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ON THE PREPARATION OF ^{80}BR OR ^{82}BR-BIOMOLECULES VIA EXCITATION LABELLING METHODS[1]

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ABSTRACT

The direct decay induced ^{82}Br (or ^{80}Br) labelling by exposing the solid substrate molecules, such as deoxyuridine, L-tyrosine, guanosine, deoxycytodine, phenylalanine and acetic acid, to gaseous $CF_3{}^{82m}Br$ (or $CF_3{}^{80m}Br$) was studied. The radiochemical yields of the brominated products are relatively small and range from 1% in the case of bromo deoxyuridine to 11% for bromoacetic acid. The modification of this technique by adding Cl_2 gas to the reaction mixture improves the yields in several cases drastically (up to 80% for bromo-guanosine and bromo-L-tyrosine). Similar improvement can be achieved by exposing crystalline $KBrO_3$ for some time to $CF_3{}^{82m}Br$ (or $CF_3{}^{80m}Br$) and dissolving subsequently the $KBrO_3$ in an acidic solution of the substrate.

Introduction

Organic molecules and biomolecules labelled with radioactive halogen have recently found increasing interest in biological and nuclear medical studies.[2-3]

Although the half-life of most of the radioisotopes used so far, e.g. $^{82}Br(t_{1/2}$ = 35 h), $^{123}I(t_{1/2}$ =13.1h) and $^{125}I(t_{1/2}$ = 60 d) allows a preparation of these labelled molecules by chemical synthesis, direct labelling via decay induced species (excitation labelling) can be of great advantage if compounds of high specific activity or carrier free products are required.

So far mostly modified classical halogenation methods[4-6] such as the chloramine-T[10] or iodide-iodate[11] have been used for incorporating radioactive halogen into aromatic systems, which worked well when the halogen species initiating the labeling are present in large amounts. However, on a carrier free scale halogenation is quite often difficult to accomplish by either of these techniques.[10-11]

Iodine-monochloride, ^{123}ICl, which is a powerful iodinating agent can be used for carrier free labelling of several organic molecules[12-13] if produced via the decay of ^{123}Xe in Cl_2, but gives only poor results for the iodination of some heteroaromatic systems as reported by Stöcklin's group.[9]

Recently, direct decay-induced labelling has been reported using reactive iodine species resulting from the decay of ^{123}Xe and ^{125}Xe.[13-15] The radioactive decay of these isotopes ^{123}Xe $(EC,\beta^+)^{123}I$ and $^{125}Xe(EC)^{125}I$, respectively, yields charged iodine species which can presumably react as such with the substrate molecules leading to radioiodine labelled molecules. The yields, however, differ widely depending on the substrate and still very little is known about the exact nature of the reacting species and reaction mechanisms involved.

An extremely effective iodination reagent, especially, for biomolecules, such as deoxyuridine, tyrosine and insuline, was found by Stöcklin et al.,[16] who exposed crystalline KIO_3 to $^{123,125}Xe$. Following the decay of the radioactive Xe they dissolved the KIO_3 crystals in an acidic solution of the substrate molecule and obtained carrier free monoiodinated products with good radiochemical yields.

In the present study several methods were developed and tested to incorporate radiobromine into molecules of biochemical interests, such as deoxyuridine, guanosine, L-tyrosine, deoxycytidine, phenylalanine and acetic acid.

Emphasis was put on a simple, fast and direct technique which would not require any chemical synthesis and which would produce carrierfree radiobrominated molecules.

For this purpose, the decay induced incorporation of bromine seemed to be the method of choice.

Among the bromine isotopes of potential nuclear medical interest, ^{76}Br, ^{77}Br and ^{82}Br, only ^{82}Br is accessible by nuclear reactor irradiation via $^{81}Br(n,\gamma)^{82m}Br(IT)^{82}Br$ and could therefore be obtained with the available facilities.

The ^{82m}Br isotope undergoes isomeric transition with a half-life of 6.1 min.

If the ^{82m}Br is incorporated in an alkylbromide, as in this study in $CF_3{}^{82m}Br$, then the isomeric transition will give rise to vacancy cascades following internal conversion and eventually lead to substantial fragmentation of the molecule via Coulomb explosion yielding ^{82}Br ions with multiple positive charges.[17-18] These species may experience partial or complete neutralization before they react with the substrate molecules.

