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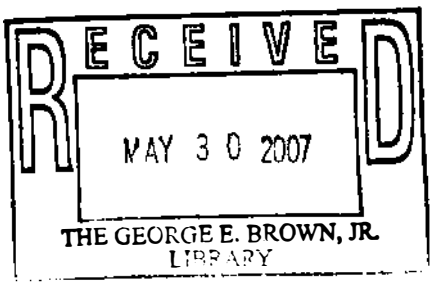

THE SYNTHESIS OF CARBON-11, FLUORINE-18, AND NITROGEN-13 LABELED RADIOTRACERS FOR BIOMEDICAL APPLICATIONS

by

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Foreword

The Subcommittee on Nuclear and Radiochemistry (SNR) is associated with the Committee on Chemical Sciences of the Commission on Physical Sciences, Mathematics, and Resources of the National Research Council. A principal purpose of the SNR is to maintain awareness of the chemical aspects of basic and applied nuclear science, to stimulate scientific and technical progress, and to identify national problems and needs in nuclear and radiochemistry. The membership of the Subcommittee is drawn from academic, industrial, and government laboratories and covers a broad spectrum of knowledge and experience in the nuclear and chemical sciences.

A major interest of the Subcommittee is the publication of monographs in areas of nuclear and radiochemistry. More than 60 titles have already been published in two series, one on radiochemistry separations of the elements and another on radiochemical techniques. This monograph is the first of a new series designed to review and describe the procedures and techniques of radionuclides in nuclear medicine. The purpose is identical with that of the monographs in the other series, namely to provide information of practical value to the laboratory scientist.

Gregory R. Choppin, *Chairman*
Subcommittee on Nuclear and Radiochemistry

Preface

This monograph is the first in a series of selected topics in the Nuclear Medicine Series. A number of reviews, many of them recent, have appeared on various aspects of ^{11}C, ^{18}F and ^{13}N-labeled radiotracers. This monograph is intended to treat the topic principally from the standpoint of synthetic organic chemistry while keeping in perspective the necessity of integrating the organic chemistry with the design and ultimate application of the radiotracer. Many of the constraints within which the synthetic organic chemist must operate when designing and implementing a synthetic strategy for a short-lived radiotracer, do not exist or are unimportant in the broader discipline of synthetic organic chemistry. However, the reactions used, the principles used to adapt these reactions to labeling with short-lived radionuclides, and the concepts of chemical reactivity are all part of the field of organic chemistry and form the framework upon which synthetic strategies for short-lived radiotracers are developed. Where possible, recent examples from the literature of organic synthesis will be introduced to suggest potentially new routes which may be applied to problems in labeling organic molecules with the short-lived positron emitters, carbon-11, fluorine-18, and nitrogen-13.

The Table of Contents provides an overview of the material covered in this monograph. We feel that the literature survey of carbon-11, fluorine-18 and nitrogen-13 labeled compounds (Tables 2,3,4,5 and 6) will be of particular value to scientists working in this field. Since the preparation of such a compilation is subject to unintentional omission and errors, we would be grateful if any omissions in this compilation of short-lived radiotracers be brought to our attention. Two appendices are included to provide supplementary general references. A subject index concludes this volume.

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Contents

Introduction

The successful application of organic molecules labeled with the short-lived positron emitting nuclides to the study of physiological processes in the living human body has generated intense interest in the biomedical community (1-6). For example, it has recently been possible to correlate regional brain metabolism with functional activity in humans during normal circumstances (7-9), under conditions of somatosensory stimulation (10-13) and in psychiatric conditions (14-17) through the use of positron emitting radiotracers. This characterization of the metabolic activity of the functioning human brain and other organs such as the heart (18) depends on the use of positron emission transaxial tomography (PETT) a method of detection which gives an image of the distribution of the labeled tracer in a transverse section of the body (4,19-22). This mode of detection makes it possible to image the internal structure of an organ without interference from overlying structures. Thus by applying the appropriate labeled tracers, mathematical models (3) and instrumentation to problems in the biomedical sciences it has been possible for the first time to obtain regional metabolic information in the living human body at little or no risk. This has resulted in the birth of a new interdisciplinary endeavor.

The monograph will deal with the problems encountered in one of the key areas on which the success of these studies depends, namely, the various aspects of labeling organic molecules with the short-lived nuclides carbon-11, fluorine-18 and nitrogen-13. This is an area in which synthetic organic chemistry plays a key role. Before considering the development of synthetic approaches for ^{11}C, ^{18}F and ^{13}N-labeled radiotracers, two general topics, the decay characteristics of the positron emitters and radiotracer design will be discussed.

Decay Characteristics of the Positron Emitters (^{11}C, ^{18}F, ^{13}N)

The use of tracer molecules to study the biochemical processes occurring in living organisms relies heavily on carbon-14 and tritium labels since these nuclides can be substituted for stable carbon and hydrogen in organic molecules without changing the biological properties of the molecule. An immense amount of information has been obtained through the use of carbon-14 and tritium labeled tracers even though their long half-lives and short-range decay characteristics largely preclude their use in humans. However, studies involving carbon-14 and tritium labeled tracers can provide guidance on both the design and synthesis of positron emitting tracers.

By comparison, the nuclides carbon-11, nitrogen-13 and, to a great extent, fluorine-18 can also be used to label organic molecules without appreciably altering their biological properties. These nuclides which are produced by a cyclotron or other charged particle accelerator decay by positron emission resulting in the production of two 511 KeV photons which, unlike carbon-14 and tritium, can be detected external to the body barrier. The short half-life and body penetrating radiation makes molecules labeled with the positron emitting nuclides suitable for safely tracing metabolic processes in the living human body. Furthermore, the much higher specific activities attainable with the short-lived nuclides makes it possible to use them as labels for toxic molecules where the resulting tracers show no measurable physiological effects. Indeed organic molecules labeled with the positron emitters have provided the means of extending many of the elegant tracer methods developed with carbon-14 and tritium to studies in humans (7,23). The physical properties of tritium, carbon-14, carbon-11, nitrogen-13 and fluorine-18 are summarized in Table 1.

Table 1. Physical Properties of Tritium, Carbon-14, Carbon-11, Nitrogen-13 and Fluorine-18

Nuclide	Half-life	Decay Mode	Maximum Energy (MeV)	Most Probable Energy (MeV)	Range[a] mm (H_2O)	λ m^{-1}	Maximum Specific Activity (Ci/mol)
Tritium	12.35y	β^-(100%)	0.0186	---	0.0072	1.07×10^{-7}	2.90×10^{4}
Carbon-14	5730y	β^-(100%)	0.155	---	0.359	2.30×10^{-10}	62.4
Carbon-11	20.4m	β^+(99+%)	0.96	0.326	4.108	3.40×10^{-2}	9.22×10^{9}
Nitrogen-13	9.96m	β^+(100%)	1.19	0.432	5.39	6.96×10^{-2}	1.89×10^{10}
Fluorine-18	109.7m	β^+(97%) EC (3%)	0.635	0.202	2.39	6.32×10^{-3}	1.71×10^{9}

[a] Maximum.

On examination of the physical properties of the positron emitters the following three properties, in addition to their ready substitution for the natural elements of organic molecules, make them exquisitely suitable as tracers which can be used in humans:

(1) Short half-life

(2) Decay by body penetrating radiation

(3) Potentially high specific activity

These three properties are also responsible for the unique problems which must be overcome in the development of a practical synthetic route to a tracer molecule labeled with the carbon-11, fluorine-18 or nitrogen-13.

RADIOTRACER DESIGN

General Considerations

The expenditure of time and resources in developing a synthetic route to a short-lived radiotracer is usually sufficiently great to warrant a careful choice of the molecular structure itself. The process of choosing a molecular structure for probing a particular physiological process thereby setting priorities for synthesis is referred to as radiotracer design. It involves the consideration of many aspects of the interaction of chemicals with living systems and can include the consideration of such factors as tissue biochemistry, molecular requirements for substrate transport into a tissue, intracellular pH, and unique functions, to name a few. In this phase of the development of a new radiotracer, a familiarity with the literature as well as the input of both physicians and other scientists with expertise in the biological sciences is necessary. Since pharmaceutical research and radiopharmaceutical research share some common problems and goals (24), the literature of this field is a valuable resource and should also be used in selecting priorities for synthesis.

