Applied Organometallic Chemistry (1987) 1, 251–260
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0268–2605/87/01306251/$03.50

Synthesis of ^{14}C-radiolabelled trimethyllead chloride

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Received 12 November 1986 Accepted 22 December 1986

Two synthetic routes to ^{14}C-labelled trimethyllead chloride ($(CH_3)_3PbCl$) from ^{14}C-methyl iodide (CH_3I) were investigated. Alkylation of $(CH_3)_3PbCl$ with labelled methylmagnesium halide, on a microscale, was less efficient for the synthesis of tetramethyllead ($(CH_3)_4Pb$) than was an electrochemical reduction of labelled CH_3I at a sacrificial lead cathode. In the Grignard approach, unlabelled decyl bromide served as an initiator for the reaction of ^{14}C-CH_3I with excess Mg and as a carrier during the subsequent alkylation of $(CH_3)_3PbCl$. In the electrochemical approach a two-compartment cell, using dimethylformamide as solvent and sodium perchlorate as supporting electrolyte, offered several advantages over a single compartment reactor. The labelled $(CH_3)_4Pb$ from both reactions was isolated by extraction, converted to $(CH_3)_3PbCl$ by controlled oxidation with HCl and purified by thin layer chromatography.

Keywords: ^{14}C labelling, trimethyllead, organic lead, Grignard synthesis, electrochemical synthesis

INTRODUCTION

A variety of deleterious effects have been demonstrated for alkyllead salts (R_3Pb^+, R_2Pb^{2+}; $R = CH_3, C_2H_5$) which may be present in low to sub $\mu g\,kg^{-1}$ concentrations in biological samples. Recently developed methods for the speciation of lead in complex samples have demonstrated residues of alkylleads in a variety of environmental compartments: air;[1–3] rain, snow and surface waters;[4] street dusts and urban soils;[5,6] freshwater fish;[7,8] cod, lobster and flounder meal;[9] fowl[10–12] and human brains.[13] These ionic salts are considered to be more persistent yet they retain much of the acute mammalian toxicity of their tetraalkyl progenitors. Moreover they accumulate, at least temporarily, in lipophilic tissues where they mediate changes which are distinctly different from classical plumbism.

Since the persistence of these toxicants has not been well delineated, and virtually nothing is known concerning the fate of the alkyl substituents, separate procedures were sought for the synthesis of alkyllead salts: (1) labelled on the alkyl groups, or (2) incorporating a radiolabelled lead atom. The objective of the current study was to synthesize $^{14}C—(CH_3)_3PbCl$; the synthesis of $^{210}Pb—(CH_3)_3PbCl$ will be the subject of a future communication.

As a basis for further study the reaction, on a microscale, of chelated alkyllead salts and excess alkylmagnesium halides (Grignard reagents) was known to be virtually quantitative (Reaction 1).[14,15] An alternate approach, which was ultimately more efficient, involved the electrochemical reduction of an alkyl halide at a sacrificial lead cathode using dimethylformamide as solvent and sodium perchlorate as supporting electrolyte[16,17] (Reaction 2).

$$*RMgX + R_3PbX \rightarrow *RPbR_3 + MgX_2 \qquad [1]$$

$$4*RX + Pb^0 \rightarrow *R_4Pb \qquad [2]$$

It was envisaged that the resulting tetraalkyllead could then be selectively dealkylated (Reaction 3) to result in labelled trialkyllead product.

$$R_4Pb \xrightarrow{k_1} R_3PbX + RH \xrightarrow{k_2} R_2PbX_2 + RH \qquad [3]$$

A judicious choice of dealkylating agent and of reaction conditions would permit the requisite selectivity both in terms of the alkyl group to be cleaved and in terms of the extent of reaction (monodealkylation vs more extensive degradation). It was known that hard acids cleaved the

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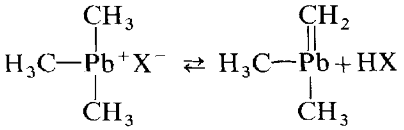
smallest alkyl group selectively from tetraalkylleads whereas softer acids cleaved the largest alkyl substituent preferentially.[18] Moreover the rate constants (k_1 and k_2 of Reaction 3) differed by a factor of 60 for $(CH_3)_4Pb$ and by a factor of 11 for $(C_2H_5)_4Pb$ for dealkylations with methanolic HCl[19] ($k_1 > k_2$).

Both ^3H and ^{14}C labelled alkyl halide of high specific activity were available commercially. Although scintillation counting of ^3H (in the presence of ^{210}Pb) is more readily accomplished than the quantitation of ^{14}C and ^{210}Pb, the latter was chosen because of the potential loss of ^3H activity in the final products by exchange reactions (Reaction 4).



$$H_3C-\overset{CH_3}{\underset{CH_3}{Pb}}{}^+X^- \rightleftarrows H_3C-\overset{CH_2}{\underset{CH_3}{Pb}}+HX \qquad [4]$$

This reaction has not been studied to our knowledge; however, analogous exchange reactions with similar organometallic cations $[(CH_3)_3Se^+, (CH_3)_4As^+]$ have been reported.[20]

MATERIALS AND METHODS

Synthesis of $^{14}C-(CH_3)_3PbCl$; Grignard method, Fig. 1

Alkylhalide mixture A

In an atmosphere of anhydrous N_2, a breakseal ampoule containing 20 μmol (1.2 μL, 2.4 mg) $^{14}C-CH_3I$ (nominally 1.85 GBq mmol^{-1}, ICN Laboratories Ltd.) was cooled to −40°C in an acetonitrile–liquid air bath, opened and diluted with 1.5 cm^3 diethyl ether (freshly distilled from $LiAlH_4$) containing 20 μL $n-C_{10}H_{21}Br$ (96 μmol, 21.3 mg). The resulting solution was quantitatively transferred to a conical Reacti-Vial containing Reagent B.

