PREPARATION OF HIGH-PURITY CARRIER-FREE ^{123}I-IODINE MONOCHLORIDE AS IODINATION REAGENT FOR SYNTHESIS OF RADIOPHARMACEUTICALS, IV

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This is the first detailed report of a satisfactory method of the production and preparation of ^{123}I iodination reagents, specifically ^{123}ICl and $^{123}ICl_2^-$, in which the iodination reagent has ≥99.8% radiochemical purity as ^{123}I (the only radioimpurity is ^{125}I). The reagent may be obtained carrier-free in nonaqueous or aqueous media. Iodine-123 fulfills the criteria for an ideal gamma-emitting radionuclide for in situ and in vivo diagnostic procedures more closely than any other isotope of iodine (*1–3*). Iodine-123 is desirable for nuclear medicine applications because the 13.1-hr half-lived isotope decays principally by electron capture emitting a 159-keV photon. This energy radiation is optimum for tissue penetration and for detection on high-resolution counting equipment. The radiation exposure from equal amounts of ^{123}I will not exceed a few percent of that delivered in ^{131}I clinical applications and diagnostic examinations. Further by using ^{123}I, a radiopharmaceutical may be administered at frequent intervals.

Undesirable negatron decay is absent in decay of ^{123}I. The upper limit of positron emission is at 0.01% (*4*). Use of ^{123}I has been delayed because most methods of production (*5–11*) have yielded ^{123}I that is contaminated at the time of production with about 0.5–2% of ^{124}I (4.2 days), ^{126}I (13.1 days), and lesser quantities of other radionuclides even in the best cases. Even with less than 1% ^{124}I contamination, the useful features of ^{123}I are negated (*12,13*).

Satisfactory methodology and techniques for obtaining ^{123}I in ≥99.8% radiochemical purity, where the only radioimpurity is ≤0.2% ^{125}I (γ = 40 keV, 60 days), have been developed by V. J. Sodd, et al (*11*) and at BNL. This paper reports the preparation of radioiodination reagents for labeling pharmaceuticals with ^{123}I on a carrier-free or diluted scale in either nonaqueous or aqueous media. The iodination reagents may be prepared from the iodine monochloride and from the iodine or iodide atom or ion by the following methods a–e which are initiated by the $^{123}Xe \xrightarrow{(\beta^+, E.C.)}{}^{123}I$ nuclear decay processes.

I. Auger Effect Activation
   (a) ICl (excess) + ^{123}Xe → ^{123}I-ICl (diluted) + ?
   (b) Cl_2 (excess) + ^{123}Xe → ^{123}ICl (carrier-free) + ?
   (c) NOCl (excess) + ^{123}Xe → ^{123}ICl (carrier-free) + ?

II. Auger Effect Activation and Chemical Synthesis
   (d) 1. ^{123}Xe (Pyrex vessel) $\xrightarrow[6\text{-}8\ hr]{77°K}{}^{123}I + \xrightarrow{NaOH}$ $^{123}I^-$ + ?
   2. 2 $^{123}I^-$ + 3H^+ + IO_3^- + 3Cl^- → 3 $^{123}ICl_2^-$ (diluted, aqueous)
   (e) 1. ^{123}Xe + ½ I_2 → ^{123}I-I_2
   2. ^{123}I-I_2 + 2NOCl → 2NO + ^{123}ICl + ICl (diluted)
   3. ^{123}I-I_2 + Cl_2 (excess) → ^{123}ICl + ICl
   $\overset{I_2}{+}\ Cl_2$ → ^{123}I-ICl

Data and methodology pertaining to the preparation of iodination reagents are presented for the chemical reactions initiated as outlined in a–d. Previously Method II(d)2 has been extensively employed as an iodination route for ^{131}I, ^{125}I, and ^{124}I. Only the last example II(e)3 is clearly not applicable as a convenient route to ^{123}ICl. Examples of use of ^{123}I in the synthesis of several model radiopharmaceuticals (diiodosalicylic acid, iophenoxic acid, ^{123}I-serum albumin and monoiodo- and diiodo-L-tyrosine) are presented. Finally the merits of the preparation of iodinated radiopharmaceuticals over direct synthesis induced by autoradiation labeling are briefly discussed.