The design of organ imaging radiopharmaceuticals has been reviewed (25-27). More recently, radiotracers have been classified according to their mechanism of concentration in the target organ (28,29). This mechanistic approach to radiotracer design is receiving increasing attention (30). Along this line, the determination of structure-activity relationships, which allow one to correlate and predict the biodistribution patterns of molecules in the body based on chemical structure, provides an extremely valuable foundation for the development of new radiotracers (31-34).

In the application of radiotracers and emission tomography to the study of biological processes in humans, the following two realities define the biodistribution characteristics which the labeled tracer must exhibit.

(1) For reasons of radiation safety and minimizing human radiation dose, the amount of radioactivity which can be injected has an upper limit.

(2) The detection of the radioactivity which is injected is limited by the sensitivity of the available instrumentation.

While the instrumentation continues to improve, the first factor, namely the amount of radiotracer which can be safely administered is limited. Therefore, the design of tracers which have a high uptake in the organ of interest is critically important because the higher the uptake in the area of interest, the lower will be the dose of the radioactivity required to provide a statistically significant count rate for imaging. In this regard, one must

consider not only whether the tracer has a desired interaction with a particular functional component of the organ which is being studied (for example, a neurotransmitter receptor, an enzyme or a carrier protein) but also whether its behavior in the whole body and its transport into the tissue of interest favors a sufficient uptake for study.

Since the literature can provide considerable information on the relationship of chemical structure to uptake of substances in tissues or cellular components the following selected references are provided as a guide:

Binding to Plasma Proteins (35-39)
Uptake by Lung (40-43)
Uptake by Liver (31,44,45)
Uptake by Muscle (46)
Receptor Binding (47-52)
Brain Uptake and Blood-Brain-barrier (53-62)
Blood:Tissue pH Gradients (63-67)
Lipophilicity and Partition Coefficients (31,33,53,65,68)
Molecular Size and Polarity (31)

The site specific delivery or targeting of radiotracers which probe particular aspects of the metabolism and function of a target organ or tissue is a particularly challenging aspect of radiotracer development. It has been approached in a number of ways including the use of enzyme inhibitors (69-70), receptor-ligand interactions (47-48,50-52,71), metabolic trapping (72-73), and liposome formation (67,74-76). Another tactic, frequently used in pharmaceutical research is to form "prodrugs" to aid the site-specific delivery of parent molecules (77-78). Prodrugs are derivatives of the parent molecule and are designed to release the active molecule *in vivo*. This approach may also prove to be useful in radiotracer design.

At this point, it is important to emphasize the value of determining localization mechanisms for radiotracers which have high organ specificities. This information, along with various studies on the relationship of chemical structure to biodistribution patterns, is a valuable resource for developing new radiotracers.

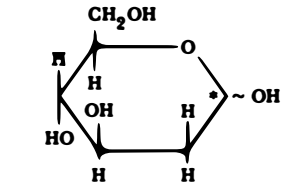
Choice and Position of the Label

After the choice of a chemical structure for a given biomedical application has been made, then the choice and position of the radioactive nuclide within the tracer molecule becomes a consideration. The time course of the biological process which is being traced is a factor which influences

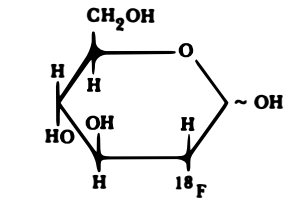
the choice of nuclide since the half-life, ideally, should be sufficiently long to obtain the desired uniform but not so long as to contribute unnecessarily to the body radiation burden. In some cases, studies of the dynamics of distribution of a tracer in animals using tritium or carbon-14 as labels can provide information on the time scale of the biological process and therefore serve as a guide in the choice of positron emitting nuclides.

The position as well as the choice of the label often is dictated by the structure of the molecule and the limited number of routes possible for introducing the radionuclide. In many cases, however, there are alternatives which must be considered. In the case of isotopic substitution there will be no perceptible alteration in the biological behavior of the molecule in most cases. However, if a foreign radioelement (for example, fluorine-18) is used to label the molecule, then the choice for the position of the label must be made so that the resulting radiotracer maintains the desired characteristics of the parent molecule. For example, the design of a positron emitting tracer which could be used to extend the ^{14}C-2-deoxyglucose method (23) to humans using PETT required the consideration of a number of factors and lead to the choice of ^{18}F-labeled 2-deoxy-2-fluoro-D-glucose (FDG) as a molecular structure. Fluorine-18 was initially the nuclide of choice because the relatively long (110 minute) half life was required for the transport of the tracer from Brookhaven National Laboratory where it was synthesized to the University of Pennsylvania where the first imaging studies were done. In addition, the half-life of fluorine-18, is compatible with the time required for clearance of free ^{18}FDG from the brain and for the plasma to be cleared of tracer thus minimizing errors in quantitation. The choice of position 2 for the fluorine-18 label was made because it was well known that this is the only position which could be altered without seriously reducing the ability of this molecule to serve as a substrate for hexokinase and that the absence of a hydroxyl group at C-2 is essential for metabolic trapping (79-81). (Figure 1)

Another factor which must be considered whether the labeling involves isotopic substitution or the use of a foreign radioelement is the metabolism of the molecule. It is important that the label be sufficiently stable in vivo to provide the information required from a particular study. Along this line, the choice of the position of the label may be judiciously made to influence its excretion rate and lower the radiation dosimetry.



1-^{14}C-2 – DEOXY-D-GLUCOSE



^{18}F-2-DEOXY-2-FLUORO-D-GLUCOSE

RADIOTRACER REQUIREMENTS

1. Radiotracer must be a substrate for hexokinase (∴ only C_2 can be modified).
2. Radiotracer must undergo carrier mediated transport into the brain (∴ only C_2 can be modified).
3. Radiotracer must be metabolically trapped (∴ C_2 hydroxyl must be absent).
4. Nuclide t½ must be compatible with free tracer clearance and shipping time.

Figure 1. Radiotracer requirements for extending the ^{14}C-2-deoxy-D-glucose method to humans using PETT.

RADIOTRACER SYNTHESIS

After the various factors which impact on the design of a particular radiotracer have been considered and a molecular structure which appears to satisfy the requirements of a particular biomedical application has been chosen, the primary challenge is the design of an appropriate synthetic approach to this radiotracer. In general, the synthetic strategy must be compatible with the following conditions:

1. The radioactivity must be introduced in the form of a readily accessible labeled precursor molecule which is obtained directly from the target or is readily synthesized from the molecular species produced in the target. In some cases the synthesis may necessitate the development of a new route to the labeled precursor.
2. The reaction steps including and subsequent to the introduction of radioactivity must be sufficiently rapid to be compatible with the half life of the nuclide. This also applies to purification procedures which are required in the synthesis.
3. The synthetic sequence must be chosen with a consideration of the mechanism of the reaction and of the specific activity of the product which is required. This will impact on the stoichiometry of various steps of the synthesis.
4. When the synthesis involving high levels of radioactivity is carried out on a routine or semi-routine basis, technical aspects of the experimental setup such as the design of the laboratory shielding, remote operations, elimination of non-essential manipulations, and radiation monitoring require attention.

On this basis, the general topics of availability of labeled precursors, the synthetic strategy, optimization of reaction rates, specific activity and stoichiometry, biosynthetic tactics and rapid purification will be discussed followed by sections devoted to the synthesis of carbon-11, fluorine-18 and nitrogen-13 labeled tracers. A section on experimental methods and related technology will conclude this monograph.