Reagent B

Degreased metallic magnesium (20 mg, 100 mesh granules, 833 μmol) was suspended in 0.2 cm^3 diethyl ether in a 5 cm^3 conical Reacti-Vial (equipped with a triangular magnetic stirring bar and a teflon lined silicon septum) and reacted with 20 μL $n-C_{10}H_{21}Br$ (96 μmol, 21.3 mg). Alkylhalide mixture A was then added dropwise to the resulting reaction mixture.

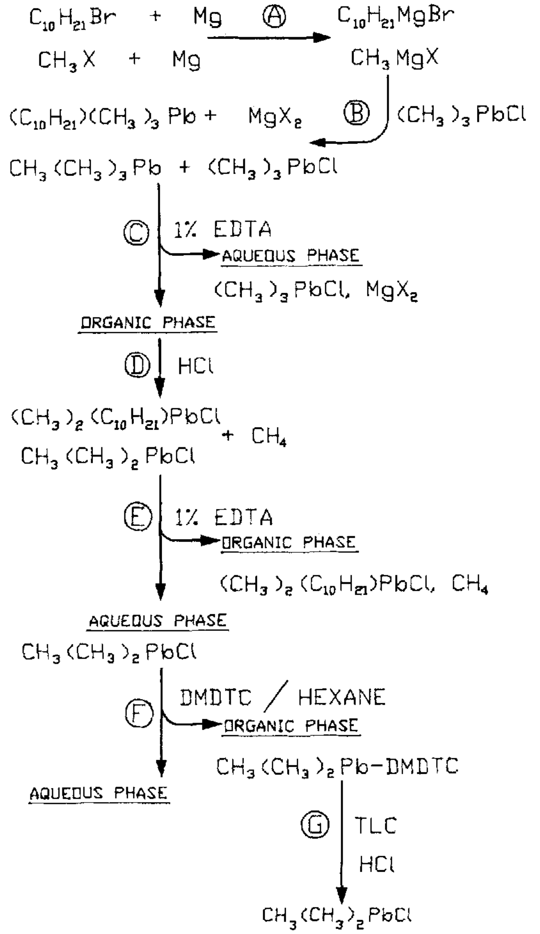


Figure 1 Synthetic route to $^{14}C-(CH_3)_4Pb$ via a Grignard reaction.

Step C

After 15 min reaction of Alkylhalide mixture A with Reagent B the supernatant was transferred to a second conical Reacti-Vial containing 41 mg $(CH_3)_3PbCl$ (260 μmol) suspended in 0.5 cm^3 anhydrous THF (freshly distilled from $LiAlH_4$). After 30 s reaction the resulting mixture was extracted with three 1 cm^3 portions of 1% tetrasodium ethylenediaminetetraacetate (Na_4EDTA). The organic phase was transferred to a 15 cm^3 graduated centrifuge tube, diluted to 8 cm^3 with Et_2O and dried over Na_2SO_4.

Synthesis of $^{14}C—(CH_3)_3PbCl$; Electrochemical method, Fig. 2

Electrochemical reactor

The reactor (Fig. 3) consisted of a 2 cm^3 filtration funnel with a built in fine porosity glass filter (Pyrex No. 36060). The lower portion of the funnel was bent so as to form a smooth 180° arc and the exit was sealed with a shaped plug of silicon glue (H, Fig. 3). A silver wire (26 gauge; I, Fig. 3), which served as the anode, was introduced 1 cm into the lower compartment (via the silicon plug) which was filled with 5% $NaClO_4$ in anhydrous DMF. The upper cathodic compartment was sealed with a rubber septum (Suba-Seal #17, W. Freeman and Co., Barnsley, UK; C, Fig. 3). The cathode consisted of a 4 cm^2 × 0.13 mm polished lead foil (D, Fig. 3) which was cut into longitudinal strips, curled and folded so as to fit into the compartment which was filled with 1 cm^3 5% $NaClO_4$ in DMF and swept with a gentle stream of N_2. Stainless steel needles (B, G, Fig. 3) served as N_2 entry and exit ports. Potential was applied to the Pb foil via a steel wire (A, Fig. 3) inserted through the rubber septum. Rectified current was controlled by a power supply. Potential and current were monitored continuously during the reaction.

Alkylhalide A

In an atmosphere of anhydrous N_2 a breakseal ampoule containing 8.8 μL $^{14}C—(CH_3)I$ (nominally 2.11 GBq mmol^{-1}, Amersham Corp., Oakville Ont.) was cooled to −60°C in a liquid air–DMF slurry, opened and diluted with two 0.5 cm^3 aliquots of 5% $NaClO_4$ in DMF. The resulting solution was diluted with 26.4 μL unlabelled CH_3I and transferred quantitatively to the cathodic compartment of the electrochemical reactor.