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EXPERIMENTAL

Cyclotron parameters. Carrier-free ^{123}I is produced by the decay of ^{123}Xe which in turn is produced by the ^{4}He bombardment of ^{122}Te; $^{122}Te(^{4}He,3n)^{123}Xe$, $^{123}Xe \xrightarrow[2.1\ hr]{\beta^+,\ E.C.} {}^{123}I$. The BNL 60-in. cyclotron provided a deflected ^{4}He beam of 7–10 μA on an external generator-type target (*11–14*) in which the alpha beam was degraded (E_α = 46–35 MeV)*. The ^{122}Te metal was purchased from Oak Ridge National Laboratory in $\gtrsim$95% enrichment as ^{122}Te. A schematic diagram of our automated apparatus is shown in Fig. 1.

The ^{123}Xe, ^{125}Xe, and radiohalogens are continuously flushed from the target in a dried helium stream passing through $\frac{3}{16}$-in. i.d. Teflon tubing (Applied Science Laboratories, Inc.) to a fume hood 80 ft external to the cyclotron vault. The radiohalogen contamination is selectively removed from the ^{123}Xe and ^{125}Xe by passing the helium stream carrying the active gases through a 10 cm × 16 mm quartz furnace containing wadded high-purity silver wire (size 6.3 mil, Handy and Harman Co.) heated to 280–320°C. The chemical scrubber is exceptionally efficient since at the elevated temperature the silver and radioiodine already in the gas react to form silver iodide. The silver furnace method is superior in all respects to the other suggested methods (*9–11*) that rely on condensation of radioiodides in copper traps held at −78°C.

The radioxenons are subsequently quantitatively condensed in Pyrex radiator traps held at 77°K. The traps are equipped with Teflon vacuum stopcocks and fabricated of 10 × 8 mm, 5 × 3 mm, and 10 × 8 mm tubing of the lengths of 22, 200, and 22 cm, respectively. Prior to use the traps are thoroughly washed in a hot H_2SO_4/HNO_3 bath, rinsed to neutral pH with distilled water, and vacuum dried. Immediately before use the traps are mounted on a vacuum line and flamed under vacuum. The traps are then cooled under vacuum, mounted on the collection line, purged with dry helium, and cooled with liquid nitrogen. After the collection period the ^{123}Xe is allowed to decay to ^{123}I; or it can be transferred by vacuum distillation to an appropriate reaction vessel (Pyrex or quartz ampoules of 2–10 cc volume), sealed off, and allowed to decay.

If the decay of the xenon isotopes is permitted to occur for 6–7 hr after the midpoint of short irradiations ($\lesssim$1 hr), the yield of ^{123}I is at the maximum obtainable via transfers involving ^{123}Xe. Under these conditions the contribution of ^{125}I is minimized. If enriched ^{122}Te is used and the incident E_α is 46 MeV, primarily ^{123}Xe and ^{125}Xe are produced. However, if the deuteron contribution in the alpha beam is significant (estimated to be $\lesssim$0.01% with the BNL cyclotron) the d,xn reactions will produce ^{121}I, ^{124}I, and ^{130}I in very low radiochemical yields (*15*). In our case the ^{124}I probably arises from the $^{122}Te(^{4}He,pn)^{124}I$ reaction.

The radionuclidic purity of ^{123}I obtained is $\geq$99.8%, and since approximately 1% of ^{124}I produced directly is scrubbed out, the only radiocontaminant is $\leq$0.2% ^{125}I. Both the ^{123}I and ^{125}I are formed by the $^{122}Te(^{4}He,3n)^{123}Xe \xrightarrow[2.1\ hr]{\beta^+,\ E.C.} {}^{123}I$ and the $^{122}Te(^{4}He,2n)^{125}Xe \xrightarrow[17.6\ hr]{E.C.} {}^{125}I$ nuclear transformations. The xenon isotopes are not affected by the silver furnace as the active gases pass through. The lines in the gamma spectrum of ^{123}Xe and ^{123}I have been published elsewhere (*4,15–17*). Our identification was made with a Ge(Li) detector using the published spectra. The production rate (based on

* Further details concerning the release of ^{123}Xe from alpha irradiated tellerium and the organic chemical reactivity of the $^{123}Xe \rightarrow {}^{123}I$ nuclear transformation are topics of a separate study to be published elsewhere (*14*).