Availability of Labeled Precursors

The factor which has the greatest impact on development of a practical synthetic strategy is the availability of the radioisotope and labeled precursor molecules. The nuclear reaction which is used and the yield of nuclide which can be obtained from a particular reaction is highly dependent

on cyclotron/accelerator characteristics. The chemical form of the nuclide which is produced after bombardment is determined by a number of factors, the most important being energy deposition in the target and chemical composition of the target. Because of the importance of precursor availability to the synthetic strategy the reader is referred to a number of articles on this topic (1,82-86) as well as the references in Table 2. In addition, consultation with individuals who have experience with targetry, precursor preparation and delivery systems is recommended.

The ideal radiotracer synthesis is one which the nuclide is introduced from a labeled precursor molecule which is available directly from the target or where the species available from the target is directly converted without handling (i.e. "on line") to a synthetically useful precursor. In addition, the incorporation of the radionuclide should proceed in high yield with a minimum number of steps and time being required after the introduction of the label thus minimizing the hazards of handling large quantities of radioactivity. Table 2 provides a list of commonly used precursor forms of ^{11}C, ^{18}F and ^{13}N. Those which are available directly from the target or "on-line" are, of course, the most attractive in terms of the simplicity of the overall synthetic strategy. Others involve conversion of the labelled species exiting the target to a useful chemical form as is indicated in the table. Although a large number of precursor molecules are listed, some have been used to a far greater extent than others as can be seen by examining the listings of ^{11}C, ^{18}F and ^{13}N labeled compounds (Tables 3, 4, 5, 6). The development of new labeled precursors or the improvement and simplification of existing methods, including automation is an important area of research since it greatly increases the diversity of the structures of labeled radiotracers which can be synthesized.

Table 2. Labeled Precursors of ^{11}C, ^{18}F and ^{13}N

Carbon-11 Labeled Precursors	References
Direct or On-Line Availability	
^{11}CO	87-89
$^{11}CO_2$	88-89
$H^{11}CN$	89-92
products from solid NH_4Cl target (^{11}C-organic halides, methylamine, formamide, cyanamide, guanidine)	93
^{11}C-guanidine	94-95
$^{11}CH_3I$	96
Synthesis Required	
$^{11}CH_3I$	97-99
$H^{11}CHO$	98,100-101
$^{11}CH_3Li$	102
[^{11}C]cyanate	103
$^{11}COCl_2$	104-109
$H^{11}CCH$	110-115
Fluorine-18 Labeled Precursors	
Direct or On-Line Availability	
$H^{18}F$ (aqueous)	116-120
$H^{18}F$ (anhydrous)	121-129
[^{18}F]F_2	125,130-132
$B^{18}F_3$(anhydrous)	133-134
$M^{18}F$ (anhydrous) where M = R_4N^+, Cs^+, K^+ and other cations or ion exchange resin. (See Table 4 for examples)	135
Ne/^{18}F (species not identified)	120,133,136
O_2/^{18}F (species not identified)	137
$NO^{18}F$	118,125
$Cl^{18}F$	125
$ClO_3{}^{18}F$	138
$CH_3CO_2{}^{18}F$	139
Synthesis Required	
$H^{18}F$ (anhydrous) from H_2O target	(See Table 4)
$H^{18}F$ (anhydrous) from KHF_2 target	140
$M^{18}F$ (anhydrous) from H_2O target	(See Table 4)
[^{18}F]CF_3OF	141-142
^{18}F-diethylaminosulfur trifluoride (^{18}F-DAST)	128
[^{18}F]XeF_2	143-144

Table 2. Labeled Precursors of ^{11}C, ^{18}F and ^{13}N (continuation).

Nitrogen-13 Labeled Precursors	
Direct or On-Line Availability	
$^{13}NO_3^-$	145-149
$^{13}NH_3$	150-152
Synthesis Required	
$^{13}NH_3$ (from H_2O target)	146,149,153-157
$H^{13}NO_2$, $^{13}NO_2^-$, ^{13}NO, $^{13}NO_2$	149,158-161
$^{13}N_2O$	113,162
$^{13}N_2$	113,149,163

General References (see Appendix 2)

Carbon-11: 86,164,170

Fluorine-18: 132,165-167,170

Nitrogen-13: 168-169

Table 3. Carbon-11 Labeled Compounds.

Compound	Labeled Precursor	Labelling Reagent	References
[^{11}C]Amino Acids			
[carboxyl-^{11}C]α-phenylglycine	$^{11}CO_2$	$^{11}CO_2$	171-174
[carboxyl-^{11}C]α-phenylglycine	H^{11}CN	H^{11}CN	175
[carboxyl-^{11}C]α-phenylalanine	$^{11}CO_2$	$^{11}CO_2$	172-174
[carboxyl-^{11}C]-α-phenylalanine	H^{11}CN	H^{11}CN	175
D-[carboxyl-^{11}C]phenylalanine*	"	"	176
L-[carboxyl-^{11}C]phenylalanine*	"	"	176
[carboxyl-^{11}C]DOPA	$^{11}CO_2$	$^{11}CO_2$	177
D,L-[1-^{11}C]alanine	"	"	115,178-179
D,L-[1-^{11}C]alanine	H^{11}CN	H^{11}CN	180
L-[1-^{11}C]alanine*	$^{11}CO_2$	$^{11}CO_2$	181-182
[3-^{11}C]alanine (partially resolved)	"	$^{11}CH_3I$	178
D,L-[3-^{11}C]alanine	"	"	183
L-[methyl-^{11}C]methionine	"	"	97,184-186
β-[3-^{11}C]alanine	H^{11}CN	H^{11}CN	172,187-188
1-aminocyclopentane[^{11}C]carboxylic acid	"	"	175,189,191
1-aminocyclobutane[^{11}C]carboxylic acid	"	"	175,190,192
1-aminocyclohexane[^{11}C]carboxylic acid	"	"	175,190,193
D,L-valine (not labeled)	none	none	194
D,L-[1-^{11}C]valine	H^{11}CN	H^{11}CN	175,190,194a
L-[1-^{11}C]valine	"	"	195
D,L-[carboxyl-^{11}C]tryptophan	"	"	175,190,196-197
L-[carboxyl-^{11}C]tryptophan	"	"	198
D,L-[4-^{11}C]aspartic acid	"	"	187
L-[4-^{11}C]aspartic acid*	$^{11}CO_2$	$^{11}CO_2$	199-200
p-[^{11}C]cyanophenylalanine	H^{11}CN	H^{11}CN	187
[^{11}C]-L-glutamic acid	"	"	201
[^{11}C]-L-α-aminoisobutyric acid	"	"	202
[^{11}C]Carboxylic Acids and Derivatives			
D,L-[1-^{11}C]lactic acid	$^{11}CO_2$	H^{11}CN	111
D,L-[1-^{11}C]lactic acid	H^{11}CN	H^{11}CN	203
D,L-[1-^{11}C]lactic acid	$^{11}CO_2$	H^{11}CCH	111,204
D,L-[3-^{11}C]lactic acid	"	"	111,204

Table 3. Carbon-11 Labeled Compounds (continuation).

Compound	Labeled Precursor	Labelling Reagent	References
L-[3-^{11}C]lactic acid*	"	$^{11}CH_3I$	183
L-[1-^{11}C]lactic acid*	"	$^{11}CO_2$	181,182,205
[carbonyl-^{11}C]nicotinamide	"	"	115,206
[carboxyl-^{11}C]nicotinic acid	"	"	115,207
[1-^{11}C]palmitic acid	"	"	115,208-211
[1-^{11}C]oleic acid	"	"	212
β-methyl[1-^{11}C]heptadecanoic acid	"	"	213
[^{11}C]acrylic acid	"	"	214
[^{11}C]citric acid*	"	"	215
[1-^{11}C]octanoic acid	"	"	41,216
[1-^{11}C]acetate	"	"	216-218
[1-^{11}C]propionic acid	"	"	219
[1-^{11}C]pyruvic acid*	"	"	181-182,205
[carboxyl-^{11}C]aliphatic carboxylates[a]	"	"	216
[1-^{11}C]acetoacetic acid	"	"	220
[carboxyl-^{11}C]salicylic acid	"	"	115,216
[carboxyl-^{11}C]anthranilic acid	"	"	115
[carboxyl-^{11}C]benzoic acid	"	"	115,216,221
[carboxyl-^{11}C]benzoic acid derivatives[b]	"	"	216
[^{11}C]hippuric acid*	"	"	221
[^{11}C]acetyl phosphate*	"	"	222
[^{11}C]acetyl carnitine*	"	"	223
[carboxyl-^{11}C]carboxylates[c]	"	"	216
[carboxyl-^{11}C]mandelic acid and esters	$H^{11}CN$	$H^{11}CN$	224
[14-^{11}C]succinic acid	"	"	225
[14-^{11}C]fumaric acid	"	"	225
^{11}C-oxalacetate*	$^{11}CO_2$	$^{11}CO_2$	200,215
N-[^{11}C]Methyl 3° Amines and [^{11}C] Methyl-Quaternary Ammonium Salts			
[N-methyl-^{11}C]morphine and heroin	$^{11}CO_2$	$^{11}CH_3I$	226
[N-methyl-^{11}C]morphine	"	$H^{11}CHO$	227
O-methyl[^{11}C]bufotenine	"	"	228

Table 3. Carbon-11 Labeled Compounds (continuation).