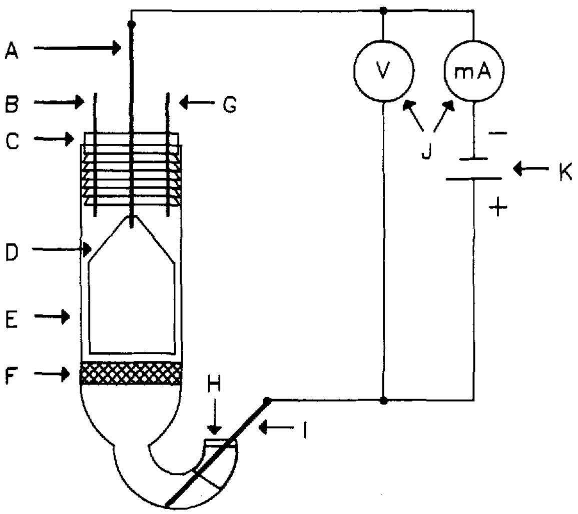


Figure 3 Electrochemical reactor composed of a 2 cm^3 capacity filter funnel and (A) stainless steel wire, (B, G) stainless steel needles for N_2 entry and exit ports, (C) rubber septum, (D) lead foil cathode, (F) fine porosity glass filter, (H) plug of silicone glue and (I) silver wire anode.

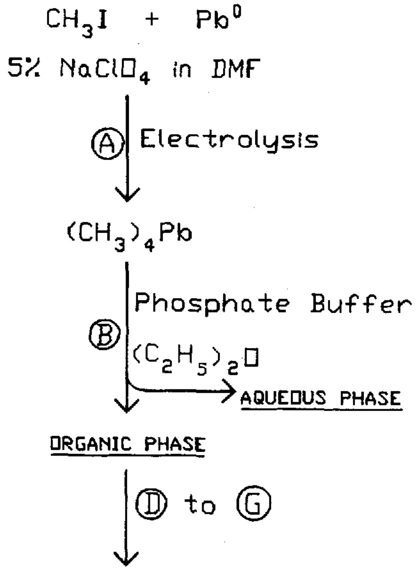


Figure 2 Synthetic route to $^{14}C—(CH_3)_4Pb$ via an electrochemical reaction.

Step C

After 9 min electrolysis (13.1 v, 35.2 μmol CH_3I) the current was stopped and the reaction mixture was quantitatively transferred to a 15 cm^3 test tube containing 5 cm^3 phosphate buffer (0.2 mol dm^{-3}, pH 9.0) and 1 cm^3 diethyl ether. The cathodic compartment was rinsed with two 1 cm^3 portions of diethyl ether; the organic phases were combined and extracted with two aliquots (5 cm^3) of pH 9.0 phosphate buffer. The aqueous washes were back extracted with 2 cm^3 diethyl ether, the organic phases were combined, dried over Na_2SO_4 and the final volume was adjusted to 5 cm^3.

Synthesis of $^{14}C—(CH_3)_3PbCl$

The dried ethereal solution (5 cm^3) containing $^{14}C—(CH_3)_4Pb$ was transferred to a 25 cm^3 three-necked conical flask equipped with a condenser–drying tube assembly, a capillary bubbler, a Suba-Seal septum and a magnetic stirring bar. A gentle flow of gaseous HCl was maintained through the reaction solution which had been cooled to 0°C. Once the reaction was complete, the reaction mixture was cooled to -50°C and the mixture was slowly neutralized with $10\,cm^3$ cold $2\,mol\,dm^{-3}$ NaOH. The reaction vessel was washed with two $5\,cm^3$ portions of 1% Na_4EDTA and the aqueous fractions were combined and neutralized.

Purification of $^{14}C-(CH_3)_3PbCl$

Aqueous sodium dimethyldithiocarbamate ($3\,cm^3$ of $3\,mol\,dm^{-3}$ NaDMDTC) was added to the crude product solution. Trimethyllead cation was extracted complexometrically with three $5\,cm^3$ portions of hexane. The organic extracts were combined, cooled to -50°C to remove water, transferred and concentrated to $0.5\,cm^3$ under a gentle stream of N_2. The concentrate was applied to the origin of a 20 × 20 cm × 0.1 mm Polyamide-6 TLC plate (Brinkmann Instruments, Toronto Ont.) and eluted with 3/1 (v/v) n-hexane/diethyl ether. Pretreatment of the thin layer plate consisted of a single light spray of 5% methanolic NaDMDTC followed by air drying for 0.5 h. The chromatographic support containing $^{14}C-(CH_3)_3Pb$ DMDTC was cut in small pieces and extracted with several $5\,cm^3$ portions of $1\,mol\,dm^{-3}$ HCl. The combined aqueous extracts were neutralized with $10\,mol\,dm^{-3}$ NaOH.