Several methods utilizing bromine species initially produced by this decay induced process, such as the direct labelling, direct labelling in presence of Cl_2 and the $KBrO_3$ exposure technique were tested with substrates of biochemical interest listed above.

For convenience in several series of experiments ^{80m}Br was used instead of ^{82m}Br. Although ^{80}Br, being a negatron emitter cannot be applied in nuclear medical studies, its reactions when formed as a result of $^{80m}Br(IT)^{80}Br$ are basically the same as those of ^{82}Br. This is due to the fact that it is also generated in a isomeric transition process which is very similar in its characteristics to $^{82m}Br(IT)^{82}Br$.

Experimental

Preparation of ^{80}Br and ^{82}Br Source

A few milligrams of CF_3Br were sealed in a quartz capillary and irradiated in the VPI and SU nuclear reactor at a neutron flux density of about 10^{12} n $cm^{-2}sec^{-1}$ for 30 min at 40°. After the reactor irradiation the contents of the quartz ampoule were subjected to gas chromatographic purification on a 2-m Poropak Q column. The CF_3Br fraction, containing ^{80m}Br-, ^{80}Br-, and ^{82}Br-labeled CF_3Br formed during the irradiation, was trapped and transferred to the reaction vessel. The other radioisotopes of bromine produced do not impose any problems, since they lead to stable daughters not giving rise to any relevant products.

The amount of CF_3Br used in the gas exposure technique was usually 35 mg which corresponds to a pressure of about 60 torr in the reaction vessel. The total quantity obtained in typical irradiation was 0.5 mCi.

Direct $CF_3{}^{82m(80m)}Br$ Gas Exposure Technique

A schematic representation of the direct (and modified) CF_3Br gas exposure technique is shown on fig. 1. The $CF_3{}^{82m(80m)}Br$ purified as described above is introduced by vacuum line techniques into a evacuated pyrex flask (50 ml) whose inner surface was previously coated with a thin layer of the solid substrate. The coating was done by dissolving the substrate in a suitable solvent and evaporating the latter under vacuum and rotation of the reaction vessel. (When liquid acetic acid was the substrate the gas exposure was carried out by shaking the reaction vessel so that a good mixing between the CF_3Br gas and the liquid substrate was established.)

After an exposure time of about 30 min in the case of ^{80m}Br and about 18 min when ^{82m}Br was the bromine source the CF_3Br was removed into a storage vessel (for complete decay) and the contents of the bulb dissolved in a suitable solvent and analyzed by high pressure liquid chromatographic methods.

Temperature studies were carried out by storing the reaction vessel in a thermostate.

Modified $CF_3{}^{82m(80m)}Br$ - Cl_2 Gas Exposure

The experimental procedure was similar to that described above with the exception that before the introduction of the $CF_3{}^{82m(80m)}Br$ a certain amount of Cl_2 was added to the reaction mixture.

(Experiments with HCl or Argon additives were carried out in a similar fashion.)

Modified $CF_3{}^{82m(80m)}Br$ - $KBrO_3$ Gas Exposure

In these experiments crystalline $KBrO_3$ (10 mg) placed in an evacuated 50 ml pyrex bulb was first exposed for about 20-40 min to $CF_3{}^{82m(80m)}Br$. The CF_3Br was then removed and a few mg of the substrate in an acidic aqueous solution were added by using a syringe. The resulting solution was allowed to stand for a few minutes and then analyzed by HPLC.

In a variation of this method an aqueous slurry consisting of 10 mg of $KBrO_3$ and 10 mg of guanosine in 0.1 N HCl was prepared in the reaction vessel to which subsequently CF_3Br was added.

The test with neutronirradiated samples of KBr and $KBrO_3$ was performed by exposing 20 mg of each compound for 10 min in the VPI and SU reactor (neutron flux 10^{12}n $cm^{-2}sec^{-1}$) and dissolving the crystals in a 0.1 N aq. HCl solution containing a few mg of guanosine.

Sample Analysis

The identification and purification of the radiobromine labelled compounds was done by high pressure liquid chromatography. The columns used and the separation conditions are given in table 1. Analysis was carried out on two different columns and the identity of the products was established by using authentic compounds as carriers. About 10 µl of the solution containing the reaction mixture were injected each time.

