No-carrier-added Radiobromination and Radioiodination of Aromatic Rings using *In Situ* Generated Peracetic Acid[1]

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Peracetic acid generated *in situ* from aqueous hydrogen peroxide and glacial acetic acid was examined as an oxidizing agent for electrophilic aromatic bromination and iodination without chlorinated side products. No-carrier-added (n.c.a.) ^{77}Br and ^{131}I were used with simple organic aromatic compounds or aryltrimethyl-tin, -germanium, and -silicon organometallic compounds to identify reaction parameters which influence this electrophilic halogenation method. N.c.a. aromatic halogenodeprotonation using peracetic acid was relatively slow and resulted in high labelling yields only with aromatic rings that were activated toward electrophilic substitution. By contrast, high radiochemical yields were rapidly obtained *via* iododestannylation of aromatic rings regardless of their degree of electronic activation. Useful labelling yields were also achieved using bromodestannylation reactions with aromatic rings deactivated toward electrophiles, but optimum yields with activated systems required the use of germylated arenes as substrates. The practical aspects of aromatic halogenodemetallation and halogenodeprotonation as n.c.a. electrophilic halogenation techniques with *in situ* generated peracetic acid are outlined.

The rapid growth of nuclear medicine imaging techniques and other tracer methods in biomedical research has created a need for the synthesis of numerous compounds which have incorporated into their structures radioisotopes of bromine and iodine. Halogen isotopes such as $^{75,76,77,82}Br$ and $^{122,123,125,131}I$ have found application as labels for positron emission tomography (PET) and single-photon emission computerized tomography (SPECT), ratiotherapeutic agents, and receptor-binding radioligands.[2–5] The radiohalogenation of these biomolecules involves special synthetic constraints, such that the halogenation conditions are mild and rapidly give high yields of product. In addition, the halogen must often be incorporated at a specific molecular site to assure retention of *in vivo* characteristics by the radiolabelled analogue.[6,7] A major labelling requirement is that the radiohalogenated compound be produced with high specific activity so that pharmacological or toxicological effects are minimized and receptor sites are not saturated.[7]

High specific-activity compounds containing halogen radioisotopes can be synthesized using no-carrier-added (n.c.a.) radiohalogenation techniques (for reviews, see ref. 8 and 9). Owing to the stability of the aromatic carbon–halogen bond, radiobromine or radioiodine are often introduced onto an aromatic site of the labelling substrate *via* n.c.a. electrophilic aromatic halogenation reactions. This technique traditionally involves the *in situ* oxidation of n.c.a. radiohalide by such oxidants as *N*-chlorosuccinimide, *N*-chlorotolylsulphonamides (chloramine-T, iodogen), and hypochlorites.[8] The use of these oxidizing agents results in high radiohalogenation yields, but also produces chlorinated side-products which are difficult to separate from the n.c.a. radiolabelled compound. Because the chlorinated analogue has biological properties which are similar to the brominated or iodinated derivatives, the presence of even trace quantities of chlorinated side-products results in low 'effective' specific activities which can be deleterious to biomedical applications.

An alternative radiohalogenation approach is to employ as an oxidizing agent peracetic acid, which is formed *in situ* from hydrogen peroxide and acetic acid.[10,11] Unlike the chlorine-bearing oxidants mentioned above, which produce chlorinated side products, peracetic acid generates protonated side-products which are relatively easy to separate chromatographically from the n.c.a. radiobrominated or radioiodinated products. Vinyl positions of estrogen analogues have been labelled with n.c.a. ^{77}Br[12,13] and ^{125}I[14] in this manner, and aromatic sites of neuroleptic compounds have been radiohalogenated in very high specific activities using *in situ* generated peracetic acid.[15–18] Despite the application of peracetic acid in radiopharmaceutical chemistry, details concerning the use of this oxidizing agent for radiohalogenation are scant.

We describe here the results of a systematic investigation of the use of *in situ* generated peracetic acid as an oxidizing agent for electrophilic aromatic halogenation with n.c.a. $^{77}Br^-$ and $^{131}I^-$. Simple aromatic compounds were employed as halogenation substrates to minimize side-reactions and to help elucidate the effect of aromatic substituents on the reactivity of the aromatic ring. The preparative aspects of n.c.a. electrophilic aromatic halogenation using peracetic acid have been emphasized in this work to allow ready adaptation to radiopharmaceutical production, although the ability of radiohalide to trace macroscopic halide also makes the results of these halogenation studies pertinent to classical organic synthesis.

Results and Discussion

General Considerations on the Generation of Peracetic Acid.— Initial experiments indicated that peracetic acid in commercially available concentrations was too harsh an oxidizing agent to be useful for radiohalogenation. We therefore produced low concentrations of the peroxy acid *in situ* for this purpose. The generation of peracetic acid from hydrogen peroxide and acetic acid is illustrated in Scheme 1. The equilibrium constant for this

$$CH_3CO_2H + H_2O_2 \overset{H^+}{\rightleftharpoons} CH_3CO_3H + H_2O$$

$$K = \frac{[CH_3CO_3H][H_2O]}{[CH_3CO_2H][H_2O_2]}$$

Scheme 1.

redox reaction is *ca.* 7,[10] and for 9.8M aqueous H_2O_2, the maximum concentration of peracetic acid which is obtained is

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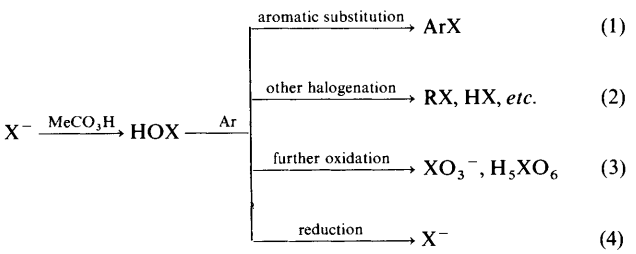
Table 1. Effect of sulphuric acid on the n.c.a. electrophilic aromatic halogenodeprotonation of anisole[a]

$[H_2SO_4]$[b]/M	Radiochemical yield (%)[c] $^{131}IC_6H_4OMe$
0	3.4 ± 0.1
0.1	7.6 ± 0.3
0.2	24.1 ± 2.0
0.5	3.8 ± 0.2
0.9	4.0 ± 0.1
1.9	1.8 ± 0.2