Speciation of alkylleads and decyl containing products

Alkylleads were speciated by gas chromatography–atomic absorption spectrometry (GC–AAS) as described previously;[21] quantitation was performed by comparison of peak areas with those of authentic standards. Alkyllead chlorides (R_3PbCl, R_2PbCl_2; $R = CH_3$, C_2H_5) and alkyllead butylates (R_3PbBu, R_2PbBu_2; $Bu = n-C_4H_9$) were prepared as previously described.[21,22] Decyl containing products, from radioinactive optimization studies, were separated on a 2 m × 0.32 cm glass column containing 10% OV 101 on 100–120 mesh Supelcoport (Supelco Canada, Oakville, Ont.) and detected by flame ionization. Operating conditions were as follows: carrier gas, N_2 $30\,cm^3\,min^{-1}$; injector temperature 150°C; detector temperature 250°C; temperature program, isothermal at 50°C for 2 min followed by linear ramping to 150°C at 5°/min. Alkanes, alkyl halides and alcohols were quantified by comparison of peak areas with those of authentic standards.

Determination of radioactivity

Activity, present in different fractions from the radiosynthesis, was determined by liquid scintillation counting. After appropriate dilution, small aliquots of key fractions were diluted with scintillation cocktail ($5\,cm^3$, Universol, Amersham Corp.) and counted after 12 h darkening. Counts were automatically corrected for background and quenching (if any) by the channels ratio method. Autoradiographic visualization techniques for thin layer chromatograms were as described previously.[23]

RESULTS AND DISCUSSION

The synthetic sequence which was employed for the Grignard route to $^{14}C-(CH_3)_4Pb$ is outlined in Fig. 1. The preparation of alkylmagnesium halides (Grignards), on a microscale, is technically demanding; in our hands acceptable yields could not be achieved if 1–2 mg of CH_3I was dissolved in sufficient solvent required for the quantitative recovery of the labelled substrate from the breakseal ampoule. As an alternate approach it was decided to initiate the reaction by adding a long chain alkyl halide (n-decyl bromide) to excess magnesium (Step A, Fig. 1) then to add the $^{14}C-CH_3I$ to the mixture once the reaction had been initiated. The resulting mixture of $^{14}C-(CH_3)MgX$ and $C_{10}H_{21}MgBr$ was removed from the excess Mg metal (the latter might catalyze the transalkylation of organoleads) and added dropwise to an excess of $(CH_3)_3PbCl$ suspended in diethyl ether. The reaction was stopped after 0.5 min by adding 1% NaEDTA. Companion control studies indicated that the reaction of RMgX ($R = CH_3$, C_2H_5, C_4H_9) with $(CH_3)_3PbCl$ was virtually instantaneous and that magnesium salts, formed during the reagent preparation and reaction, caused a slow redistribution of alkyl groups (transalkylation) among the lead containing species. To minimize redistribution the reaction was quenched after 0.5 min.

The crude reaction mixture was extracted with 1% Na_4EDTA (Step C, Fig. 1). The addition of this reagent increased the extraction efficiency of ionic alkylleads from the organic phase into the aqueous phase. At levels used in this synthesis $(CH_3)_3PbCl$ is appreciably soluble in more polar organic solvents. The organic phase containing ^{14}C—$(CH_3)_4Pb$ was chlorinated selectively with gaseous HCl (Step D, Fig. 1). The course of the oxidation in companion control studies (using unlabelled substrates) was monitored by gas chromatography–atomic absorption spectroscopy (GC–AAS). Although some tailing of the products, $(CH_3)_3PbCl$ (B, Fig. 4) and $C_{10}H_{21}(CH_3)_2PbCl$ (D, Fig. 4) was evident in the chromatograms the progress of the reaction was readily monitored. After 1 h, the reaction solution was carefully neutralized then extracted with 1% Na_4EDTA to selectively recover ^{14}C—$(CH_3)_3Pb^+$ cation. This procedure was surprisingly ineffective at removing $C_{10}H_{21}(CH_3)_2Pb^+$ moiety from the reaction solution. Only traces of decyldimethyllead chloride were recovered in the aqueous phase of control runs. The aqueous phase (Step E, Fig. 1) was extracted complexometrically with hexane-dimethyldithiocarbamate (DMDTC) to recover ^{14}C—$(CH_3)_3Pb^+$ cation and residues of $C_{10}H_{21}(CH_3)_2Pb^+$ cation. This extract was dried, concentrated and separated by preparative thin layer chromatography on a polyamide-6 plate using 3:1 (v/v) n-hexane diethyl ether as eluent.

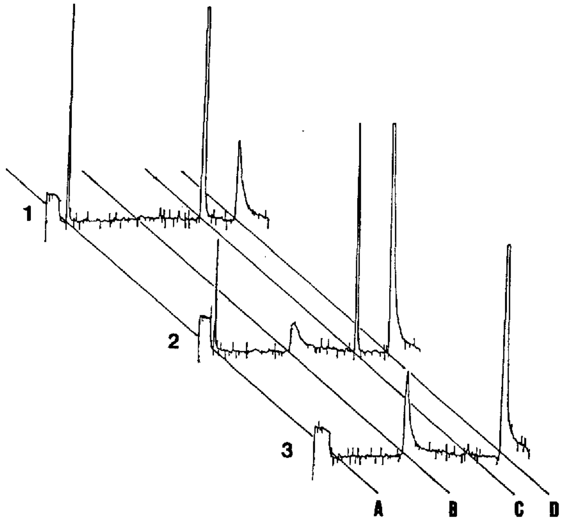


Figure 4 GC–AAS chromatograms of aliquots from the reaction of HCl with a mixture of $(CH_3)_4Pb$ and $(CH_3)_3(C_{10}H_{21})Pb$ after 1, 0 min; 2, 30 min; or 3, 60 min reaction. The components are: A, $(CH_3)_4Pb$; B, $(CH_3)_3PbCl$; C, $(CH_3)_3(C_{10}H_{21})Pb$ and D, $(CH_3)_2(C_{10}H_{21})PbCl$.