A typical separation including the mass and radioactivity traces are shown on fig. 2.

Materials

CF_3Br, Cl_2, Argon and HCl were obtained from Matheson Chemical Co., with a stated purity level of greater than 99% and were used as such.

Deoxyuridine, 5-bromodeoxyuridine, L-tyrosine, guanosine, 8-bromoguanosine, deoxycytidine, were purchased from ICN Life Sciences Group, Cleveland Ohio. Acetic acid and bromoacetic acid were Fisher Scientific reagent grade.

Radioactivity Assay

The ^{80}Br labelled products separated by high pressure liquid chromatography were assayed by collecting the effluent from the HPLC column discontinuously in vials containing 10 ml of dioxane solutions containing liquid scintillation fluors.

The ^{80}Br-counting was done by liquid scintillation spectrometry applying appropriate energy discrimination.

In the case of ^{82}Br labelled the effluent was collected in small 1 ml vials and counted in a well type NaI detector.

The radiochemical yields of the products, i.e., the ratio of the ^{80}Br or ^{82}Br activity present at the end of the reaction in each individual product to the total ^{80}Br or ^{82}Br activity (at end of the reaction) were computed by using the well known equations for radioactive decay and growth.

Another alternative which was found to be a quite satisfactory approximation was to evaluate the radiochemical yield of the brominated substrate by setting the sum of the activities of all products separated by HPLC including the activity appearing as Br^- equal to 100%. The amount of ^{80}Br or ^{82}Br activity incorporated in the bromine labelled substrate depends on exposure time, the activity of $CF_3{}^{80m}Br$ and the nature of the compound and ranged in typical experiments up to 10 μCi for ^{80}Br and 1 μCi for ^{82}Br. These activities are directly related to the activity of the bromine source and can be drastically increased by using more active sources.

Results and Discussion

A. Direct $CF_3{}^{80m}Br$ (or $CF_3{}^{82m}Br$) Gas Exposure Technique

As shown in table 2 the radiochemical yields of the monobromonated substrate molecules are relatively small, ranging from a low value of less than 1% when crystalline deoxyuridine, L-tyrosine or deoxycytidine are the substrates up to 2.7% for phenylalanine. The effect of a phase change can be seen in the case of the acetic acid where the radiochemical yield of $^{82}Br^-$ acetic acid decreased from 11% in the liquid state to 3% in the solid state (table 2). Otherwise a variation of temperature seems to have very little effect on the yields. Freezing the $CF_3{}^{80m}Br$ on top of the (solid) substrate to provide better contact between the bromine source and substrate molecules did not significantly improve the labelling process either.

Changes in coating procedures leading to different corn sizes of the substrate crystals deposited on the surface of the pyrex reaction vessel have generally no significant effect on the yields, nor is the amount of substrate used of any great consequence as long as a certain minimum amount of substrate is present (vide infra).

Exposing solutions of guanosine in 0.1 N aq. HCl to $CF_3{}^{80m}Br$ shows no improvement of the yields (table 3).

In agreement with previous results observed with the xenon gas exposure technique[16] leading to iodinated compounds it can be concluded that the direct gas exposure labelling is applicable only for liquid systems. For solid substrates the yields are too small to be of any practical value.

B. Modified $CF_3{}^{80m(82m)}Br$-Cl_2 Gas Exposure Labelling

The bromine incorporation observed in the direct gas exposure technique is probably the result of an electrophilic attack of a Br^+ ion at a carbon atom of the substrate molecule. The low yields, however, seem to indicate that Br^+ is not a powerful brominating agent for solid substrates. This may be due to deactivation prossibly by charge transfer etc. of the Br^+ before it can sufficiently diffuse into the solid.

Thus, in order to improve the labelling process the above gas exposure method was modified by adding Cl_2 to the reaction mixture. It was hoped that the interaction between the decay produced bromine species and Cl_2 would lead to the formation of intermediates of the BrCl or $BrCl_2^-$ type which may prove to be a much superior brominating agent than the Br^+.

As can be seen from the data in table 2 the addition of Cl_2 gas results indeed in most cases in substantially improved radiochemical yields of the monobrominated substrate molecules, e.g., $^{82}Br^-$ guanosine from ca. 1% without Cl_2 present up to 52.5% with Cl_2 present.