[a] Reaction conditions: 100 μCi (0.92—1.85 MBq) dry $^{131}I^-$, 10μl PhOMe, 0.6M-$MeCO_2Na$ in $MeCO_2H$, 0.5 ml oxidant, 25 °C, 6 h. The oxidant consisted of the above concentrations of H_2SO_4 in a mixture of 11.4M aqueous H_2O_2 plus glacial $MeCO_2H$ (volume ratio 2:1) which was allowed to stand at 25 °C for 2 h prior to application to $^{131}I^-$. [b] In oxidant; the concentration of H_2SO_4 in the iodination mixture is one-half the values listed. [c] Percentage of total radioactivity in solution; values represent the mean and range from 2—4 experiments.

of the order of 10%.[19] The acid-catalysed reaction reaches completion after *ca.* 2 h, which was the equilibration time used throughout the present work. From the equilibrium equation, it is obvious that the equilibrium can be shifted toward the generation of peracetic acid by increasing the hydrogen peroxide concentration, by increasing the concentration of acetic acid, or by removing water from the reaction environment. Since hydrogen peroxide in concentrations >12M is potentially detonatable, and because excess of acetic acid reacts with peracetic acid to give diacetyl peroxide,[20] decreasing the effective concentration of water by acidification is the most convenient manner for enhancing the production of peracetic acid.

Scheme 2 shows reaction pathways which are possible



Scheme 2.

following the oxidation of n.c.a. radiohalide (X = Br^- or I^-) by *in situ* generated peracetic acid. Peracetic acid is a monosubstituted analogue of hydrogen peroxide, which is reduced in acid solution by halide to produce hypohalous acid.[21,22] This mechanism has been used to explain the kinetics of bromide oxidation by peracetic acid,[23] and is also applicable to the reactions of n.c.a. radio-bromide and -iodide. The present work is unique in that the halogenation products resulted only from reactions of the hypohalous acids that were generated from the action of peracetic acid on radiohalide. This is because the tracer (p*M*) concentrations of n.c.a. radio-bromide or -iodide prevented the formation of molecular halogen, which is seen with macroscopic halide.[22—24] Thus, the reactive n.c.a. species were of a cleaner nature than that at carrier concentrations, and complicating side reactions such as molecular halogenation or reduction of hydrogen peroxide and peracetic acid by bromine or iodine were avoided. In a further attempt to allow experimental parameters of n.c.a. aromatic halogenation with peracetic acid [Scheme 2, step (1)] to be examined, only simple substituted aromatic compounds were

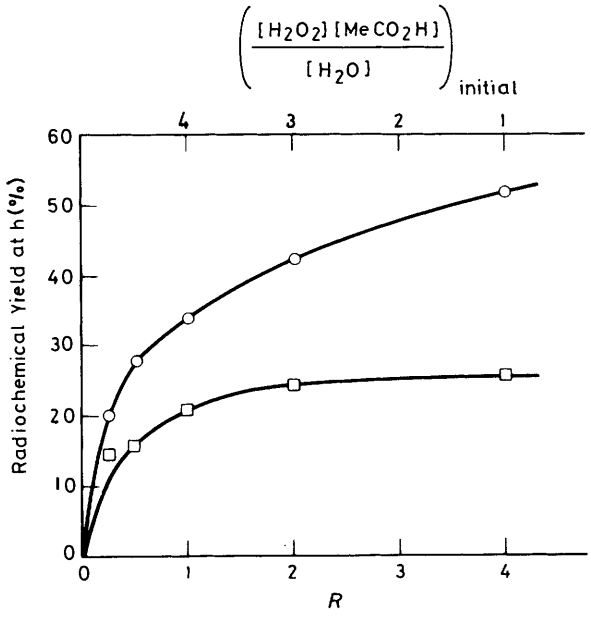


Figure 1. Effect of the relative volume ratio of 35 wt% (11.4M) aqueous H_2O_2 to glacial $MeCO_2H$ on the n.c.a. electrophilic aromatic halogenodeprotonation of anisole. The initial molarities of H_2O_2, $MeCO_2H$, and H_2O in the oxidant mixture are also given. Reaction conditions: 50—100 μCi (1.85—3.70 MBq) dry $^{77}Br^-$; 25—50 μCi (0.92—1.85 MBq) $^{131}I^-$, 10 μl PhOMe, 0.5 ml 0.6M-$MeCO_2Na$ in $MeCO_2H$, 0.5 ml oxidant, 25 °C, 6 h. Oxidant consisted of 11.4M aqueous H_2O_2 and glacial $MeCO_2H$ mixed in the above proportions and allowed to stand at 25 °C for 2 h prior to application to radiohalide. Oxidant contained 0.2M-H_2SO_4 for $^{131}I^-$. Data points represent the mean from 2—4 experiments. ○, ^{77}Br; □, ^{131}I

employed as labelling substrates to minimize the complicating effect of side reactions [Scheme 2, step (2)].

Aromatic Halogenodeprotonation.—In the optimization of conditions for n.c.a. halogenodeprotonation, anisole was employed as a halogenation substrate since the aromatic ring of this compound is moderately activated toward electrophilic substitution. Significant radiohalogenation yields could therefore be measured without masking the sensitivity of the substitution process to subtle chemical changes.

A major difference between n.c.a. bromo- and iodo-deprotonation was that the latter required acidification of the hydrogen peroxide–acetic acid mixture to achieve useful radiochemical yields. As indicated in Table 1, for a hydrogen peroxide–acetic acid mixture 0.2M in H_2SO_4, the aromatic iodination yield increased to *ca.* 25%. Further acidification of the oxidant resulted in a decreased iododeprotonation yield. Unlike n.c.a. $^{77}Br^-$, which was prepared in non-buffered aqueous solution,[25,26] the radioiodide was purchased as a buffered phosphate (pH 6.9—7.5) solution. Because the spontaneous decomposition rate of peracetic acid at this pH is over an order of magnitude greater than at pH <5.5,[20] additional sulphuric acid was needed to shift the equilibrium toward generation of peracetic acid to compensate for this loss. The use of >0.2M-H_2SO_4 apparently produced too high a concentration of peracetic acid, and the resulting highly oxidizing environment promoted n.c.a. $^{131}I^-$ to high oxidation states, as in iodate or periodic acid [Scheme 2, step (3)]. For all subsequent halogenation experiments, the hydrogen peroxide–acetic acid mixture contained 0.2M-H_2SO_4 for $^{131}I^-$, but not for $^{77}Br^-$.