Compound	Labeled Precursor	Labelling Reagent	References
N-[^{11}C]methylputrescine, spermine and spermidine	"	"	229
[N-methyl-^{11}C]imipramine	"	"	185,230-231
[N-methyl-^{11}C]clomipramine	"	"	232-233
[N-methyl-^{11}C]chlorpromazine	"	"	185,234
[N-methyl-^{11}C]etorphine	"	"	235
[N-methyl-^{11}C]nicotine	"	"	185,231,236
[N-methyl-^{11}C]thioproperazine	"	"	231
[^{11}C]ephedrine	—	—	237
[^{11}C]methylephedrine	—	—	237
N-[^{11}C]methyl albumin and fibrinogen	$^{11}CO_2$	H^{11}CHO	238
N-[^{11}C]methyl ovine lutenizing hormone	"	"	239
Gly-[^{11}C-methyl]Met-Gly	"	$^{11}CH_3I$	240
[N-methyl-^{11}C]diazepam	"	"	231,241
[N-methyl-^{11}C]caffeine	"	"	231,237
[N-methyl-^{11}C]flunitrazepam	"	"	241,242
[N-methyl-^{11}C]hexamethonium	"	"	243,244
[^{11}C]-erythromycin A lactobionate	"	H^{11}CHO	244a
1,1'-[^{11}C]methyl-4,4'-dipyridinium diiodide	"	$^{11}CH_3I$	245
chlorpromazine-[^{11}C]methiodide	"	"	246
quinuclidinyl benzilate [^{11}C]-methiodide	"	"	247-249
[1-^{11}C]Primary Amines and Derivatives			
[1-^{11}C]dopamine·HCl	H^{11}CN	H^{11}CN	250-252
[1-^{11}C]norepinephrine·HCl	"	"	253
[1-^{11}C]5-hydroxytryptamine·HCl	"	"	254
[1-^{11}C]aliphatic amines(C_4-C_8, C_{10})	"	"	41,255
[1-^{11}C]branch chain aliphatic amines	"	"	256
[^{11}C]aliphatic diamines (C_4 - C_9)	"	"	257
[1-^{11}C]dimethoxyphenethylamine	"	"	258
[1-^{11}C]phenethylamine	"	"	259,260

Table 3. Carbon-11 Labeled Compounds (continuation).

Compound	Labeled Precursor	Labelling Reagent	References
[1-^{11}C]-6-iododopamine	"	"	261
[^{11}C]-N-alkyl-p-iodobenzenesulfonamides	"	"	262
[3-^{11}C]6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline	"	"	252
[α-methylene-^{11}C]salsolinol	"	"	252
[^{11}C]Alcohols			
[^{11}C]methyl alcohol	$^{11}CO_2$	$^{11}CO_2$	263
[1-^{11}C]ethyl alcohol	"	"	212,263-265
[1-^{11}C]hexadecanol	"	"	187
[2-^{11}C]2-propanol	"	"	263
[U-^{11}C]mannitol*	"	"	266
[U-^{11}C]glycerol*	"	"	266
[1-^{11}C]octanol	"	"	41
[^{11}C]Sugars			
[U-^{11}C]glucose*	$^{11}CO_2$	$^{11}CO_2$	267-270
[U-^{11}C]glucose*	"	$H^{11}CO_3$	271
^{11}C-galactose*	"	$^{11}CO_2$	266
3-[^{11}C]-methyl-D-glucose	"	$^{11}CH_3I$	271a,272
[1-^{11}C]-2-deoxy-D-glucose	$H^{11}CN$	$H^{11}CN$	273-277
[1-^{11}C]-glucose	"	"	278
[1-^{11}C]-mannose	"	"	278
[cyano-^{11}C]Nitriles			
lacto[^{11}C]nitrile	$H^{11}CN$	$H^{11}CN$	203
octane[^{11}C]nitrile	"	"	41
2-phenylethylaminoalkane[^{11}C]-nitrile·HCl	"	"	279
mandelo[^{11}C]nitrile	"	"	224
α-p-iodoanilinophenylaceto[^{11}C]nitrile	"	"	280
α-N-alkylaminophenylaceto[^{11}C]nitriles	"	"	281
α-N-arylaminophenylaceto[^{11}C]nitriles	"	"	281

Table 3. Carbon-11 Labeled Compounds (continuation).

Compound	Labeled Precursor	Labelling Reagent	References
[^{11}C] Hydantoins			
[^{11}C]dialkylhydantoins	H^{11}CN	H^{11}CN	282-283
[^{11}C]diarylhydantoins	"	"	105,282-287
[^{11}C]spirohydantoins	"	"	283
[^{11}C]alkylarylhydantoins	"	"	282-283,286
[^{11}C]alkylarylhydantoins	^{11}CO	$^{11}COCl_2$	286
Steroids			
17-α-[^{11}C]methylestradiol	$^{11}CO_2$	$^{11}CH_3Li$	288-289
17-α-[^{11}C]methyltestosterone	"	"	288,290
17-α-[^{11}C]methylestradiol 3-methyl ether	"	"	288
17-α-[^{11}C]ethynyl estradiol	"	H^{11}CCH	112
[^{11}C]moxestrol	"	"	289
Miscellaneous ^{11}C-Labeled Compounds			
[1-^{11}C]octanal	^{11}CO	^{11}CO	291
[carbonyl-^{11}C]benzaldehyde	"	"	291-292
[carbonyl-^{11}C]pimozide	"	$^{11}COCl_2$	293
[^{11}C]ethylchloroformate	"	"	105,109
[^{11}C]diethylcarbonate	"	"	105,109
[^{11}C]diphenylurea	"	"	105,109
[^{11}C]5,5-diethylbarbiturate	"	"	105,286
[^{11}C]5,5-ethylphenylbarbiturate	"	"	105,286
[1-^{11}C]hexobarbital	$^{11}CO_2$	$^{11}CH_3I$	294-295
[^{11}C]hydroxyurea/isohydroxyurea	H^{11}CN	^{11}C-cyanate	103
[^{11}C]urea	^{11}CO	$^{11}COCl_2$	296
Benzyl-[^{11}C]methyl ether	$^{11}CO_2$	$^{11}CO_2$	297
[methylene-^{11}C]benzyl methyl ether	"	"	297
Butyl[^{11}C]methyl ether	"	"	297
[^{11}C-methylene]diethyl ether	"	"	297
^{11}C-labeled aliphatic and aromatic hydrocarbons[d]	"	$^{11}CH_3I$	298
[^{11}C]benzene, toluene, xylene	H^{11}CCH	H^{11}CCH	299
[2-^{11}C]-acetone	$^{11}CO_2$	$^{11}CO_2$	300

Table 3. Carbon-11 Labeled Compounds (continuation).