Neither silica gel, alumina nor polyamide TLC plates were effective media for the separation of alkyllead-diphenylthiocarbazone (dithizone) complexes. Only free dithizone was observed to migrate on any of the three stationary phases indicating extensive degradation of the test complexes. The corresponding alkyllead-DMDTC complexes were also extensively degraded on both silica gel and alumina plates. These observations were somewhat surprising in that the inorganic lead-DMDTC complex has been reported to be a stable and mobile analyte in both gas chromatographic[24, 25] and liquid chromatographic separations.[26] When visualized by fluorescence quenching (UV-254 nm) alkyllead-DMDTC complexes were observed to have migrated as concentrated spots on the relatively less polar polyamide-6 plates if n-hexane or diethyl ether had been used as eluent. With 3/1 n-hexane diethyl ether a complete separation of the DMDTC complexes of Pb^{2+}, $(CH_3)_3Pb^+$, $(CH_3)_2Pb^{2+}$, $(C_2H_5)_3Pb^+$, $(C_2H_5)_2Pb^{2+}$ and $C_{10}H_{21}(CH_3)_2Pb^+$ was achieved. Relative mobilities of these complexes are recorded in Table 1.

Table 1 Relative mobilities of alkyllead–DMDTC complexes on polyamide-6 TLC plates using 3:1 n-hexane/diethyl ether as eluent

Species	R_f
Pb–$(DMDTC)_2$	0.00
$(CH_3)_2Pb$–$(DMDTC)_2$	0.35
$(C_2H_5)_2Pb$–$(DMDTC)_2$	0.49
$(CH_3)_3Pb$–DMDTC	0.68
$(C_2H_5)_3Pb$–DMDTC	0.75
$(CH_3)_2C_4H_9Pb$–DMDTC	0.75
$(CH_3)_2C_{10}H_{21}Pb$–DMDTC	0.80

Recovery trials, using unlabelled substrates, indicated that recoveries of up to 30%, as $(CH_3)_4Pb$, were possible when starting with 2–3 mg CH_3I. To probe the fate of decyl and methyl groups during the synthetic sequence (Steps A to C, Fig. 1) crude product mixtures from radioinactive optimization trials, were analyzed by both GC–AAS and GC–FID. Reactions were replicated at least twice under each experimental condition to assess the reproducibility of the observations which are recorded in Table 2.

Using reaction conditions and substrate concentrations which replicated the proposed

Table 2 Organolead and decyl containing products in reaction mixtures

Experiment	Reactants (µmol)	Products	µmol	% yield
1		Organolead		
		$(CH_3)_4Pb$	12 ± 3	24 ± 6
	$C_{10}H_{21}Br$ (200)	$C_{10}H_{21}(CH_3)_3Pb$	9 ± 4	4 ± 2
	CH_3I (50)	Aliphatic		
	Mg^0 (833)	$C_{10}H_{22}$	40 ± 7	20 ± 3
	$(CH_3)_3PbCl$ (260)	$C_{10}H_{21}OH$	92 ± 9	46 ± 4
		$C_{10}H_{21}Br$	1.4 ± 0.6	0.7 ± 0.3
		$C_{11}H_{24}$	3.3 ± 0.5	1.6 ± 0.2
		$C_{20}H_{42}$	25 ± 5	25 ± 5
2		Organolead		
		$(CH_3)_4Pb$	ND	ND
	$C_{10}H_{21}Br$ (200)	$C_{10}H_{21}(CH_3)_3Pb$	ND	ND
	Mg^0 (833)	Aliphatic		
	$(CH_3)_3PbCl$ (260)	$C_{10}H_{22}$	43 ± 5	21 ± 2
		$C_{10}H_{21}OH$	98 ± 10	49 ± 5
		$C_{10}H_{21}Br$	3 ± 1	1.5 ± 0.5
		$C_{11}H_{24}$	ND	ND
		$C_{20}H_{42}$	24 ± 6	24 ± 6
3		Organolead		
	$C_{10}H_{21}Br$ (200)	$(CH_3)_4$	0.2 ± 0.1	0.4 ± 0.2
	CH_3I (50)	$C_{10}H_{21}(CH_3)_3Pb$	ND	ND
	Mg^0 (833)	Aliphatic		
	$(CH_3)_3PbCl$ (260)	$C_{10}H_{22}$	9 ± 3	4.5 ± 1.5
		$C_{10}H_{21}OH$	72 ± 13	36 ± 6.5
		$C_{10}H_{21}Br$	79 ± 8	39 ± 4
		$C_{11}H_{24}$	ND	ND
		$C_{20}H_{42}$	16 ± 4	16 ± 4