As Figure 1 illustrates, both n.c.a. bromo- and iodo-deprotonation yields increased as the volume ratio (*R*) of 11.4M

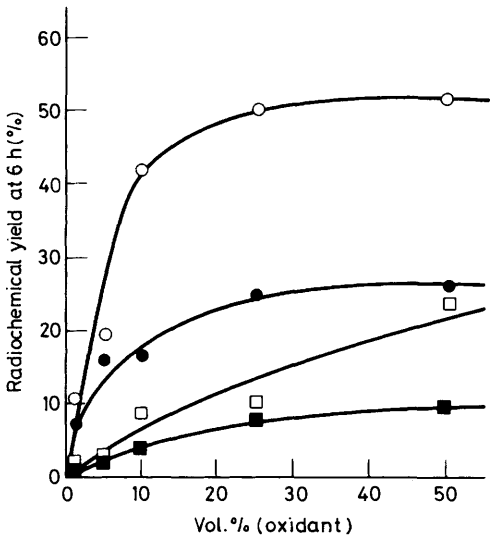


Figure 2. Relationship between n.c.a. electrophilic aromatic halogenodeprotonation yields from anisole as a function of oxidant concentration in methanol and buffered acetic acid. Data points represent the mean from 2—4 experiments using reaction conditions as Figure 1, with R 2. Filled symbols, MeOH; empty symbols, 0.6M-$MeCO_2Na$ in $MeCO_2H$. ● and ○, ^{77}Br; ■ and □, ^{131}I

generated. It therefore appears that high concentrations of peracetic acid were suboptimal for the aromatic halogenodeprotonation process, in agreement with the fact that commercially available concentrations of peracetic acid are not useful for n.c.a. radiohalogenation. At very large R values, the minimum concentration of peracetic acid required to oxidize n.c.a. halide was barely produced, which may explain why increasing R resulted in a less dramatic increase in halogenodeprotonation yields for $R > 2$ compared with $R < 1$. It should be noted that at large R, halide oxidation by *in situ* generated peracetic acid is expected to predominate over oxidation by hydrogen peroxide due to the more rapid kinetics of the former process. The oxidation of bromide by peracetic acid follows a second-order rate law with a rate constant of 0.258 l mol^{-1} s^{-1},[23] while the corresponding oxidation by hydrogen peroxide involves two rate-determining steps with rate constants of 2.3×10^{-5} l mol^{-1} s^{-1} and 1.40×10^{-2} l^2 mol^{-2} s^{-1}.[22] A similar difference in oxidation kinetics is seen for iodide.[21,23] For all subsequent n.c.a. halogenation experiments, the oxidant consisted of 11.4M aqueous H_2O_2–glacial $MeCO_2H$, R 2, with an additional 0.2M-H_2SO_4 for use with $^{131}I^-$. This corresponds to an oxidant solution initially 7.6M in H_2O_2 and 5.8M in $MeCO_2H$.

The effects of the oxidant concentration and of the reaction solvent on the n.c.a. halogenodeprotonation of anisole are illustrated in Figure 2. These experiments were performed to

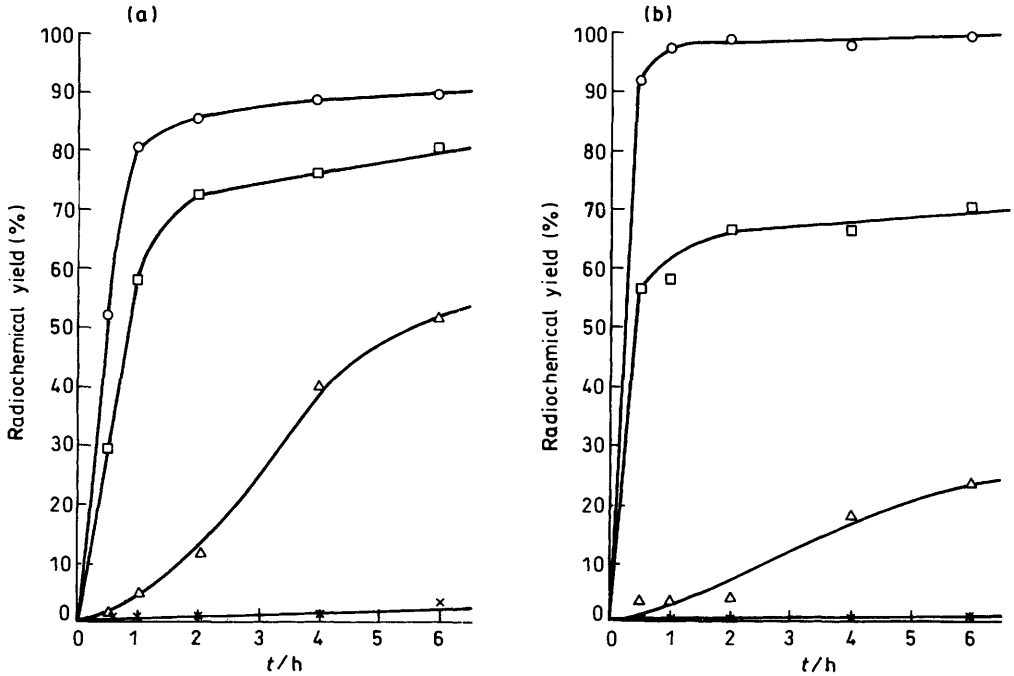


Figure 3. N.c.a. electrophilic aromatic halogenodeprotonation yields from PhG as a function of time. Data points represent the mean from 2—4 experiments using reaction conditions as Figure 2. ○, G = NH_2; □, G = OH; △, G = OMe; X, G = Me. (a) ^{77}Br. (b) ^{131}I