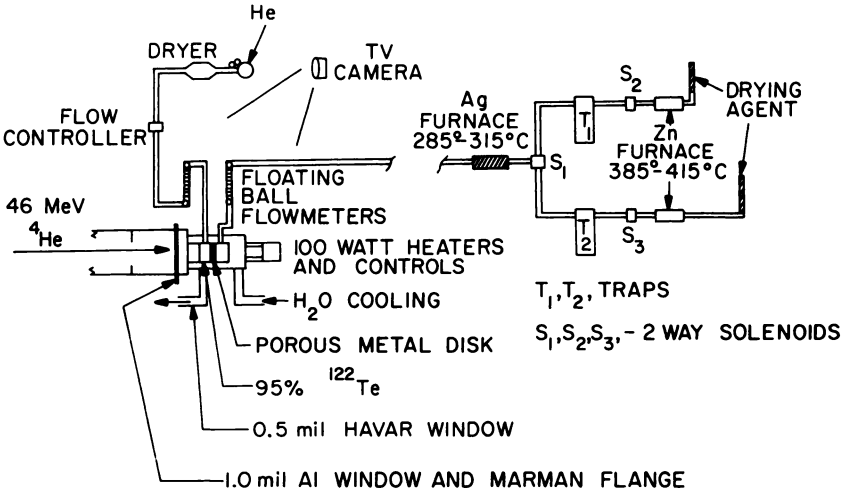

FIG. 1. Automated apparatus for ^{123}I production.

recovery) of ^{123}I at 6.5 hr from the midpoint of a short irradiation (T_0) may (depending on irradiation conditions) range from 1 to 470 μCi/μA-hr of beam current. The production rate usually obtained is ~200 μCi/μA-hr. When using a 1-hr irradiation with a 5-μA beam, the activity from the generator-type target at T_0 is about 1 mCi of ^{123}I. By using a 50 μA internal beam, we anticipate that we can produce ~50 mCi of ^{123}I (at T_0) during a 6-hr irradiation on a generator target. The production rate is satisfactory for experimental and clinical studies at the BNL Medical Research Center.

Methods of preparation of ^{123}ICl: materials. Research grade chlorine gas supplied by the Matheson Co. in 99.965 minimum volume percent purity was vacuum dried at 600°C on 40–60-mesh activated charcoal impregnated with copper and barium as an activator (*18*). Iodine monochloride stored under argon was from Alpha Inorganics; nitrosyl chloride in 97% purity was from Matheson; the salicylic acid was supplied by Baker Chemicals; the L-tyrosine by K and K Laboratories; and the crystallized human serum albumin was purchased from Nutritional Biochemical Corp.

Procedure a for ^{123}Xe + ICl. The scrubbed ^{123}Xe collected from the helium stream was vacuum distilled on to 0.5 cc (~10^{-2} moles) of ICl that had been thoroughly degassed; or in addition contained known amounts of either Cl_2, O_2, or H_2O. Following the addition of ^{123}Xe the ICl solution was agitated at 25°C for 6–10 hr. Details concerning these experiments are given in Table 1 or are subsequently discussed. The ^{123}I-ICl was subsequently dissolved in 1 *N* aqueous HCl (*19*) or in acetic acid (*20*), and after the absolute activity determination was used for the iodination reactions. In >0.3 *N* HCl solutions the chemical form of ^{123}I is $^{123}ICl_2^-$, and it is impossible to extract the complex ion with solvents such as CCl_4 or benzene. In acetic acid media the chemical form is ^{123}ICl.

Procedure b and c for ^{123}Xe + Cl_2 or NOCl. Pressures ranging from 10 to 760 torr of Cl_2 or NOCl were introduced into flamed Pyrex or quartz ampoules attached to a vacuum line. The additive was condensed to 77°K, and ^{123}Xe was distilled into the ampoule, following which the vials were sealed and permitted to stand at ambient temperature for several hours. Control experiments were performed in the absence of light, under normal illumination, and also at 77°K.