The relative radiochemical yields are fairly independent of exposure time. No significant change in the radiochemical yield of ^{80}Br labeled acetic acid was observed when the exposure time was extended from 20 to 80 minutes (table 3), nor was there any significant temperature dependence observed between 20° and 80°C.

The effect of increasing amounts of chlorine gas added on the efficiency of the incorporation process can be seen from fig. 3.

The experiments were carried out under standard conditions with 10 mg Guanosine coated on the surface of a 50 ml pyrex bulb and 60 torr $CF_3{}^{80m}Br$ present in each case. Various amounts of Cl_2 gas were added. The highest yields of ^{80}Br-guanosine were obtained with 5-25 x 10^{-4} moles of Cl_2 present, which corresponds roughly to 200-1000 torr Cl_2. A further increase of Cl_2 pressure reduces the yields, probably due to interferring secondary reactions of the brominating agent with Cl_2.

If Cl_2 is replaced by HCl or argon gas the yields drop to the low levels obtained with the direct labelling procedure (table 3).

Dissolving the substrate molecule in H_2O and exposing it in this form simultaneously to $CF_3{}^{80m}Br$ and Cl_2 reduces the yields to 13.9%.

In agreement with the results obtained by direct $CF_3{}^{80m}Br$ gas exposure it was found that the amount of substrate has very little effect on the obtained yields as long as it exceeds a certain minimum which is under our experimental conditions 10 mg coated on the surface of a 50 ml pyrex reaction vessel.

C. $CF_3{}^{80m(82m)}Br$ - $KBrO_3$ Gas Exposure Technique

In another series of experiments crystalline $KBrO_3$ was exposed to $CF_3{}^{80m}Br$ or $CF_3{}^{82m}Br$ following a procedure recently reported by Stöcklin et al.[16] for iodine labelling. It is assumed that in this case reactive halogen species are trapped on the surface of the crystals which upon solution in 0.1N HCl, containing the substrate molecules, form reactive intermediates, which can carry out the exchange reactions.

The yields obtained via this procedure are shown in table 2 and indicate a drastic improvement over those obtained by the direct gas exposure technique if guanosine and L-tyrosine are the substrate, where the yields are better or comparable to those achieved by the modified CF_3Br-Cl_2 method.

In all other systems under investigation the results are the same or show only a slight improvement. (It should be pointed out that the bromination of deoxyuridine by this method yields about 6-10% whereas the iodination of the same compound via the comparable Xe-KIO_3 technique gives yields of about 90%.)

While the reactive species for this labeling process has not been identified the following experiments using guanosine as an example, may, however, provide some additional information about the mechanisms involved and perhaps exclude certain intermediates.

As shown in table 3, the replacement of $KBrO_3$ by other oxidizing agents such as KIO_3 or $KClO_3$ completely supresses the exchange process, the same effect is observed if NaCl or KBr are exposed to $CF_3{}^{80m}Br$ and subsequently dissolved in an acidic solution of the substrate.

The exchange process requires an acidic medium. When 0.1 N aqueous HCl or H_2SO_4 solutions of guanosine are used to dissolve the exposed $KBrO_3$ crystals the yields are quite high >50%, whereas if the $KBrO_3$ crystals are dissolved in H_2O or 0.1 N aq. NaOH containing the substrate no labelling (<1.0%) occurs (table 3).

By exposing the $KBrO_3$ crystals to air the bromine species presumably trapped on the surface of the crystals don't lose their reactivity. Thus the crystals can be transferred from one vessel to the other. Subsequent dissolution of the crystals in (acidic) substrate solutions still yields a more than 50% bromine incorporation in the guanosine.

As can be seen from table 3, the simultaneous exposure of a $KBrO_3$ slurry containing an acidic solution of guanosine to $CF_3{}^{80m}Br$ does not affect the yields, which still remain in the 50% range. In this connection it seems important to point out that the dissolution of neutron irradiated $KBrO_3$ or KBr crystals in 0.1N aqueous HCl containing guanosine does not result in radiobromine labelled guanosine (table 3). This seems to indicate that the bromine recoil species commonly observed in hot atom chemistry are not responsible for the labelling process.

The above experiments also exclude BrCl or $BrCl_2^-$ as intermediates and seem to point in the direction of species like BrO^- etc. Moreover, the fact that other oxidizing compounds such as KIO_3 or $KClO_3$ do not enhance the labelling, emphasizes the importance of the presence of $KBrO_3$ and suggests that a rather subtle mechanism is involved in the exchange.