aqueous H_2O_2 to glacial acetic acid was increased. These results can be understood by considering the relative molar concentrations of acetic acid, hydrogen peroxide, and water (from the hydrogen peroxide solution) that were originally present in the oxidant mixture. As the relative volume of aqueous hydrogen peroxide was increased, the ratio of the initial molarities, $([H_2O_2][MeCO_2H]/[H_2O])_{initial}$, decreased. Because the equilibrium (Scheme 1) is shifted to the right in direct proportion to this ratio, increasing the R value diminished the concentration of peracetic acid that was ascertain whether high oxidant concentrations or acidic solvents are necessary for halogenation with peracetic acid, since in many cases biomolecules are sensitive to oxidation or are poorly soluble at low pH. For both $^{77}Br^-$ and $^{131}I^-$, the aromatic halogenation of anisole increased with increasing oxidant concentration. In addition, the n.c.a. halogenodeprotonation yields were greater when the reactions were performed in acidic (buffered acetic acid) rather than polar organic (methanol) solvents. This effect may be due to enhanced cleavage of the oxygen–halogen bond of n.c.a. hypohalous

Table 2. N.c.a. aromatic halogenodemetallation of $PhM(Me)_3$[a]

M	Radiochemical yield (%)[b]	
	$Ph^{77}Br$	$Ph^{131}I$
Sn	66.3 ± 4.0	94.6 ± 0.8
Ge	2.4 ± 0.2	18.2 ± 1.1
Si	0.9 ± 0.1	9.4 ± 0.3

[a] Reaction conditions: 50—100 μCi (1.85—3.70 MBq) dry $^{77}Br^-$; 25—50 μCi (0.92—1.85 MBq) $^{131}I^-$, 10 μl $PhM(Me)_3$, 1 ml 0.6M-$MeCO_2Na$ in $MeCO_2H$, 10 μl oxidant, 25 °C, 30 min. The oxidant consisted of 11.4M aqueous H_2O_2 and glacial $MeCO_2H$ mixed in the volume ratio 2:1 (and containing 0.2M-H_2SO_4 for $^{131}I^-$) and was permitted to stand at 25 °C for 2 h prior to application to radiohalide. [b] As Table 1.

species in acidic media, as described for the general acid catalysis of hydrogen peroxide reduction,[27,28] or because there is oxidation of water as the pH is increased.[29] For optimum halogenodeprotonation, an oxidant concentration of 25 vol % was required for $^{77}Br^-$ and 50 vol % for $^{131}I^-$.

The radiochemical yields which were achieved and the rapidity with which aromatic halogenodeprotonation reached completion were enhanced by the presence of electron-donating substituents on the aromatic ring, as shown in Figure 3. For $^{77}Br^-$, n.c.a. bromodeprotonation of aniline resulted in a radiochemical yield of *ca.* 80% within 1 h. N.c.a. bromination of phenol also gave high yields with a slightly longer reaction time, while anisole gave moderate (50%) yields after 6 h, and bromination of toluene was negligible. The trend of slower reaction kinetics with decreased electronic activation of the aromatic halogenation substrate was also noted for $^{131}I^-$, although the effect of electron-donating substituents on the aromatic halogenation yield was more dramatic than for $^{77}Br^-$. With the highly activated aniline, radioiodination yields exceeded radiobromination yields (95 and 80%, respectively, after 1 h), whereas with the moderately activated aromatic ring of anisole, they were less (after 6 h, 25% for $^{131}I^-$ and 50% for $^{77}Br^-$). The greater sensitivity of aromatic iododeprotonation yields to changes in the electronic activation of the aromatic substrate by substituents indicates that a competitive reaction pathway was more important for n.c.a. radioiodide than radiobromide. Most likely, this pathway was further oxidation of the reactive hypohalous acid to species which do not take part in electrophilic aromatic substitution reactions, such as iodate or periodic acid [Scheme 2, step (3)]. For the highly activated aromatic ring of aniline, n.c.a. halogenodeprotonation yields were determined principally by the rate of oxidation of halide, which was greater for iodide (E° 0.535 V[30]) than bromide (E° 1.07 V[30]). With the less activated ring of anisole, the halogenodeprotonation process was slower with respect to competitive oxidation of hypohalous acid. Since the oxidation potential of hypoiodous acid (E° 1.14 V[30]) is less than that of hypobromous acid (E° 1.49 V[30]), oxidative degradation of the iodinating reagent was more prevalent and the halogenation yields were lower for $^{131}I^-$ than for $^{77}Br^-$.

Aromatic Halogenodemetallation.—The above results indicate that n.c.a. electrophilic aromatic halogenodeprotonation reactions were useful only for labelling aromatic rings that were activated toward electrophilic substitution, which is a severe limitation for the many biomolecules which contain only aromatic rings which are non-activated or deactivated toward electrophiles. An alternative to labelling *via* aromatic halogenodeprotonation is to use halogenodemetallation reactions, in which electrophilic halogenating species displace a labile metal moiety from an aromatic ring to yield an aryl halide. Not only does this technique allow for the labelling of non-activated aromatic systems, but in addition appropriate choice of the organometallic precursor permits regioselective control over the site of halogenation.

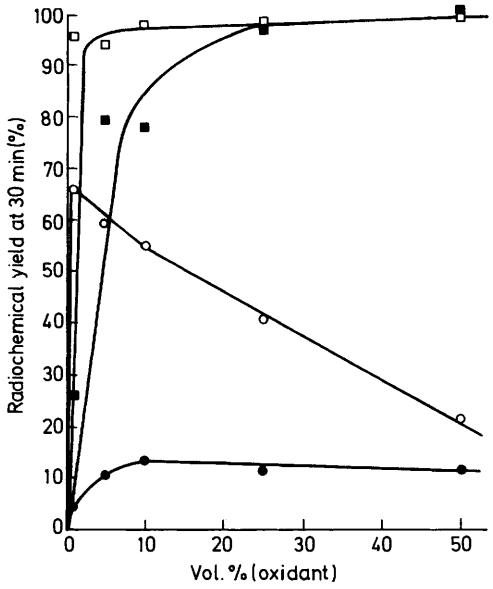


Figure 4. N.c.a. electrophilic aromatic halogenodestannylation of trimethylphenyltin in methanol and buffered acetic acid. Data points represent the mean from 2—4 experiments using reaction conditions as Figure 2. Filled symbols, MeOH; empty symbols, 0.6M-$MeCO_2Na$ in $MeCO_2H$. ● and ○, ^{77}Br; ■ and □, ^{131}I