Compound	Labeled Precursor	Labelling Reagent	References
[methyl-^{11}C]thymidine and thymidylate*	"	$H^{11}CHO$	100,301
[methyl-^{11}C]thymidine	"	$^{11}CH_3I$	301a
^{11}C-1-methoxy-3-nitrobenzene	"	"	302
[^{11}C]-5,6-benzouracil	^{11}CO	$^{11}COCl_2$	106
[benzoyl carbonyl-^{11}C]spiroperidol	$H^{11}CN$	$H^{11}CN$	303,304
2-amino[2-^{11}C]pyrimidines	[^{11}C]guanidine	[^{11}C]guanidine	94,95
[^{11}C]iodoantipyrine	$^{11}CO_2$	$^{11}CH_3I$	305

*Biosynthesis.

a. acetate, propionate, acrylate, butyrate, isobutyrate, trimethylacetate, pentanoate, hexanoate, heptanoate, cyclohexanecarboxylate, octanoate.

b. p-chlorobenzoate, 3,4-dimethoxybenzoate, p-hydroxybenzoate, salicylate, m-trifluoromethylbenzoate, p-phenoxybenzoate.

c. phenylacetate, 2-thiophenecarboxylate, 3-camphorcarboxylate, 1-naphthoate, 5-acenaphthenecarboxylate, 9-anthracenecarboxylate, 9-phenanthrene-carboxylate.

d. [1-^{11}C]pentane, nonane, undecane; 2-[^{11}C]methyl-naphthalene, [^{11}C]methyl-benzene.

Table 4. Fluorine-18 Labelled Compounds.

Compound	Labelled Precursor	Labelling Reagent	Labelling Reaction	Reference
[^{18}F]Aryl Fluorides				
o, m, and p-[^{18}F]fluorophenylalanine	$LiB^{18}F_4$	$LiB^{18}F_4$	Schiemann	306
m and p-[^{18}F]fluorophenylalanine	Ne/$^{18}F^a$	Ne/$^{18}F^a$	"	136
L-p-[^{18}F]fluorophenylalanine*	"	"	"	307,308
L-m-[^{18}F]fluorophenylalanine*	"	"	"	308
3-[^{18}F]fluorotyrosine	"	"	"	136
L-3-[^{18}F]fluorotyrosine*	"	"	"	308
5 and 6-[^{18}F]fluorotryptophan	$LiB^{18}F_4$ or $^{18}F^-$	$LiB^{18}F_4$ or $^{18}F^-$	"	309
L-5 and 6-[^{18}F]fluorotryptophan*	Ne/$^{18}F^a$	Ne/$^{18}F^a$	"	136,308
p-[^{18}F]fluorobenzoic acid	"	"	"	136,133
p-[^{18}F]fluorobenzoic acid	$^{18}F^-$	$HB^{18}F_4$	Schiemann	310
3,5-[^{18}F]difluoro-L-tyrosine	$^{18}F^-$(aq)	$K^{18}F$-CH_3CO_2H	nucleophilic substitution	311
5-[^{18}F]fluoro-DOPA	$^{18}F^-$(aq)	$^{18}F^-$(aq)	"	312-314
5 [^{18}F]fluoro-DOPA	Ne/$^{18}F^a$	Ne/$^{18}F^a$	"	308
L-6-[^{18}F]fluoro-DOPA	$^{18}F^-$(aq)	$Bu_4N^{18}F$, XeF_2	electrophilic fluorination	315-316
6-[^{18}F]fluorodopamine	"	$^{18}F^-$(aq)	Schiemann	317
o-[^{18}F]fluorohippuric acid	$K^{18}F$	$K^{18}F$	exchange	318
[^{18}F]haloperidol	$^{18}F^-$(aq)	$^{18}F^-$(aq)	Schiemann	319
[^{18}F]-β-(4-fluorobenzoyl)propionic acid	"	"	"	320

Table 4. Fluorine-18 Labelled Compounds (continuation).

Compound	Labelled Precursor	Labelling Reagent	Labelling Reaction	Reference
[^{18}F]haloperidol	H^{18}F	Cs^{18}F	triazene decomposition	321-322
[^{18}F]spiroperidol	"	"	"	323
[^{18}F]fluorobenzene	"	"	"	324
4'-[^{18}F]fluoroantipyrine	^{18}F$^-$(aq)	^{18}F$^-$(aq)	Schiemann	325
[^{18}F]-arylfluorides[b]	"	HB^{18}F$_4$	"	310
[^{18}F]-fluorobenzene	[^{18}F]F$_2$	[^{18}F]F$_2$	electrophilic substitution	326,327
[^{18}F]-p-fluoronitrobenzene	"	Rb^{18}F	"	328
[^{18}F]-p-fluorobenzonitrile	"	"	"	328
[^{18}F]Fluorocarboxylic Acids and Derivatives				
[^{18}F]fluoroacetic acid	^{18}F$^-$(aq)	Dowex 1x4 (^{18}F$^-$)	exchange	329-330
[^{18}F]fluoroacetamide	"	"	"	329
2-[^{18}F]fluorohexanoic acid	"	"	"	329
2-[^{18}F]fluorotetradecanoate	"	"	"	329,330
2-[^{18}F]fluoroacetic acid, ethyl ester	"	"	"	331
2-[^{18}F]fluoroacetic acid, ethyl ester	Ne/^{18}F[a] or O$_2$/^{18}F[a]	K^{18}F	exchange	137
2-[^{18}F]fluorovaleric acid, methyl ester	^{18}F$^-$(aq)	Dowex 1x4 (^{18}F$^-$)	"	331
2-[^{18}F]fluoropropanoic acid, methyl ester	"	K^{18}F (anhyd)	nucleophilic substitution	331
16-[^{18}F]fluorohexadecanoic acid	"	K^{18}F (molten acetamide)	exchange	332-333
17-[^{18}F]fluoroheptadecanoic acid	"	"	"	332-333
2-[^{18}F]fluorostearic acid	"	"	"	115,332-333
9,10-[^{18}F]fluorostearic acid	"	"	"	332-333
7-[^{18}F]fluoropalmitic acid	H^{18}F (anhyd)	Cs^{18}F	nucleophilic substitution	334

Table 4. Fluorine-18 Labelled Compounds (continuation).

Compound	Labelled Precursor	Labelling Reagent	Labelling Reaction	Reference
Fluorosteroids				
2,4-[^{18}F]difluoroestrone	$^{18}F^-$(aq)	K^{18}F-CH_3CO_2H	nucleophilic substitution	311
4-[^{18}F]fluorotestosterone	"	"	"	311
21-[^{18}F]fluoroprogesterone	"	K^{18}F[18-crown-6]	nucleophilic substitution	335-338
21-[^{18}F]fluoropregnenolone-3-acetate	"	"	"	339
3-[^{18}F]fluorocholestene	$^{18}F\cdot$	Ag^{18}F	nucleophilic substitution	133
4-[^{18}F]fluoroestrone and 4-[^{18}F]fluoroestradiol	Ne/$^{18}F^a$	Ne/$^{18}F^a$	Schiemann	340-341
3-acetoxy-5-hydroxy-6-[^{18}F]fluorocholestane	$^{18}F\cdot$	B$^{18}F_3$	H^{18}F addition	133,134
3-acetoxy-5-[^{18}F]fluoro-6-hydroxycholestane	"	"	"	134
cholesteryl[^{18}F]fluoride	—	—	—	134
[^{18}F]Fluorosugars				
6-deoxy-6-[^{18}F]fluoro-α-D-galactopyranose	$^{18}F^-$(aq)	$Et_4N^{18}F$	nucleophilic substitution	342
β-D-glucosyl-[^{18}F]fluoride	"	Ag^{18}F	"	343
2-deoxy-2-[^{18}F]fluoro-D-glucose	$^{18}F[F_2]$	$^{18}F[F_2]$	electrophilic addition	72-73,344-349 276
2-deoxy-2-[^{18}F]fluoro-D-mannose	"	"	"	344
3-deoxy-3-[^{18}F]fluoro-D-glucose	H^{18}F (anhyd)	Cs^{18}F	nucleophilic substitution	124,350-352

Table 4. Fluorine-18 Labelled Compounds (continuation).