The ampoules containing the ^{123}ICl and excess halogen reagent were broken in vacuo using the apparatus shown in Fig. 2. The excess Cl_2 or NOCl was removed by distillation at low temperature. A dry ice-acetone slurry will condense ICl (m.p. 25–27°C),

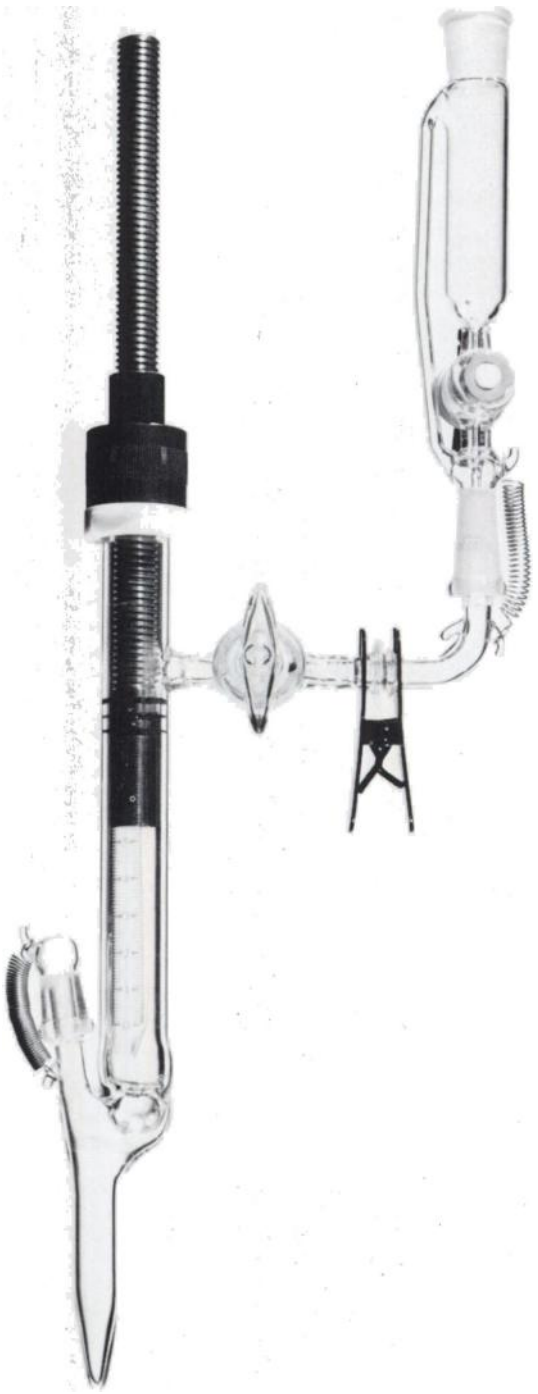

FIG. 2. Titantium-tipped ampoule breaker for preparation of carrier-free ^{123}ICl.

while permitting Cl_2 to be easily removed under vacuum. The (if) desired carrier ICl was added either in aqueous HCl, NaCl solution or acetic acid solution. The results of these experiments are summarized in Table 2.

^{123}I-labeling of selected radiopharmaceuticals. Diiodosalicylic acid (*20*), teridax (iophenoxic acid) (*21,22*), human serum albumin (*23–26*) and L-tyro-

sine (*27*) were labeled using ^{123}ICl according to the methods cited in the references. All radiopharmaceutical preparations yielded a range of millimoles to 10^{-2} μmoles of product. In order to compare the potential of the iodination procedure using ^{123}ICl labeled by the autoradiation activation associated with the decay of ^{123}Xe, several experiments were performed in which ^{123}ICl was obtained via oxidation of ^{123}I as discussed by McFarlane, et al (*23*). The method of Welch (*28*) of condensing ^{123}Xe onto frozen serum albumin was explored, and the results are compared to those obtained by synthetic methods.

RESULTS AND DISCUSSION

In order to incorporate radioiodine in a high radiochemical yield into certain pharmaceuticals, it is mandatory that the conversion of iodine to a more active species such as electrophylic halogen (i.e., I^+) be achieved rather than using molecular iodine. One of the most convenient sources of the I^+ species is iodine monochloride. For this reason, attention was focused on the preparation of ^{123}ICl on a carrier-free scale in nonaqueous or in aqueous media. The presence and efficacy of this iodinating reagent is derived from chemical evidence and radiochemical and chemical yields. Physical analytical methods, such as UV or IR spectroscopy, are inapplicable to the analysis of such trace quantities ($\sim 10^6$–10^{10} molecules) of ^{123}ICl.