Arenes bearing σ-bonded Group IVb metals have found particular success as substrates for regioselective halogenation of aromatic rings at both macroscopic[31] and tracer[29,32] levels. Table 2 lists the radiochemical yields obtained by treating trimethylphenyl-tin, -germanium, and -silicon with n.c.a. $^{77}Br^-$ or $^{131}I^-$ oxidized with peracetic acid. For all three organometallic compounds, the aromatic iododemetallation yields exceeded those of bromodemetallation, and for both $^{77}Br^-$ and $^{131}I^-$, the aromatic halogenation yields using $PhM(Me)_3$ as substrate decreased in the series M = Sn > Ge > Si. The identical rank order of halogenodemetallation yields has been noted with molecular halogenation[31] as well as with n.c.a. halides oxidized *in situ* using dichloramine-T.[32] In those investigations, the variation in aromatic halogenodemetallation yields with altered metal substituent was attributed to differences in the rate of formation of an intermediate σ-complex, and the same arguments apply to the results of the present work. Table 2 indicates that for n.c.a. radiohalide oxidized by peracetic acid, halogenodestannylation allowed the incorporation of bromine or iodine atoms onto non-activated aromatic sites with high yields. Although n.c.a. aromatic halogenodestannylation reactions which use dichloramine-T also result in high labelling yields, the application of that oxidant produces a high yield of macroscopic chlorinated arene.[32]

The relationship between the percentage of oxidant and the radiochemical yields which were obtained from halogenodestannylation differed from that seen for halogenodeprotonation (Figure 2). As indicated in Figure 4, the relatively high oxidation potential of bromide resulted in low bromodestannylation yields (*ca.* 10%) in methanol even when 50 vol % oxidant was employed. The use of an acidic solvent (0.6M-$MeCO_2Na$ in $MeCO_2H$) enhanced the electrophilic bromination reaction, an effect also noted with aromatic metal

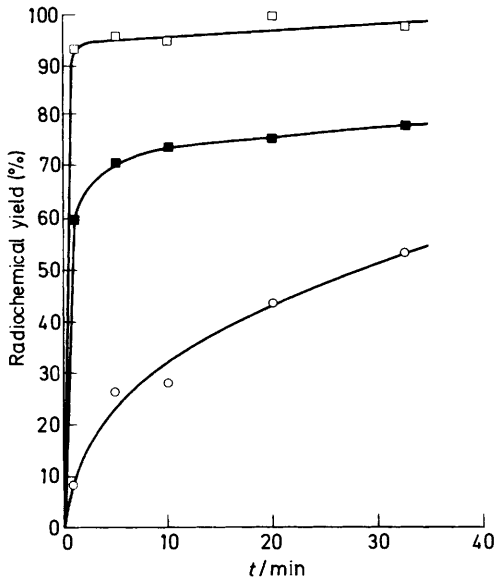


Figure 5. Effect of reaction time on the n.c.a. electrophilic aromatic halogenodestannylation of trimethylphenyltin in methanol and buffered acetic acid. Data points represent the mean from 2—4 experiments using reaction conditions as Figure 2 with 0.9 ml solvent and 0.1 ml oxidant. Filled symbol, MeOH; empty symbols, 0.6M-$MeCO_2Na$ in $MeCO_2H$. ○, ^{77}Br; ■ and □, ^{131}I

substitution processes that employed *N*-chloroamines as oxidizing agents.[29,32] Noteworthy is that n.c.a. bromodestannylation yields decreased from a maximum of *ca.* 65% to *ca.* 20% as the percentage of oxidant in the acidic buffer was increased. This suggests that in the highly oxidizing environment consisting of *in situ* generated peracetic acid at low pH, the rate of aromatic bromodestannylation was slower than the rate of protodestannylation. As the percentage of oxidant increased, competitive protodestannylation side reactions were enhanced, greater acid hydrolysis of the stannylated labelling substrate took place, and bromination yields consequently decreased. In contrast to the $^{77}Br^-$ results, the relatively low oxidation potential of iodide and rapid kinetics of the electrophilic iododestannylation gave high labelling yields with n.c.a. $^{131}I^-$ in both acidic and organic solvents. Acidification of the reaction medium was not necessary, and radioiodination yields exceeded 95% when 25 vol % oxidant in methanol was used. In buffered acetic acid, iodination yields were practically quantitative with oxidant concentrations that varied from 1—50 vol %, indicating that n.c.a. electrophilic aromatic iododestannylation was so rapid that the labelling yields were impervious to competitive hydrolytic decomposition of the metallated substracted. Based on these data, 10 vol % oxidant was employed in subsequent n.c.a. halogenodemetallation experiments.

The effects of the reaction solvent on the radiochemical yields obtained from n.c.a. halogenodestannylation of trimethylphenyltin are shown in Figure 5. The iododestannylation process was extremely rapid, with halogenation yields of *ca.* 95% after 1 min in buffered acetic acid and *ca.* 70% after 10 min in methanol. N.c.a. aromatic bromodestannylation kinetics in acidic media were slower, with labelling yields of *ca.* 50% after a reaction interval of 30 min. The yields for iodination and bromination seem to reflect the relative ease of oxidation of n.c.a. $^{77}Br^-$ and $^{131}I^-$ to the corresponding hypohalous acid species by peracetic acid. The labelling yields and kinetics of both halides indicate that this halogenation method can be conveniently applied to such short-lived radionuclides as ^{75}Br (β^+, $T_{\frac{1}{2}}$ 1.6 h) or ^{122}I (β^+, $T_{\frac{1}{2}}$ 3.6 min), particularly since the data in Figure 5 pertain to an aromatic ring which was not activated toward electrophilic substitution.