radiolabelled synthesis (Experiment 1) $C_{10}H_{21}(CH_3)_3Pb$ accounted for $4 \pm 2\%$ and n—$C_{10}H_{22}$ accounted for a further $20 \pm 3\%$ of the reactant $C_{10}H_{21}Br$. The latter product indicated that dimerization of decyl radicals was extensive. Undecane ($1.6 \pm 0.2\%$) resulting from the analogous combination of decyl with methyl radicals and unreacted $C_{10}H_{21}Br$ ($1.5 \pm 0.5\%$) were minor products. Decanol ($46 \pm 4\%$) was the major side product. Surprisingly, if crude mixtures of n—$C_{10}H_{21}Br$ and Mg^0 were quenched with water approximately equal amounts of n—$C_{10}H_{22}$ and n—$C_{10}H_{21}OH$ were formed.

The recoveries of decyl-containing products (Experiment 2, Table 2) were not appreciably changed if CH_3I was omitted in Step A (Fig. 1) indicating that the addition of 0.25 equivalents of CH_3I (relative to $C_{10}H_{21}Br$) had little effect on the fate of the decyl groups. Interestingly, $C_{10}H_{21}(CH_3)_3Pb$ was not formed in the absence of CH_3I. Low yields of $C_{10}H_{21}(CH_3)_3Pb$ (attributed to the lower reactivity of the decyl Grignard) had been anticipated and was considered an advantage of the synthetic approach. Apparently, decylation of the $(CH_3)_3PbCl$ was not possible in this system unless a co-factor originating from RMgX ($R = CH_3$, C_2H_5 or C_4H_9) was present.

In a modification of the synthetic sequence (Experiment 3) CH_3I (50 µmol) and $C_{10}H_{21}Br$ (100 µmol) were added directly to the supernatant from the reaction of $C_{10}H_{21}Br$ (100 µmol) with excess Mg metal. The amended reaction mixture was added to excess $(CH_3)_3PbCl$. The absence of $C_{11}H_{24}$ in the product mixture excludes the possibility of a nucleophilic displacement of iodine (in CH_3I) by $C_{10}H_{21}^-$. This observation supports the radical recombination mechanism for the formation of $C_{11}H_{24}$. Efforts to initiate the reaction with decyl bromide, remove the supernatant and then add CH_3I to the activated Mg metal, resulted in only traces of the desired product.

Earlier work had indicated that if limited quantities of alkyllead salts were to be alkylated with excess Grignard reagent yields were improved appreciably if the salts were present as complexes (either dithizonates or dithiocarbamates). The converse was not true; if alkyllead salt was to be alkylated with limited quantities of Grignard, yields were depressed if the salts were complexed prior to reaction. These observations were corroborated when attempts were made to monoalkylate dimethyllead chloride. The insolubility of the salt in organic solvents required that it be complexed prior to reaction. No trimethyllead moiety was detected in crude product mixtures from this reaction.

Despite the low yield anticipated in this synthetic approach a run was conducted with ^{14}C—CH_3I to evaluate the efficiency of subsequent stages of the synthesis. Losses of activity at each step of the synthesis are reported in Table 3. The recovery of ^{14}C—$(CH_3)_4Pb$ was disappointingly low (6.5% as determined by GC–AAS). Considerable activity was lost as volatile products (possibly as CH_4, C_2H_6 or as CH_3OH); however the subsequent oxidation, isolation and purification by TLC resulted in a recovery of 85% for these steps. The specific activity of the final product was lower than anticipated ($0.89\,\mathrm{GBq\,mmol^{-1}}$ vs $0.75 \times 1.85\,\mathrm{GBq\,mmol^{-1}}$), reflecting a loss of activity resulting from exchange processes.

Whereas TLC of micromolar amounts of $(CH_3)_3Pb$–DMDTC complex resulted in a single well resolved spot in the system under study, identical chromatography of 1 nmol of labelled complex (autoradiography for 48 h) indicated that tailing and/or degradation was extensive (Chromatogram 1, Fig. 5). The same amount of complex was successfully chromatographed if the polyamide-6 plate was lightly sprayed with 5% methanolic DMDTC and air dried for 0.5 h prior to chromatography. If the chromatographic sup-

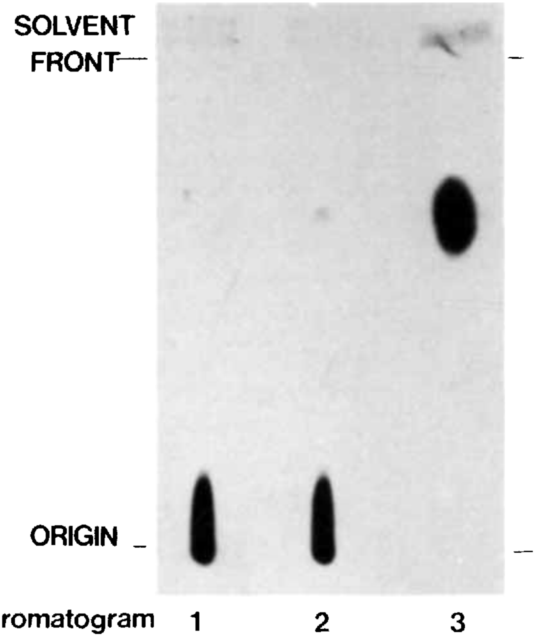


Figure 5 Autoradiograms of: 1, 1 nmol ^{14}C—$(CH_3)_3PbCl$ on a polyamide-6 plate using 3:1 hexane/diethyl ether as eluent; 2, reeluted after overspotting the origin of (1) with 1 μmol $(CH_3)_3Pb \cdot$DMDTC; 3, reeluted after spraying the plate (2) with 5% methanolic DMDTC and air drying for 0.5 h.