Compound	Labelled Precursor	Labelling Reagent	Labelling Reaction	Reference
[^{18}F]Fluoropyrimidines				
5-[^{18}F]fluorouracil	$^{18}F[F_2]$	$^{18}F[F_2]$	electrophilic addition	353-354
5-[^{18}F]fluoro-2'-deoxyuridine	"	"	"	355-356
5-[^{18}F]fluorouridine	"	"	"	357
5-[^{18}F]trifluoromethyluracil	$^{18}F^-$(aq)	K^{18}F[18-crown-6]	exchange	358
2'-fluoro-2'-deoxyuridine	$^{18}F\cdot$	Ag^{18}F	nucleophilic substitution	359
Miscellaneous ^{18}F-Labeled Compounds				
acetyl[^{18}F]fluoride	$^{18}F^-$(aq)	^{18}F-resin	nucleophilic displacement	360-361
1-[^{18}F]fluorohexane	"	"	"	360-361
benzoyl[^{18}F]fluoride	"	"	"	360-361
benzyl[^{18}F]fluoride	"	$Et_4N^{18}F$	"	360-361
p-toluenesulfonyl[^{18}F]fluoride	"	K^{18}F	"	360
[^{18}F]trifluoromethylbenzene and derivatives	"	K^{18}F [18-crown-6]	exchange	358
2-[^{18}F]trifluoromethylbenzothiazole	"	"	"	358
2-[^{18}F]trifluoromethylphenothiazine	"	"	"	358
3-[^{18}F]fluoro-p-menthane	"	K^{18}F	nucleophilic substitution	362
diethylamino sulfur[^{18}F]trifluoride	H^{18}F or $^{18}F[F_2]$	H^{18}F or $^{18}F[F_2]$	exchange	128
3-[^{18}F]fluoropropanol	$^{18}F^-$(aq)	K^{18}F	"	362
2-[^{18}F]fluoroethanol	"	K^{18}F	"	362
2-[^{18}F]fluoroethanol	"	Dowex 1x4 ($^{18}F^-$)	exchange	329

Table 4. Fluorine-18 Labelled Compounds (continuation).

Compound	Labelled Precursor	Labelling Reagent	Labelling Reaction	Reference
2-[^{18}F]fluoroethanol	H^{18}F (anhyd)	^{18}F-DAST	substitution	128
2-[^{18}F]fluoroethanol	"	Cs^{18}F	nucleophilic substitution	363
methyl[^{18}F]fluoride	"	^{18}F-DAST	substitution	128
ethyl[^{18}F]fluoride	"	"	"	128
[^{18}F]fluoroalkanes[c]	^{18}F$^-$(aq)	Et$_4$N^{18}F	nucleophilic substitution	364
[^{18}F]oxytocin	^{18}F$^-$(aq)	K^{18}F-CH$_3$CO$_2$H	nucleophilic substitution	311
[^{18}F]fluorotrichloromethane	"	Ag^{18}F	"	365
dichloro[^{18}F]difluoromethane	"	Ag^{18}F$_2$	"	365
4-[^{18}F]fluoroantipyrine	^{18}F[F$_2$]	[^{18}F]F$_2$	electrophilic addition	366-367
[^{18}F]fluoronitriles	^{18}F$^-$(aq)	Dowex 1x4 (^{18}F$^-$)	exchange	330
6-[^{18}F]fluoro-9-benzylpurine	^{18}F·	Ag^{18}F	nucleophilic substitution	133

* Biosynthesis.

a. ^{18}F species not identified.

b. ^{18}F-labeled fluorobenzene, fluorobiphenyl, 2-fluoronaphthalene, 1,3-chlorofluorobenzene, o-fluoroanisole, m-fluoroacetanilide, p-fluorobenzoic acid, p-fluoronitrobenzene, 1-fluoro-2,3,5-tribromobenzene.

c. RF (R = CH$_3$, C$_2$H$_5$, n-C$_3$H$_7$, i-C$_3$H$_7$).

Table 5. Enzymatic Syntheses of ^{13}N-L-Amino Acids.

^{13}N-Source	Substrate	Enzyme	^{13}N-L-Amino Acid	References
A. $RCCO_2H + {}^{13}NH_3 \longrightarrow R\text{-}CH(^{13}NH_2)CO_2H$				
$^{13}NH_3$	α-ketoglutaric acid	GAD[a]	glutamic acid	152,154,368-375
"	pyruvic acid	"	alanine	152,373-374,376-377
"	α-ketoisocaproic acid	"	leucine	152,373
"	α-ketoisovaleric acid	"	valine	152,373
"	α-ketobutyric acid	"	α-aminobutyric acid	373
"	α-keto-γ-methiol-butyric acid	"	L-methionine	373
B. $HO_2CCH_2CH_2CH(^{13}NH_2)CO_2H + RCCO_2H \longrightarrow RCH(^{13}NH_2)CO_2H$				
^{13}N-glutamic acid	pyruvic acid	GTP[b]	alanine	369
"	oxalacetic acid	GOT[c]	aspartic acid	370,374
"	p-hydroxyphenyl-pyruvic acid	"	tyrosine	378
"	phenylpyruvic acid	"	phenylalanine	378
C. $HO_2C(CH_2)_nCH(NH_2)CO_2H + {}^{13}NH_3 \longrightarrow H_2{}^{13}NCO(CH_2)_nCH(NH_2)CO_2H$				
$^{13}NH_3$	glutamic acid	GS[d]	[amide-^{13}N]glutamine	152,154,368,370,374,379
"	aspartic acid	AS[e]	[amide-^{13}N]asparagine	380-381

a. glutamic acid dehydrogenase
b. glutamate-pyruvate transaminase
c. glutamate-oxaloacetate transaminase
d. glutamine synthetase
e. asparagine synthetase

Table 6. Nitrogen-13 Labeled Compounds Prepared by Direct Chemical Synthesis.

Compound	Labelling Reagent	Reference
1-(2-chloroethyl)-3-cyclohexyl-1-[^{13}N]nitrosourea	$H^{13}NO_2$	158,161
1,3-bis(2-chloroethyl)-1-[^{13}N]nitrosourea	"	159,161
[^{13}N]streptozotocin	"	382
[^{13}N]nitrosocarbaryl	"	382
[^{13}N]urea	$^{13}NH_3$	383
[^{13}N]asparagine	"	384
[^{13}N]octylamine	"	385
[^{13}N]amphetamine	"	386

The Synthetic Strategy

In developing a practical synthetic approach leading to a new short-lived radiotracer, the advantage of being acquainted with the general methods and new developments in synthetic organic chemistry cannot be overemphasized. This is especially true considering the difficulties in synthesizing relatively complex molecules from a limited number of precursor molecules within the restricted time period imposed by the half-life of the nuclide. As is the case in approaching any problem in synthetic organic chemistry, the first step should be a detailed search of the relevant chemical literature. A search of the unlabeled compound itself or model compounds may suggest routes which can be modified to be compatible with the half-life and precursor restrictions. In some cases, synthetic strategies involved in related syntheses of short-lived tracers or carbon-14 labeling can serve as a guide. Tables 3, 4, 5 and 6 provide listings of ^{11}C, ^{18}F and ^{13}N labeled compounds along with the labeled precursor from which they were synthesized. In general, the following two factors influence the potential adaptation of a given synthetic approach to high specific activity labeling with short-lived nuclides.

1. The reaction should proceed in high radiochemical yield.
2. The reaction should be one in which the radioisotope undergoes low or no dilution with carrier.

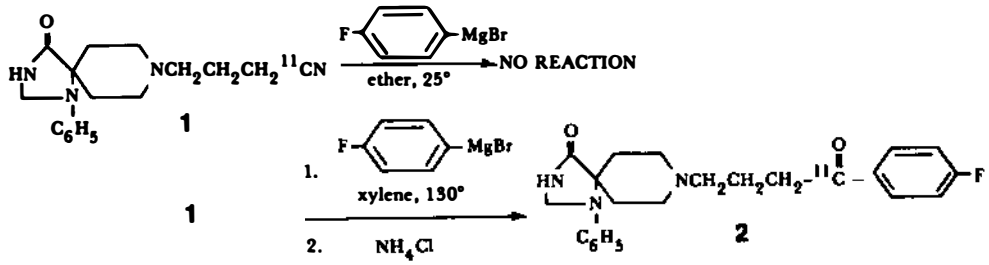
The initial literature search and the planning of the synthetic approach is usually followed by a more detailed investigation of reagents, protecting groups etc. A brief guide to location of useful information on the use of the literature in organic synthesis appears in Appendix 1. A selected list of review articles on the general topics of organic synthesis with positron emitting nuclides is included in Appendix 2. "Non-synthetic" techniques (164) including recoil labeling, radiation labeling, and excitation labeling to produce radiotracers will not be covered here, although some of the simple labeled precursors listed in Table 2 are produced using these methods.