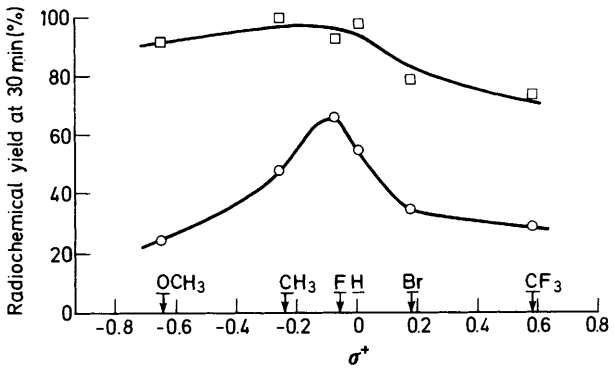


Figure 6. Regioselective n.c.a. electrophilic aromatic halogenodestannylation of various *para*-substituted aryltrimethyltin compounds as a function of substituent σ^+ constant. Data points represent the mean from 2—4 experiments using reaction conditions as Figure 5. ○, ^{77}Br; □, ^{131}I

The influence of electronic ring activation or deactivation on the electrophilic substitution of the aromatic trimethyltin group is illustrated in Figure 6. These substituent effects are succinctly described by the Brown–Okamoto σ^+ substituent constants,[33] so we have plotted the radiochemical yields obtained from n.c.a. radiohalogenation using peracetic acid with various *para*-substituted aryltrimethyltin compounds as a function of the σ^+ constant of the respective aromatic substituent. As discussed above for the n.c.a. halogenation of non-activated trimethylphenyltin (Figure 5), the n.c.a. aromatic iododestannylation yields exceeded those from bromodestannylation in aromatic systems which were activated ($\sigma^+ < 0$) or deactivated ($\sigma^+ > 0$) toward electrophilic attack. As the aromatic substituent was changed from the highly deactivating CF_3 (σ^+ 0.6) to non-activating F (σ^+ −0.1), the n.c.a. halogenodestannylation yields increased, more so for $^{77}Br^-$ than $^{131}I^-$. This increase in radiohalogenation yields was probably due to greater stabilization of the intermediate σ-complex that is involved in the substitution mechanism[31,32] as the substituent was made less electron-withdrawing. $^{77}Br^-$ was more sensitive than $^{131}I^-$ to this effect due to the greater tendency of the reactive hypobromous acid species to undergo reduction[30] [Scheme 2, step (4)]. When strongly electron-donating ($\sigma^+ < -0.1$) substituents were present, the resulting activation of the aromatic ring to electrophilic substitution made protodestannylation a significant reaction in competition with n.c.a. halogenodestannylation. Because in these experiments hydronium ions were in much greater concentration than tracer (p*M*) $^{77}Br^-$ or $^{131}I^-$, n.c.a. halogenodestannylation yields decreased for both radiohalogens. The decrease in labelling yields with increased ring activation was slight for $^{131}I^-$, since the kinetics of iodide oxidation by peracetic acid and subsequent aromatic iododestannylation were very rapid in comparison with acid hydrolysis of the aryltin substrate. The halogenation kinetics for $^{77}Br^-$ were apparently much slower, so that acid decomposition of activated aromatic systems occurred more rapidly than n.c.a. bromodestannylation, and the radiochemical yields decreased. This effect is cogently illustrated by the low n.c.a. bromodestannylation yield from electronically activated (*p*-anisyl)-trimethyltin, which was even less than that from highly deactivated *p*-(ααα-trifluoromethylphenyl)trimethyltin.

Comparison of N.c.a. Aromatic Halogenodemetallation with Halogenodeprotonation.—It is beneficial to examine the

Table 3. N.c.a. aromatic halogenation of anisole derivatives[a]

$$p\text{-}GC_6H_4OMe \xrightarrow[\text{oxidant}]{\text{N.c.a. } X^-} XC_6H_4OMe$$

X	G	Total aromatic substitution yield (%)[b]	Relative isomeric distribution (%)[c]		
			p	*m*	*o*
^{77}Br	$Sn(Me)_3$	28.7 ± 1.8	90	0	10
	$Ge(Me)_3$	53.9 ± 2.4	98	0	2
	$Si(Me)_3$	43.2 ± 2.4	98	0	2
	H	51.8 ± 0.8	74	1	25
^{131}I	$Sn(Me)_3$	91.1 ± 1.1	93	1	6
	$Ge(Me)_3$	80.4 ± 2.3	98	0	2
	$Si(Me)_3$	78.6 ± 0.3	99	0	1
	H	24.1 ± 2.0	78	1	21

[a] Reaction conditions: For G = H: 50—100 μCi (1.85—3.70 MBq) dry $^{77}Br^-$; 25—50 μCi (0.92—1.85 MBq) $^{131}I^-$, 10μl PhOMe, 0.5 ml 0.6M-$MeCO_2Na$ in $MeCO_2H$, 0.5 ml oxidant, 25 °C, 6 h. Otherwise: as for G = H except 0.9 ml 0.6M-$MeCO_2Na$ in $MeCO_2H$, 0.1 ml oxidant, and 30 min. Oxidant as described in Table 2. [b] As Table 1. [c] %*o* + %*m* + %*p* = 100%.

Table 4. Effect of water on n.c.a. electrophilic aromatic halogenation

	Vol % H_2O in solvent	Total M-H_2O[b]	Aromatic substitution yield (%)[a]	
			^{77}Br	^{131}I
Halogeno-deprotonation[c]	0	12.0	51.8 ± 4.4	24.1 ± 2.0
	5	13.0	46.7 ± 3.0	23.2 ± 1.6
	10	14.8	47.7 ± 5.6	26.4 ± 2.2
	25	18.9	35.9 ± 3.8	14.9 ± 1.9
	50	25.9	23.6 ± 0.2	5.7 ± 0.7
	75	32.8	2.6 ± 0.3	<0.5
Halogeno-demetallation[d]	0	2.4	54.8 ± 4.4	98.1 ± 1.8
	5	4.9	35.8 ± 2.3	96.3 ± 1.8
	10	7.4	26.0 ± 1.5	91.5 ± 4.8
	25	14.9	8.7 ± 2.5	78.1 ± 0.8
	50	27.4	0.5 ± 0.1	77.0 ± 0.2
	75	39.9	<0.5	79.1 ± 4.7