In order to determine the yield of the ^{123}ICl, a standard iodination reaction was chosen, which was known to give a high chemical yield for iodination. The conversion of salicylic acid to diiodosalicylic is convenient for this purpose (*20*). The synthesis time is conveniently short, being only 2–4 hr to dry crystalline product-^{123}I. Following the optimization of the parameters affecting the preparation of the iodinating reagents, the other selected radiopharmaceuticals were prepared.

Labeling of ICl by ^{123}Xe decay in ICl. Table 1 summarizes the results of using ^{123}I-ICl as the iodination reagents. This reagent was prepared by dissolving ^{123}Xe in ICl, and subsequently using the active solution directly for the iodinations. If the ICl was prepared under a nitrogen atmosphere and degassed by repeated freezing and pumping on a vacuum line, ~90% of the ^{123}I activity [in the form of greater than 95% $^{123}ICl_2^-$, (Ref. *19,29*)] in an aliquoted fraction of the original ICl mixture was extracted with >0.3 *N* HCl. The remaining ~10% of the activity was soluble in CCl_4 or C_6H_6 and was presumably mostly ^{123}I-I_2 and organically soluble forms of iodine (*30*) and other than ^{123}ICl and $^{123}ICl_2^-$. The presence of ^{123}I-I_2 is not unexpected, since the ICl $\rightleftharpoons$ ½ I_2 + ½ Cl_2 equilibrium constant at 25°C is 1.8×10^{-3} (*31*). The further reaction of the ICl reactants to yield ICl_3 is only 0.42% complete at 25°C (*19*).

However, the effective labeling of ^{123}I-ICl by this method is very sensitive to the presence of oxygen and water. In two sets of experiments with 0.4 and 1.6 mole % O_2 and H_2O present, respectively, the ^{123}I activity extractable as $^{123}ICl_2^-$ was reduced to 83 and 73.5%, respectively. The corresponding yields of ^{123}I-diiodosalicylic acid were likewise reduced, whereas the organic ^{123}I soluble fraction increased to 26.5% in the ICl containing water in the latter case.

In a separate study, pressures of undried chlorine gas of 0, 80, and 760 torr were added to the ICl solution immediately after the introduction of one or two transfers of the ^{123}Xe. The resulting solution was dissolved in acetic acid and used without further treatment to synthesize ^{123}I-iophenoxic acid. As shown in Table 1, the radiochemical yield as teridax was ~40% and was independent of the excess pressure of chlorine above the ICl. However, if several transfers of ^{123}Xe onto the ICl were employed, the radiochemical yield as teridax was reduced to ~10%. Presumably in the latter case, moisture as water and/or air was also present from the Cl_2 or possibly also vacuum distilled onto the ICl during the ^{123}Xe transfers. In any case the chemical form of the ^{123}I must not have been as ^{123}I-ICl. The presence of a trace of H_2O in the ^{123}I-ICl can result in the reaction (*4*) which is rapid under ordinary conditions (*19*).

$$5\ ^{123}\text{I-ICl} + 3H_2O \rightarrow 5HCl + \underbrace{(HO\ ^{123}I + HOI)} \rightarrow (HIO_3 + H^{123}IO_3) + 2\ ^{123}\text{I-I}_2 \quad (3)$$

Iodic acid and hypoiodous acid are not effective iodination reagents and may account for the reduction in radiochemical yields in either teridax or ^{123}I-diiodosalicylic acid.

We conclude from the data of Table 1 that ICl may be effectively labeled by the dissolution of ^{123}Xe in very dry, oxygen free iodine monochloride. The principal advantages of the method are: the ^{123}I-ICl may be obtained without subsequent addition of carrier ICl; the reagent may be used in nonaqueous form; or, an aqueous solution of ≧0.3 *N* HCl may be added and one can obtain ^{123}I-ICl_2^- as the iodination reagent. The inherent disadvantage of the method is the low specific activity obtained. The labeling mechanism is under investigation but may involve both activation by the Auger cascade (autoradiation) and halogen exchange reactions.