More mechanistic studies will have to be carried out to assess the role of the reactive species participating in the labelling process.

Summary

Thus in conclusion it can be said that the CF_3Br-Cl_2 gas exposure technique in combination with HPLC purification provides a simple and efficient tool of incorporating radioactive bromine to form (carrier free) radioactive molecules of biochemical interest. It seems to be the most generally applicable method of all three techniques studied in this investigation.

It should be pointed, however, that the CF_3Br-$KBrO_3$ technique is also an extremely rapid and especially mild brominating method, since it exposes the substrate only to a minimum of radiation. It should be applied whenever possible.

The carrier free radiobrominated molecules obtained by these techniques can be readily separated from the unlabelled starting material and purified by HPLC and used for medical purposes.

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Captions

Fig. 1 Schematic presentation of the direct $CF_3{}^{82m(80m)}Br$ and modified $CF_3{}^{82m(80m)}Br$-Cl_2 gas exposure technique.

Fig. 2 High pressure liquid chromatography and Radioassay of ^{80}Br-bromoacetic acid labelled by exposure of acetic acid to $CF_3{}^{80m}Br$-Cl_2.

Fig. 3 Radiochemical yields of ^{80}Br-guanosine obtained by the modified $CF_3{}^{80m}Br$-Cl_2 gas exposure technique as a function of the amount of Cl_2 additive present.

Table I

COLUMNS AND CONDITIONS USED FOR HIGH PRESSURE LIQUID CHROMATOGRAPHY

METHOD	A	B
COLUMN PACKING	AMINEX A-25 ANION EXCH.	AS-PELLIONEX-SAX ANION EXCH.
GRAIN SIZE, μ	17.5	37 to 57
INT. DIAMETER, mm	1.8	2.0
VOID VOLUME, ml	1	1.3
COLUMN LENGTH, mm	500	1000
PRESSURE, psi	300-1700	250 to 550
FLOW RATE, ml/min	0.26-0.53	0.65 to 1.33
TYP. SAMPLE VOL, μℓ	5 to 10	5 to 10
COUNTER ION	NO_3^-	NO_3^-
ELUENT	$NaNO_3$-sol.	borax
TEMP., ^oC	20-85	25

Table 2

^{80}Br- and ^{82}Br- Labeling of Biomolecules

Product	Radiochemical Yield in % of Total ^{80}Br- or ^{82}Br-Formed*		
	Direct Gas Exposure	$KBrO_3$ Gas Exposure	Cl_2 Gas Exposure
^{80}Br-Acetic Acid	11.0 ± 0.3	4.4 ± 0.4	13.1 ± 0.7
^{82}Br-Acetic Acid	3.4 ± 0.5	9.9 ± 0.9	20.1 ± 1.7
^{80}Br-Deoxyuridine	< 1.0	5.4 ± 0.8	27.6 ± 4 5
^{82}Br-Deoxyuridine	< 1.0	9.8 ± 0.6	27.3 ± 1.2
^{80}Br-Guanosine	< 1.0	51.4 ± 1.3	52.5 ± 1.6
^{82}Br-Guanosine	2.0 ± 0.5	33.1 ± 5.2	26.4 ± 1.4
^{80}Br-Deoxycytidine	< 1.0	< 1.0	24.4 ± 1.2
^{82}Br-Deoxycytidine	1.5 ± 0.7	1.2 ± 0.1	34.0 ± 3.8
^{80}Br-Phenyl-Alanine	2.7 ± 0.5	< 1.0	6.7 ± 0.8
^{80}Br-L-Tyrosine	< 1.0	80.2 ± 0.9	85.3 ± 4.8
^{82}Br-L-Tyrosine	< 1.0	87.6 ± 2.0	86.3 ± 8.3

*Exposure times ranged from 20 to 80 minutes

Experiments were carried out at room temperature, except in the case of acetic acid where T = 0°C.

The results listed are the average percentages obtained in 3-5 individual runs.