Table 3 Percent of initial activity and chemical yields at various stages of the synthetic sequences

Method	Reaction		% Activity[a]	% Chemical yield[b]
Grignard	Step C	aqueous	17.6	
		organic	12.9	6.5
	Step F	organic	4.7	
	Step G	final product	3.5	5.5
Electrochemical	Step B	organic	74.5	55.7
		aqueous	20.0	
	Step F	organic	47.3	
		aqueous	16.7	
	Step G	final product	23.6	30.7

[a] Activity expressed as a percent of initial activity nominally present in the breakseal ampoule

[b] Chemical yield based on quantity of CH_3I nominally present in the breakseal ampoule

port was extracted with dilute HCl appreciable amounts of zinc from the manganese activated zinc silicate fluor, which had been incorporated into the chromatographic support, were co-extracted resulting in contamination of the final solution. This was eliminated by switching to polyamide-6 plates which did not contain any fluorescent indicator.

The stability of the complex during chromatography was investigated by chromatography (and consequently degrading) 1 nmol of labelled complex on a plate which had not been pretreated (Chromatogram 1, Fig. 5). One μmol of unlabelled complex was then applied to the origin of the eluted plate and the plate was rechromatographed in the same solvent system (Chromatogram 2, Fig. 5). Visualization by fluorescence quenching indicated a single sharp spot (R_f 0.68); autoradiography indicated a longitudinal spot at the origin and only a trace of activity at R_f 0.68. However when the plate was sprayed with 5% methanolic DMDTC, dried and eluted a third time both fluorescence quenching and autoradiography indicated only a single sharp spot, R_f 0.70 (Chromatogram 3, Fig. 5). These observations are consistent with an immobilization of nanomolar quantities of $^{14}C—(CH_3)_3Pb^+$ cation on the chromatographic support which was not remobilized by exchange with inactive $(CH_3)_3Pb^+$ cation present in large excess as complex. By treating the plate with DMDTC the activity was recomplexed and remobilized. More importantly, there was no evidence of oxidative decomposition during chromatography.

An alternate approach to the synthesis of tetraalkylleads proved to be more successful. It had been reported that high yields of tetraalkylleads could be obtained by electrolyzing dimethylformamide (DMF) solutions of alkylhalides in an undivided cell using a zinc cathode and a sacrificial lead anode.[27] The process is considered to involve a cathodic production of alkylzinc compounds which react at the anode to produce the desired tetraalkyllead.

Using a miniaturized cell (4 cm^3 capacity) fitted with a zinc cathode and a lead foil anode and 5% $NaClO_4$ in DMF as supporting electrolyte, yields were dependant on the concentration of CH_3I as well as on the reaction time and temperature. At higher applied potentials the reaction solution coloured rapidly and developed a non-conducting precipitate. At higher concentrations of CH_3I (800 μmol) yields approached 90%, however they decreased very rapidly with longer reaction times. The colour resulted, in part, from the production of I_2 which rapidly oxidized the desired $(CH_3)_4Pb$. To minimize the reaction of I_2 with tetraalkylleads a two-compartment cell (Fig. 3) was designed which employed a lead cathode and a silver anode.

A series of optimization experiments were used to define conditions for the radiochemical synthesis. Reaction parameters and maximum yields are presented in Table 4. The progress of each reaction with time is presented in Fig. 6. If 88 μmol CH_3I (10 times the quantity to be used in the radiosynthesis) was added to the cathodic compartment containing 1 cm^3 of electrolyte nearly quantitative yields (R1, Fig. 6) were observed after 9 min of electrolysis. Moreover the product was relatively stable to further electrolysis. If only 35.2 μmol CH_3I were electrolyzed (R2, Fig. 6) lower yields of $(CH_3)_4Pb$ were observed. By doubling the applied voltage while maintaining other variables constant the yield was restored (R3, Fig. 6). The higher current

Table 4 Maximum yield of $(CH_3)_4Pb$ from reactions performed under different experimental conditions

Reaction	$[CH_3I]$ (mM)	Voltage (V)	Cathode surface area (cm^2)	Maximum % yield $(CH_3)_4Pb$	(time)[a]
R1	88.0	13.1	1.0	91.5	(9.0)
R2	35.2	12.9	1.0	66.4	(9.0)
R3	35.2	26.5	1.0	88.0	(3.0)
R4	35.2	13.1	4.0	71.8	(6.0)
R5	8.8	13.1	1.0	18.0	(6.0)
R6	8.8	13.1	2.0	24.0	(3.0)
R7	8.8	12.0	4.0	49.0	(3.0)

[a] Number in brackets indicates the time (min) at which the maximum yield of product was observed