Carrier-free ^{123}ICl from ^{123}Xe decay in Cl_2 or NOCl. Table 2 presents data which suggest that the ^{123}I atoms born from the decay of ^{123}Xe by the ^{123}Xe (β^+, E.C.)^{123}I processes in a chlorine gas environment results principally in the formation of ^{123}ICl. The yield as carrier-free ^{123}ICl (as measured by two chemical techniques) is essentially invarient at about 90% under a variety of conditions. The ^{123}I activity extracted as $^{123}ICl_2^-$ is 93 ± 2% in all cases tested. (We are attempting to identify the chemical forms of the remaining ^{123}I activity.) The activity incorporated into ^{123}I-diiodosalicylic acid is 85 ± 5%. Considering the reproducibility of the chemical synthesis (±5%) and the fact that the overall chemical yield giving the acid is about 90% (*20–22*), one observes that the radiochemical yields as diiodosalicylic acid and as $^{123}ICl_2^-$ are the same within experimental error.

The radiochemical yield as ^{123}ICl is not affected, within experimental error, if the total pressure of the $^{123}Xe + Cl_2$ mixture is varied between 10 and 760 torr of chlorine. Further the yield as ^{123}ICl is not affected by 89% or 99% xenon moderation at a total pressure of 92 or 484 torr. Likewise the synthesis of ^{123}ICl is not sensitive to normal laboratory illumination. It is noteworthy that if 92 torr of nitrosyl chloride is substituted for 90 torr of chlorine as the reactant, the yield of ^{123}I-diiodosalicylic acid is reduced from 82.5 to 62%. This suggests that the reactive ^{123}I may be a positively charged species showing preferential attack or reaction at the more electronegative halogen in NOCl. The alternate prod-

TABLE 1. DISTRIBUTION OF ^{123}I ACTIVITY FOLLOWING ^{123}Xe DECAY IN SELECTED ICl MIXTURES

Run No.	Conditions*	% activity in H_2O/HCl	% activity in CCl_4	% activity diiodosalicylic acid	Incorporated as iophenoxic acid (teridax)
1,6	no additive	90	10	81	43
2	O_2 (0.4 mole %)	83	17	82	—
3	H_2O (1.6 mole %)	73.5	26.5	73.0	—
4	Cl_2 (80 mm)	—	—	—	40
5	Cl_2 (760 mm)	—	—	—	40

* All samples were degassed under vacuum and Samples 1–3 were also prepared under a N_2 atmosphere. Experimental error ±5% a.d.

TABLE 2. SYNTHESIS OF ^{123}ICl BY ^{123}Xe DECAY IN Cl_2 AND NOCl

Run No.	Cl_2 (torr)	Radiochemical yield as ^{123}ICl: Extracted as $^{123}ICl_2^-$ in 1 N HCl solution (%)	Radiochemical yield as ^{123}ICl: Incorporated into ^{123}I-diiodosalicylic acid (%)	Comments*
1	10	95		
2	10		87	
3	10		90	10 torr Cl_2 + 82 torr-Xe Total pressure 92 torr
4	10		90	10 torr Cl_2 + 479 torr-Xe Total pressure 484 torr
5	90		82	
6	90		86	
7	90		81	^{123}Xe decay in the dark
8	90		80	^{123}Xe decay in the light
9	90			
10	90	92		
11	100	93		
12	337		83	
13	444		84	
14	594	93		
15	673	91		
16	740		86	
17	760	91		
18	92 NOCl		62	
19	92 NOCl	57		

* In Runs No. 1, 5, 11, 15, and 17, the Cl_2 contained 1.5 mole % H_2O. Experimental error is ±5% a.d.

TABLE 3. ^{123}I-LABELING OF SOME RADIOPHARMACEUTICALS BY ^{123}ICl

		Percent radiochemical yield*					
				Human serum albumin†		L-tyrosine	
Method No.	Method of preparation of ^{123}ICl	Diiodo-salicylic acid	Iophenoxic acid‡	This work†	Literature yield (%) Ref	This work	Literature yield (%)
1	^{123}Xe + ICl	85 ± 5	41 ± 2	80 ± 2			
2	$^{123}I^- \rightarrow ICl_2^-$	70 ± 5	17 ± 17	40 ± 5	85 (24,25)		
				80 ± 2	35 (26)		
						32 diiodo	50 diiodo
3	^{123}Xe + Cl_2	85 ± 5	47 ± 5	40 ± 5		21 monoiodo	25 monoiodo (27)
				80 ± 2			
4	^{123}Xe + crystalline substrate§ (77°K)			18‖	80‖ (23)	1.1 diiodo 1.0 monoiodo	

* Average yield for three experiments excepting the diiodosalicylic acid from which ten experiments were done to establish the actual figure of the radiochemical yield.

