean from 2—4 experiments.

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