Table 3

Radiochemical yields of ^{80}Br-guanosine obtained by using various experimental conditions

Method	Radiochemical Yields
$CF_3{}^{80m}Br$ (gas) + HCl (760 Torr, gas) + 10 mg guanosine subsequently in dissolved in H_2O	2.0 ± 0.5
$[CF_3{}^{80m}Br(gas) + KIO_3(solid)]$ exposed crystals were subsequently dissolved in an acidic guanosine solution	<1
$[CF_3{}^{80m}Br(gas) + HClO_3(solid)]$ exposed crystals were subsequently dissolved in an acidic guanosine solution	<1
$[CF_3{}^{80m}Br(gas) + NaCl(solid)]$ exposed crystals were subsequently dissolved in an acidic guanosine solution	<1
$[CF_3{}^{80m}Br$ (gas) + $KBrO_3$ (solid)] subsequently dissolved in aq. Guanosine solution	<1
Neutron irradiated $KBrO_3$ (solid) subsequently dissolved in acidic Guanosine solution	0
Neutron irradiated KBr (solid) subsequently dissolved in acidic Guanosine solution	0
$[CF_3{}^{80m}Br(gas) + KBrO_3$ (solid)] exposed $KBrO_3$ crystals were transferred (in air) to another reaction vessel and subsequently dissolved in acetic guanosine solution.	>50
$[CF_3{}^{80m}Br(gas) + Cl_2$(760 Torr, gas) + aq. guanosine slurry]	13.9 ± 1.0
$[CF_3{}^{80m}Br$ + 0.1 N HCl solution of guanosine (slurry)]	< 1
$[CF_3{}^{80m}Br$ + 0.1 aq. HCl slurry of $KBrO_3$ and guanosine]	81.6 ± 1.0