† The radiochemical yield quoted in Ref. 24,25 is given for gamma globulins. In Ref. 26 and the present work a molar ratio of IHSA to iodine of 1:0.5 was used to obtain a 40% radiochemical yield. The radiochemical yield could be improved at the same HSA to iodine ratio by preoxidizing the protein.

‡ Using the direct labeling of ICl (Method No. 1), a decrease in the radiochemical yield was observed if several transfers of ^{123}Xe were made. The radiochemical yield remained constant for Method No. 3 even if the total activity increase by a factor of 50. See text for discussion.

‖ The radiochemical yield was 18% for ^{123}I-IHSA labeled by direct decay of ^{123}Xe in HSA and purified over a Dowex column using a 4 mg crystalline sample of HSA. Welch (28) has reported labeling yields of HSA (100 mg) of up to 80% although the sample provided a very low specific activity and without mentioning the purification of the labeled compound. Please refer to text for discussion.

§ 3 mg crystalline L-tyrosine.

uct NO^{123}I is not a characterized compound, and its decomposition may not lead to ^{123}ICl.

The recoil energy spectrum of the ^{123}Xe(β^+, E.C.) ^{123}I decay has not been measured. However, one would expect the maximum translational energy of the ^{123}I to be 38–27 eV. After one elastic collision with Cl_2 the average kinetic energy of the ^{123}I species is ~3.5 eV. This suggests most of the reactions of ^{123}I proceed via atomic or ionic iodine and/or possibly atomic chlorine reactions, rather than as a result of the excess translational energy produced by an internal conversion electron (~0.25 eV) and the subsequent Auger electron cascade. Attempts are being made to distinguish the thermal and hot reactions of ^{123}I, and to determine the role of I^+, I· and/or thermal scavenging reactions in contributing to the high yield of ^{123}ICl in Cl_2 mixtures. Further details concerning the reactivity of radiohalogen induced by autoradiation activation have been discussed elsewhere (*32–34*).

The inherent advantage of synthesizing ^{123}ICl by the ^{123}Xe(β^+, E.C.)^{123}I decay processes in Cl_2 is that the iodination reagent can be obtained carrier-free, and hence extremely high specific activities are obtainable. Once the free Cl_2 has been vacuum distilled from the ^{123}ICl, the chemist may add the appropriate reagents and perform the synthesis directly. Alternately the ^{123}ICl may be readily converted to the complexed anion $^{123}ICl_2^-$ for use as the iodination reagent. The preparation of ^{123}ICl from chlorine is convenient and is superior to the other preparative methods involving ICl or the oxidation of iodide, as Na^{123}I, to $^{123}ICl_2^-$*. The iodine monochloride method described by McFarlane in 1958 (*23*) used radioiodine as the source of label. Helmkamp, et al (*24–27*) extended this procedure to use sodium radioiodide (^{131}I or ^{125}I), and to work at high activity levels. However, the efficiency of radioiodination depends on a critical step that required one to rapidly mix Na*I with ICl and jet the mixture into protein. This persistence on rapidity is due to the fact that the tracer Na*I, and the carrier ICl(ICl_2^-) are not in the same chemical form. As a result a random exchange could precede the iodination reaction. In the method of iodination using ^{123}ICl described in the present work, this inconvenience is eliminated, because the tracer (^{123}ICl) and the carrier ICl (if added) are in the same chemical form. The iodination of the compound proceeds only via $^{123}I^+$ substitution without competing side reactions.