Optimization of Reaction Rates

In contrast to most problems in synthetic organic chemistry where the rate of a chemical reaction is not a great concern if it is within a reasonable time scale, the problem of reaction rates as well as the time scale of experimental manipulations is a primary concern to labeling with short-lived positron emitters. Both classical chemical synthesis and biosynthesis have been used in the incorporation of positron-emitting nuclides into radiotracers. The optimal yield and reaction time can be derived from rate equations including the radioactive decay constant. This has been

validated using a model reaction (i.e. the synthesis of 1-[^{11}C]-methoxy-3-nitrobenzene starting with [^{11}C]methyliodide) (302). The incorporation of any short-lived nuclide into radiotracers usually requires the adjustment of such reaction conditions as temperature, solvents, substrate reactivity and reagents so that the synthesis, purification and formulation for injection can be carried out within a few half-lives of the nuclide. This imposition of a restricted time scale on the synthetic approach is somewhat unique to labeling with short-lived nuclides and challenges the ingenuity of the chemist. Some examples serve to illustrate these points.

Temperature effects: It is important to investigate a range of temperatures in carrying out a given transformation. As an example, the conversion of ^{11}C-labeled nitrile (1) to ^{11}C-spiroperidol (2) by reaction with p-fluorophenylmagnesium bromide proceeded rapidly at 130° whereas no reaction was observed at 25°. The elevation of the reaction temperature required

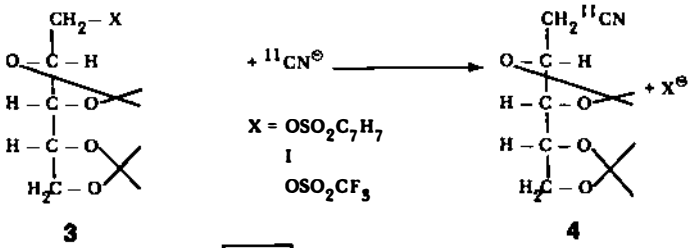


the substitution of xylene for ether as the reaction solvent another factor which probably increased the reaction rate (304).

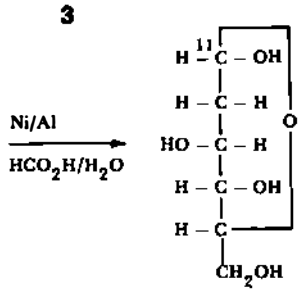
Substrate Structure, Reducing Agents, Protective Groups and Solvents

There is a large body of information concerning the effect of structure on the degree of reactivity of organic molecules to various reagents. This information can be exploited when designing synthetic approaches to short lived radiotracers. For example, the reaction of protected substrate 3 with ^{11}C-cyanide was required to produce nitrile 4 which was then converted to [1-^{11}C]-2-deoxy-D-glucose, 5 (277). The 20 minute half-life of carbon-11 required that this step be rapid. The rates of displacement of three different leaving groups on the protected substrate 5 were investigated. When the leaving group was tosylate (x = $OSO_2C_7H_7$) the reaction required several days at room temperature. However, when the leaving group was iodide the reaction only required 5 min at 120°. The most satisfactory leaving group, however, was trifluoromethanesulfonate (x = OSO_2CF_3) which is well known for

its reactivity in nucleophilic displacement reactions and reacts in 5 minutes at 25°. The nitrile 4 was not purified before carrying out step 2.



3 4



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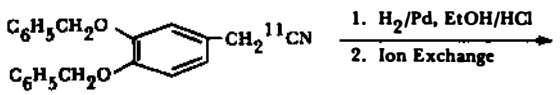
It was found that iodide ion but not trifluoromethanesulfonate anion present in the reaction mixture after the displacement poisoned the catalytic reduction (Step 2). It is a time advantage to be able to carry out the second step of the synthetic sequence without an intermediate purification step, but as the above synthesis points out, the interference of reaction products as well as reagents may require modification of the substrate.

Another related tactic which has been used to advantage is the simultaneous accomplishment of two transformations in one step. For example in the second step of the ^{11}C-2DG synthesis described above, the protective isopropylidene groups which are acid labile are cleaved during the reduction of the ^{11}C-nitrile to the ^{11}C-2DG. In another example, the conversion of nitrile (6) to ^{11}C-labeled dopamine·HCl (7) involved the simultaneous reduction of the nitrile to an amine and removal of the benzyl protective groups.



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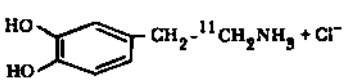

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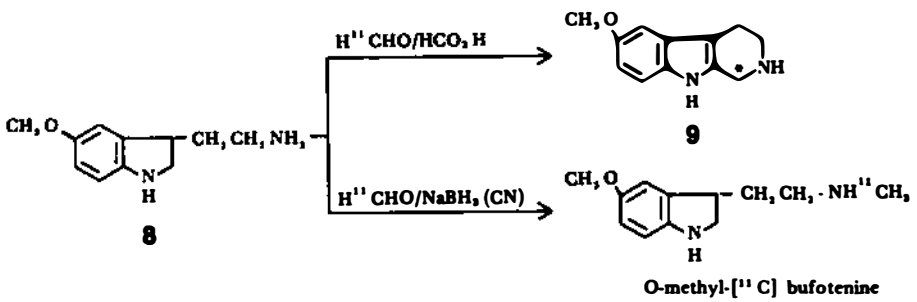
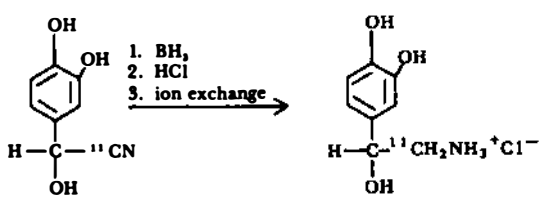
The use of ion exchange as a purification step allowed the separation of the ^{11}C-dopamine·HCl from toluene and other non-amine impurities in the reaction mixture (252).

An important consideration in the design of a synthetic strategy is the availability of a wide variety of reducing agents which differ in their functional group selectivity can be used to advantage in the selective reduction of functional groups in complex molecules (see references in Appendix 1). For example, in the synthesis of O-methyl-[^{11}C]bufotenine via the reductive methylation of O-methyltryptamine (8), the conventional Eschweiler-Clark reductive methylation using H^{11}CHO/HCO$_2$H which is used in the preparation of many N-[^{11}C]methylamines (see Table 3) lead to the undesired tetrahydrocarboline derivative, (9), whereas the use of a milder reducing



8 9 O-methyl-[^{11}C] bufotenine

agent, sodium cyanoborohydride, resulted in the desired transformation (224). In another example ^{11}C-labeled cyanohydrin (10) is reduced to ^{11}C-labeled norepinephrine hydrochloride (11) using borane, a Lewis acid type reducing agent (253).



10 11

Attempts to carry out this transformation with lithium aluminum hydride were unsuccessful probably due to the presence of the catechol moiety which formed insoluble complexes with the reducing agent and to the instability of the

substrate in a basic medium. Catalytic hydrogenation could not be used in this case because of the known hydrogenolysis of benzyl alcohols.