Figure 1

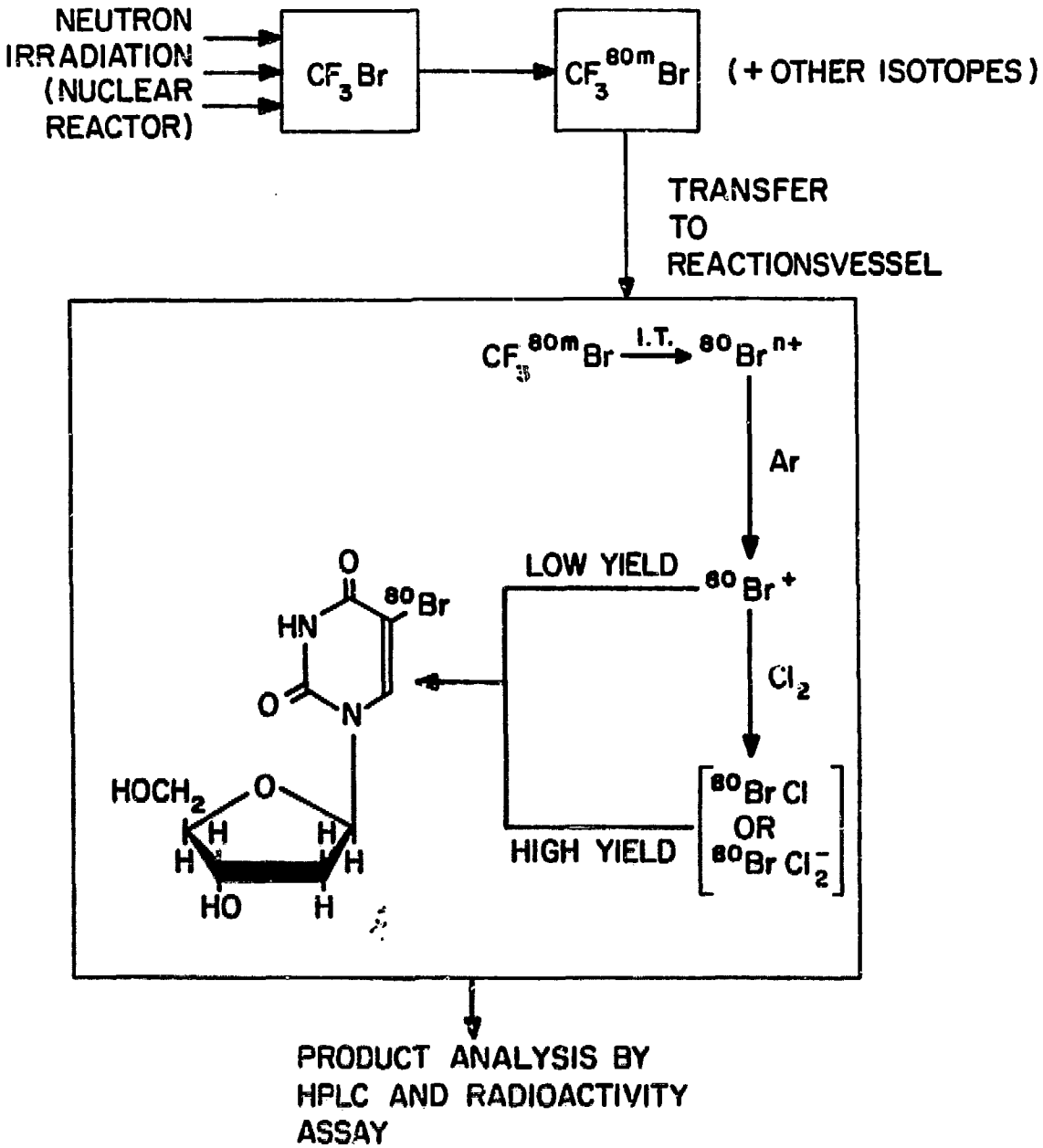

NEUTRON
IRRADIATION
(NUCLEAR
REACTOR)
CF_3Br
$CF_3{}^{80m}Br$
(+ OTHER ISOTOPES)
TRANSFER
TO
REACTIONSVESSEL
$CF_3{}^{80m}Br$ I.T. $^{80}Br^{n+}$
Ar
LOW YIELD
$^{80}Br^{+}$
Cl_2
HIGH YIELD
$^{80}Br\,Cl$
OR
$^{80}Br\,Cl_2^-$
HN
O
N
^{80}Br
$HOCH_2$
HO
PRODUCT ANALYSIS BY
HPLC AND RADIOACTIVITY
ASSAY

Figure 2

HIGH PRESSURE LIQUID RADIOCHROMATOGRAPHY OF ^{80}Br-BROMOACETIC ACID LABELLED BY EXPOSURE OF ACETIC ACID TO $CF_3{}^{80m}Br-Cl_2$