Radiopharmaceuticals containing ^{123}I. In Table 3 we have summarized the results of testing the various labeling procedures for the preparation of labeled

* We routinely prepare Na^{123}I by condensation of the ^{123}Xe onto the walls of the trap and subsequently permit the ^{123}I to adhere to the walls. The activity is flushed from the trap with 0.1 *N* NaOH and neutralized to the appropriate pH with 0.1 *N* and 0.01 *N* HCl and 0.01 *N* NaOH. $Na_2S_2O_3$ is added to prevent oxidation of iodide to iodine. Na^{123}I prepared in this manner is currently being investigated for clinical usage (R. M. Lambrecht, A. P. Wolf, J. Klopper, and H. Atkins).

^{123}ICl or $^{123}ICl_2^-$ for the synthesis of several model radiopharmaceuticals. The radiochemical yields obtained are those expected on the basis of theoretical yield and published results. Of the various ^{123}ICl preparative methods, the one we prefer and recommend for use in radiopharmaceutical preparations is the ^{123}Xe + 10 torr Cl_2 procedure. As shown in Table 3, the integrity of the labeling method as evidenced in the preparations of ^{123}I-diiodosalicylic acid, ^{123}I-human serum albumin (similarly applicable to ^{123}I-gamma-globulin), and monoiodo- and diiodo-L-tyrosine are convincing proof that the ^{123}ICl iodination reagent so obtained is well suited to labeling pharmaceuticals with ^{123}I. We have checked the toxicity of ^{123}I-IHSA and the ^{123}I-L-tyrosine prepared by this method. Needless to say the chlorine gas is expected to show toxic effects if it is not removed from the radiopharmaceutical.

Also included in Table 3 are results we have obtained by condensing the ^{123}Xe onto crystalline serum albumin or L-tyrosine, and permitting the ^{123}Xe autoradiation process to label the substrate with ^{123}I. Welch (*28*) reported obtaining yields of up to 80% for a 100-mg crystalline sample of serum albumin. However, in many clinical applications of ^{123}I, one must obtain a very high specific acvitity for useful results. For example, in cisternography a desirable specific activity of ^{123}I-IHSA is 1 mCi/mg. Our results using a 4-mg crystalline sample of serum albumin indicate a radiochemical yield of ~18% is obtained after the removal of the inorganic iodine. With 1 mCi of ^{123}I activity this corresponds to a final specific activity of 45 μCi/mg. The specific activity calculated for Welch's data (*28*) for the 100-mg sample is only 8 μCi/mg. Thus the optimum sample size that one should choose, if this labeling method is employed, must be a compromise between specific activity and radiochemical yields. This is to be contrasted with the ^{123}ICl method (3 on Table 3) which will permit both a high overall radiochemical yield, and indeed quite high specific activities, if the iodination reaction is performed on a carrier-free scale. By preoxidizing the HSA (*26*) one could obtain a specific activity of 700 μCi/mg when starting with an initial 1 mCi of ^{123}I. The further advantage of the synthetic procedures is that one may obtain the substrate to iodine ratio that is desirable for a particular application. In the Auger electron-induced labeling processes the ^{123}I may randomly react with the protein, but in the synthetic procedure the ^{123}I will be in the aromatic rings of the protein molecule (*26*).

We have also labeled a 3-mg crystalline sample of L-tyrosine with the ^{123}Xe decay processes and obtained about a 1–2% radiochemical yield of each of the ^{123}I-monoiodo- and ^{123}I-diiodo-L-tyrosine. Presumably the radiochemical yield could be increased by using a larger sample. The parameters affecting the labeling of organic and biological compounds by irradiation, nuclear transformations, and nonsynthetic methods has been recently reviewed (*35–37*).

SUMMARY

The $^{122}Te(^4He,3n)^{123}Xe \xrightarrow[2.1\ hr]{(\beta^+,\ E.C.)} {}^{123}I$ nuclear transformations and a silver scrubber produce ^{123}I in greater than 99.8% radionuclide purity. The ^{123}I has been incorporated into several model radiopharmaceuticals by use of ^{123}ICl as the iodination reagent. The parameters affecting the synthesis of ^{123}ICl as a result of the Auger cascade and the coulombic explosion associated with the ^{123}Xe decay in mixtures of ICl, Cl_2 and NOCl are reported. The influence of pressure, the effects of additives, as well as the use of ^{123}ICl as an iodination reagent are discussed and compared with other methods of iodination of radiopharmaceuticals.

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