[a] As Table 1. [b] Total water content of oxidant plus solvent. [c] Reactions using PhOMe as a substrate. Conditions as Table 3. [d] Reactions using $PhSn(Me)_3$ as a substrate. Conditions as Table 3.

relative synthetic advantages of using peracetic acid with n.c.a. electrophilic halogenodemetallation and halogenodeprotonation reactions for introducing n.c.a. radiohalogens onto aromatic rings. Important criteria for evaluating a labelling technique include radiochemical yield, reaction time, mildness of reaction conditions, and isomeric purity of the radiohalogenated aromatic product. Table 3 compares, using anisole and its analogues as examples, the radiochemical yields from n.c.a. electrophilic aromatic halogenodemetallation and halogenodeprotonation when *in situ* generated peracetic acid was employed as an oxidant. For both $^{77}Br^-$ and $^{131}I^-$, halogenodeprotonation reactions required much longer reaction periods (6 h) and higher oxidant concentrations (50 vol %) to achieve labelling yields that approximated those obtained within 30 min *via* halogenodemetallation with only 10 vol % oxidant. Thus, the use of organometallic substrates has the advantages of more rapid halogenation with higher yields and milder reaction conditions. In addition, regioselectivity of halogenation (in this case, the *para*-position) was possible only *via* halogenodemetallation; halogenodeprotonation reactions generated a mixture of aromatic isomers, the relative abundance of which reflected each aromatic site's degree of electronic activation or steric ease of electrophilic attack. Whereas radiochemical yields were higher for n.c.a. bromodeprotonation than iododeprotonation, the halogenation yields with $^{131}I^-$ were greater than those with $^{77}Br^-$ when aromatic metal substitution reactions were used. As discussed above, these results can be explained by the lower oxidation potentials of iodine species, which led to more rapid halogenation in the case of facile aromatic demetallation reactions, or to highly oxidized inorganic iodine species for the relatively slower aromatic iododeprotonation process. Considering only the results of n.c.a. aromatic iododemetallation, it is seen that the regioselective iodination yields were high for all three types of organometallics, with a slight decrease in the order M = Sn > Ge > Si. Thus, electrophilic iododestannylation is the preferable labelling method for activated, as well as non-activated (Table 2), aromatic systems. For the n.c.a. aromatic bromodemetallation reactions, the radiochemical yields decreased in the series M = Ge > Si > Sn. This rank order reflects the relative lability of each metal toward substitution by electrophilic n.c.a. ^{77}Br species in competition with decomposition of the substrate by hydronium ions in the reaction medium. The relatively high production of *ortho*-brominated product from n.c.a. bromodestannylation may have resulted from the electrophilic halogenation of non-stannylated anisole which was generated in the reaction mixture by protodestannylation of (*p*-anisyl)trimethyltin. Germylated and silylated anisole derivatives were both resistant to hydrolysis by acid, and of the two substrates, (*p*-anisyl)trimethylgermanium was more susceptible to electrophilic substitution of the aryl metallic group by the n.c.a. brominating species.

A fifth parameter which influences the choice of a radiohalogenation technique is whether the labelling reaction can be performed in the presence of water. Eliminating the necessity of drying the aqueous n.c.a. radiohalide solution before the aromatic halogenation reaction, reduces decay losses with such short lived isotopes as ^{75}Br ($T_{\frac{1}{2}}$ 1.6 h) or ^{122}I ($T_{\frac{1}{2}}$ 3.6 min), and has advantages in laboratory safety due to the volatile tendency of radioiodide to oxidize while drying. As Table 4 shows, n.c.a. aromatic halogenation using peracetic acid was tolerant to appreciable quantities of water in the reaction medium. This was contrary to the deleterious influence of water on the *in situ* generation of peracetic acid (Scheme 1), suggesting that the rate of hydrolysis of peracetic acid was not as rapid as the rate of halide oxidation. Useful radiohalogenation yields were obtained *via* n.c.a. aromatic bromo-and iodo-deprotonation of anisole with up to 25 vol % water in the reaction solvent. With n.c.a. halogenodestannylation of trimethylphenyltin, moderate radiochemical yields were obtained with $^{77}Br^-$ using up to 10 vol % water in the solvent, whereas with $^{131}I^-$ very high yields were obtained even with 75 vol % of the reaction medium consisting of water. For *ca.* >50 vol % water for halogenodeprotonation or 10 vol % water for bromodestannylation reactions, the radiochemical yields rapidly decreased, probably as a result of aqueous redox side reactions.[29]

Conclusions.—This investigation has examined the utility of *in situ* generated peracetic acid as an oxidant for n.c.a. electrophilic bromination and iodination of aromatic rings without the production of chlorinated aromatic side products. Useful aromatic halogenation yields were achieved when 11.4M aqueous H_2O_2 and glacial acetic acid were mixed in the volume ratio 2:1 2h prior to application as an *in situ* oxidant of n.c.a. $^{77}Br^-$ or $^{131}I^-$. The oxidant for $^{131}I^-$ required 0.2M-H_2SO_4 due to buffer present in the aqueous radioiodide solution.

N.c.a. aromatic halogenodeprotonation yields were highest

when the labelling reaction was performed in an acidic solvent containing 50 vol % oxidant. Aromatic proton substitution was dramatically affected by the presence of electron-donating substituents on the aromatic substrate. Whereas high labelling yields were achieved within 1—2 h with aniline or phenol, negligible halogenation was seen even after 6 h with toluene as substrate. N.c.a. radioiodination yields were more sensitive to the substrate's susceptibility to electrophilic attack because of the relative ease of oxidation of radioiodine from hypoiodous species to higher oxidation states which do not partake in aromatic iodination reactions.

In aromatic systems which were non-activated toward electrophiles, n.c.a. halogenodemetallation yields decreased in the order Sn > Ge > Si, which reflects the relative ease of formation of the σ-complex hypothesized for metal substitution mechanism.[31,32] Unlike n.c.a. electrophilic aromatic halogenodeprotonation, labelling yields from demetallation reactions using $^{131}I^-$ exceeded those from $^{77}Br^-$. Aromatic bromodestannylation yields were high only when an acidic solvent was employed, and decreased as the percentage of oxidant was increased. By contrast, n.c.a. aromatic iododestannylation yields were high in both acidic and polar organic solvents irrespective of the oxidant concentration. Also, whereas iododestannylation yields were high in aromatic systems that were activated toward electrophilic substitution, the corresponding bromodestannylation yields decreased dramatically when electron-donating substituents were present on the aromatic ring. These differences between ^{77}Br and ^{131}I yields are probably due to differences in the relative efficiency of oxidation of the n.c.a. halide with subsequent halogenodestannylation *versus* competitive hydrolysis of the stannylated halogenation substrate.