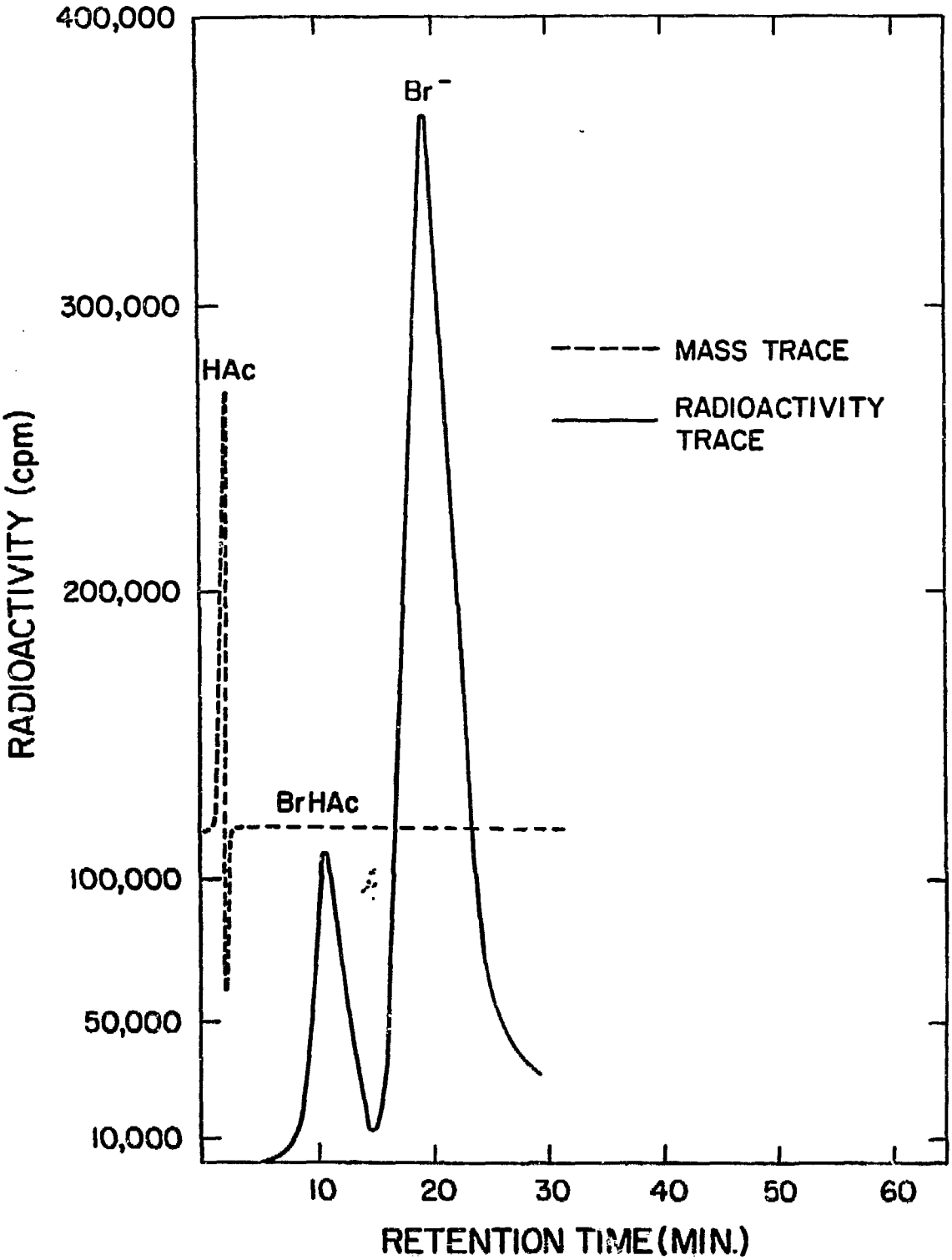
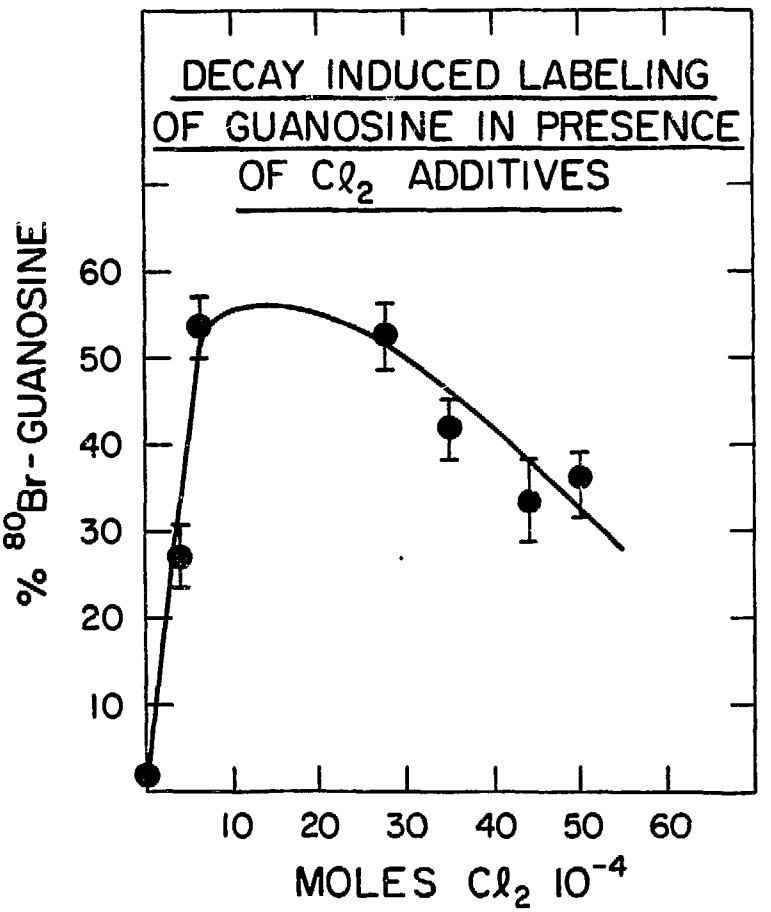


Figure 3


DECAY INDUCED LABELING
OF GUANOSINE IN PRESENCE
OF Cl2 ADDITIVES
% 80Br-GUANOSINE
60
50
40
30
20
10
10
20
30
40
50
60
MOLES Cl2 10-4