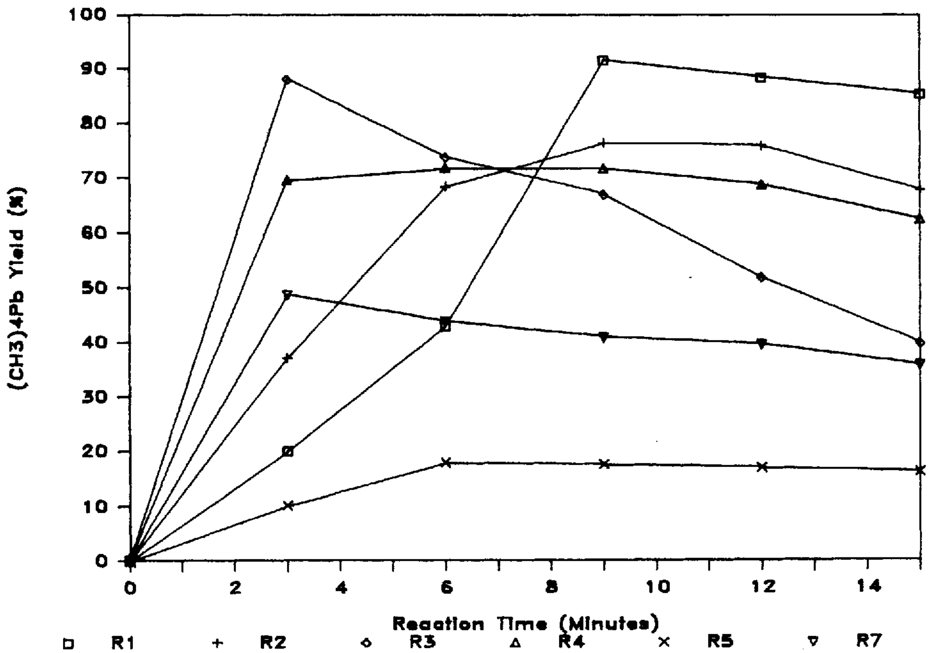


Figure 6 Yield of $(CH_3)_4Pb$ as a function of time for the electrochemical reaction of CH_3I with Pb^0.

density resulted in 88% yield after 3 min; however further electrolysis rapidly degraded the product at an average rate of −10%/min. Reaction R4 replicated the conditions of R2 except that the area of the cathode was quadrupled. An acceptable yield of $(CH_3)_4Pb$ was observed after 6 min and the product remained stable during subsequent electrolysis. Reacting only 8.8 μmol CH_3I resulted in comparatively lower yields (R5, Fig. 6) which could be improved by increasing the surface area of the cathode (R6, R7).

Optimum conditions were considered to be those of Reaction 4 (applied voltage, 13.1 v; cathode surface area, 4 cm^2; CH_3I, 35.2 μmol). Since the stoichiometry of the reaction required $4CH_3I$ per reacting Pb atom, the addition of three parts of unlabelled CH_3I (26.4 μmol) to the $^{14}C—CH_3I$ (8.8 μmol) would not dilute the specific activity of the product. If the chemical yield is not a primary consideration, the specific activity of the $(CH_3)_4Pb$ could be quadrupled relative to the reactant. Alternately, a nearly quantitative yield of tetraalkyllead could be achieved if the starting $^{14}C—CH_3I$ was diluted with 9 parts of unlabelled CH_3I. In this case the specific activity of the product would be diluted 2.5 fold.

The product $^{14}C—(CH_3)_4Pb$ was separated from the basified crude reaction mixture by extraction with diethyl ether (Step B, Fig. 2). The organic phase was dried, oxidized, extracted complexometrically and purified by TLC (Steps D to G, Fig. 1). Losses in activity at key stages in the electrochemical synthesis were monitored by liquid scintillation counting (Table 3). Recovery of $^{14}C—(CH_3)_4PbCl$ (55.7% by GC–AAS), although lower than expected, was acceptable. There was no apparent loss of activity from the formation of volatile products and the specific activity of the product $^{14}C—(CH_3)_3PbCl$ recovered from the TLC plate (1.54 ± 0.03 GBq mmol^{-1}) was equal to the anticipated activity (0.75 × 2.11 GBq mmol^{-1}). Despite precautions the combined recovery for steps D to G was lower than anticipated (56%). The oxidation is difficult to control and was more rapid at −50°C than at 0°C once the reaction had commenced. The oxidation of tetraalkylleads to dialkyllead salts can be accomplished with a variety of oxidizing agents;[28] the electrochemical synthesis of $^{14}C—R_4Pb$ followed by controlled oxidation thus provides a general route to these salts as well.

The availability of these products will permit the initiation of studies into two aspects of concern to environmental chemists. The potential of these organolead toxicants to inhibit enzymes by methylating active sites or by binding to these sites has not, to our knowledge, been studied in detail by radiolabelling methods. Additionally, persistence trials will be greatly facilitated. Although generally considered to be more persistent than their tetraalkyl progenitors there remains a paucity of information on the environmental stability of these triorganolead salts.

Acknowledgement Financial support from the National Science and Engineering Research Council of Canada (G0316 and A6687) is gratefully acknowledged.

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