From the context of practical applications of *in situ* generated peracetic acid as an oxidant for electrophilic aromatic halogenation in synthetic or radiosynthetic schemes, it can be concluded that aromatic halogenodemetallations are useful halogenation techniques due to their rapidity, regioselectivity of halogenation, and their ability to incorporate halogen onto aromatic sites that are non-activated toward electrophilic substitution. The great lability of the aromatic trimethyltin group to facile electrophilic displacement makes n.c.a. iododestannylation the substitution method of choice in the aromatic systems examined. Similarly, n.c.a. electrophilic bromodestannylation is a useful method for the incorporation of bromine onto non-activated positions of aromatic rings using peracetic acid. However, for aromatic systems which are activated toward electrophiles, the use of aryltrimethylgermanium or -silicon as halogenation substrates is preferable due to the greater resistance of these organometallic substrates to acid decomposition and consequential higher bromination yields.

Experimental

Reagents.—*ortho*-, *meta*-, and *para*-Isomers of the arenes shown in Figure 6 were purchased in 98—99% purity from EGA Chemie (Steinheim, FRG) for use as reference compounds in the g.c. or h.p.l.c. analysis of reaction products. *para*-Substituted aryltrimethyl-tin, -germanium, and -silicon compounds were synthesized *via* the Grignard compound of the corresponding *para*-brominated arene, purified by fractionation, and spectroscopically identified.[34] All solvents used in this investigation were of analytical grade and were obtained from E. Merck (Darmstadt).

Peracetic acid was generated[10] *in situ* by allowing a mixture of 35 wt % (11.4M) aqueous hydrogen peroxide and glacial acetic acid to stand at 25 °C for 2 h prior to application as an oxidant for n.c.a. radiohalogenation. Mixtures to be used with $^{131}I^-$ contained H_2SO_4 (typically 0.2M). All oxidant solutions were prepared fresh for each new experiment, and except for those experiments which evaluated the effect of the hydrogen peroxide to acetic acid ratio (Figure 1), a volume ratio of 11.4M aqueous H_2O_2:glacial $MeCO_2H$ = 2:1 was used.

Radioisotopes.—The $^{77}Br^-$ used in these experiments was produced *via* the $^{75}As(\alpha, 2n)^{77}Br$ 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.[25,26] The specific activity of the n.c.a. $^{77}Br^-$ was 5.6×10^4 Ci mmol^{-1}.[35] The $^{131}I^-$ used in these investigations was purchased from Amersham-Buchler (Braunschweig) with a specific activity of 5—15 Ci per mg NaI (750—2 250 Ci mmol^{-1}) 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 (1.85—3.70 MBq; 20 μl) $^{77}Br^-$ solution or 25—50 μCi (0.92—1.85 MBq; 5 μl) $^{131}I^-$ solution was dried completely in the reaction vessel.

The general labelling sequence used for the n.c.a. halogenodeprotonation reactions was to place the aromatic substrate (10 μl) into the reaction vessel and add the reaction solvent (0.5—1.0 ml), followed by addition of 10—500 μl of the oxidant (hydrogen peroxide–acetic acid mixture containing *in situ* generated peracetic acid) prepared as detailed above. The identical procedure was used for the halogenodemetallations, with the exception that the solvent and oxidant were mixed immediately prior to addition to the reaction vessel to minimize acidic decomposition of the organometallic substrate before the oxidant was added.

After stirring the mixtures for a pre-determined interval, each reaction was quenched by transferring the vessel contents to 1M aqueous $NaHSO_3$ (5 ml) cooled to 0 °C. The organic products were extracted into a dichloromethane solution of the respective halogenated standards (1 μl ml^{-1}; 5 ml), and the organic layer removed and dried ($CaCl_2$). Portions of each phase were removed and the radioactivity content was measured in a well-type γ-scintillation counter to allow calculation of the percentage organic yield.

Analysis of the Radiohalogenated Reaction Products.—The organic reaction products in the dichloromethane phase were analysed using either g.c. or h.p.l.c. For the majority of the experiments, samples (100 μl) of the organic phase were analysed by radio-gas chromatography using a discontinuous technique in which the eluted products were individually adsorbed on charcoal-filled tubes.[36] The isomeric brominated and iodinated analogues of ααα-trifluorotoluene, bromobenzene, and benzene were separated using a 4 mm × 4 m column of 6% Bentone-38 and 20% silicon oil DC-200 on Chromasorb W-AW-DMCS (60—80 mesh),[37] while the isomers of brominated and iodinated anisole, toluene, and fluorobenzene were separated using a 4 mm × 4 m column of 80% Igepal CO-880 on Chromasorb W-AW-DMCS (60—80 mesh).[38] Radiohalogenated analogues of aniline and phenol were analysed using radio-h.p.l.c. The dichloromethane phase (25 μl) was injected onto an h.p.l.c. system comprising a 0.5 × 50 cm Lichrosorb Si-60 column (Merck) with a mobile phase of either 1.5% glacial $MeCO_2H$ in n-heptane or n-heptane–di-n-butyl ether–glacial $MeCO_2H$ (500:400:7),[39] and the individual product fractions collected. The individual g.c. fractions adsorbed on charcoal or liquid h.p.l.c. fractions were counted with a well-type γ-scintillation counter. The radioactivity of the individual fractions was directly compared with that of the total

radioactivity found in portions of the inorganic and organic phase, and the radiochemical yield of each product was calculated in terms of the percentage of total radioactivity in the reaction solvent. All yields reported in this work represented the mean from 2—4 experiments.

Acknowledgements

We thank Mr. G. Blessing and Mr. H. Rosezin for the production of the $^{77}Br^{-}$.

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Received 25*th November* 1986; *Paper* 6/2269