The importance of the wise choice of protective groups in rapid organic synthesis should be reemphasized. The presence of more than one reactive center in the same molecule often complicates the transformation of a single functional group and requires protecting these other reactive functional groups during the synthesis. However it is also essential that the protective group be removed rapidly after the desired reaction step and that the protective moiety be separable from the product. Along this line, the development of many protective groups of varying stability in different chemical environments has played an important role in synthetic organic chemistry (see Appendix 1). The application of their diverse properties to problems in rapid organic synthesis is an important aspect of developing reasonable synthetic approaches to complex short-lived radiotracers.

Following the above examples, solvent effects can be used to enhance the rates of a variety of chemical reactions. This is most dramatically illustrated by the use of dipolar aprotic solvents to increase the reactivity of anions in nucleophilic displacement reactions. For example, in the reaction of cyanide ion with methyl iodide, the reaction is $> 5 \times 10^5$ faster in dimethylformamide (DMF) than in water. This rate enhancement is due to the poor solvation of the cyanide ion in DMF coupled with a favorable solvation of the polarized charged transition state. There is a large amount of information concerning the use of dipolar aprotic solvents to enhance reaction rates (387). These solvents have been used many times in the rapid synthesis of ^{11}C-labeled nitriles (Table 3).

Specific Activity and Stoichiometry

Specific activity is frequently defined as radioactivity per unit of mass (388). The maximum specific activity for a radionuclide is a function of the half-life of the nuclide and is attained when there is no dilution by other isotopes of the same element. This is referred to as the carrier-free (CF) state. In practice, it is possible to approach the CF state within an order of magnitude for some radionuclide species. However, it is difficult to exclude the stable nuclide in most cases. For example, the unintentional and largely unavoidable dilution of ^{11}C with ^{12}C is approximately 1:3000 in the case of $H^{11}CN$ and 1:8,000 in the case of $H^{11}CHO$, frequently used ^{11}C-labeled precursors.

The need for a consistent terminology for identifying the extent of dilution of the radiotracer has been recognized and the use of the following three unambiguous terms has been recently suggested (303,389):

Carrier Free, CF, should mean that the radionuclide or stable nuclide is not contaminated with any other radio or stable nuclide of the same element.

No Carrier Added, NCA, should apply to an element or compound to which no carrier of the same element or compound has been intentionally or otherwise added during its preparation.

Carrier Added, CA, should apply to any element or compound to which a known amount of carrier has been added.

It should be clear that these terms refer to a specific position or positions when applied to a molecule.

When the specific activity of the short-lived radiotracer is very near CF, the mass of the product is not detectable by ordinary chemical or spectroscopic means. With NCA ^{11}C-labeled radiotracers the specific activity of the product can be determined by measuring the mass of a large (radioactivity) amount labeled precursor using sensitive analytical techniques. This was done in the case of $H^{11}CN$, and this value can be used to calculate the specific activity of radiotracers which are synthesized from $H^{11}CN$ (304). It has been possible to determine the specific activity of NCA receptor ligands such as ^{11}C-spiroperidol using a highly sensitive radioreceptor assay method (304).

When the maximum specific activities for the positron emitters ^{11}C, ^{18}F and ^{13}N is compared to ^{14}C and ^{3}H (Table 1) it is apparent that far less mass is associated with CF or NCA levels of tracers labeled with the positron emitters than with carbon-14 or tritium. With NCA or CF short-lived radiotracers, the mass of the tracer is at the same time usually below the threshold where any physiological response is invoked but where there is sufficient radioactivity associated with this mass to be detected with statistical significance. For example, the radioactive concentration in the tissue of interest should be in the range 0.1-0.5 μCi/g to provide statistically significant count rates with present PET instruments. In using positron emitting ligands to study receptors where the receptor-ligand dissociation constant is ~ 10^{-9}M, the specific activity of the radiotracer should be in the range 100-500 Ci/mmol at the time of measurement (52). Furthermore, even highly toxic molecules can be studied if the radiotracer can be prepared in sufficiently high specific activity.

While the high specific activity possible with positron emitting tracers is frequently an essential requirement for tracer studies in humans, it places more restrictions on the synthetic approach. This is manifested in terms of the scale of the reaction and the stoichiometry. For example, in a NCA

synthesis with $Na^{11}CN$ (specific activity: 2000 Ci/mmol) the quantity of NaCN used if one starts with 100 mCi, is 50 nmol. With this small quantity of ^{11}C-labeled NaCN, all other substrates or reactants used in the synthesis are necessarily in huge excess. This can often pose difficulties when an excess of a given reagent cannot be tolerated. For example, in the synthesis of ^{11}C-2-deoxy-D-glucose at high specific activity the reduction is most conveniently carried out using Raney alloy (Ni-Al) in acidic solution (HCO_2H/H_2O) (277). Since the reduction is carried out in acidic solution the imine formed is hydrolyzed to the aldehyde *in situ*, thus minimizing the amount of amine formed. This *in situ* hydrolysis makes the relative ratio of the nitrile to reducing agent unimportant in contrast to the use of a hydride reducing agent (see ref. 390 for a discussion of the problems of reduction of $R^{11}CN \rightarrow R^{11}CHO$).

Dealing with high specific activity labeled precursors also requires that the synthesis be carried out on a very small scale. This is important both in terms of the relative ease and speed with which one can handle small quantities of reagents and solvents and in the interest of introducing the minimum amount of substances to be removed in the final purification. It is also important in terms of avoiding the unintentional introduction of impurities which may negatively influence the course of the reaction. One thing which must be kept in mind is that the substrate which will undergo reaction with the labeled precursors be in sufficient concentration to react both with the labeled precursors *and* other competing reactants which may be present in the reaction mixture. Even though the labeled precursor may be far more reactive than other species in the mixtures relatively higher concentrations of less reactive species in the reaction mixture may consume all of the substrate before the desired labeling reaction may take place. For example, in the synthesis of labeled nitriles from ^{11}C-labeled cyanide, the $H^{11}CN$ from the target is trapped in sodium hydroxide. Therefore since the reaction mixture contains both $^{11}CN^-$ and OH^- as nucleophiles which can react with an added substrate, the amount of the substrate should be equal to the amount of the $^{11}CN^-$ plus OH^-. Some of the problems of ultramicro-scale organic synthesis have been addressed recently using ^{11}C labeling with a number of different types of reactions in which the relative ratios of ^{11}C-precursor and other reactants varied (391). The influence of equilibrium displacement, competing reactions and solvent impurities was examined.

Expression of Yields and Specific Activity with Short-Lived Nuclides

When describing radiotracer synthesis with short-lived radionuclides, it is essential that there is no ambiguity in expression of quantities of radioactivity, specific activity and radiochemical yields. This requires the decay correction of all relevant yields to some reference time point. This time point is most conveniently taken as the time of the end of cyclotron or accelerator bombardment (EOB). The use of EOB as a reference time point normalizes the variable of synthesis time. In cases where it is useful to express the yield at the end of the synthesis time, EOS should be used to denote this. The format is generally to use the expression EOB directly following the yield (i.e. 300mCi (EOB)). When EOS is used, the synthesis time should be included (i.e. 20mCi (EOS, 45 min)). In this way radiochemical yields can be readily calculated and there are no ambiguities having to do with synthesis time.

Biosynthetic Tactics

Biosynthetic approaches to short lived radiotracers have been reviewed (392) and have the advantages of speed and the introduction of asymmetric centers into natural products and the potential disadvantages of producing complex mixtures of products and introducing pyrogenic macromolecular contaminants. Carbon dioxide and ammonia are precursors to complex molecules in nature and therefore enzymes which catalyze their conversion into organic molecules are well characterized. For this reason the readily available short lived precursors $^{11}CO_2$ and $^{13}NH_3$ have served as precursors in a number of biosynthetic approaches to ^{11}C and ^{13}N-labeled organic molecules. In addition, $H^{11}CHO$ has been used as a precursor in the enzymatic synthesis of ^{11}C-thymidine (100). Although ^{13}N-labeled nitrate and molecular nitrogen have been used to study the nitrogen assimilation and metabolism in bacteria (393-397), they have not actually been used with biosynthesis of ^{13}N-labeled molecules as a goal. Tables 3, 4, and 5 provide a listing of ^{11}C and ^{18}F- and ^{13}N-labeled molecules with those being produced by biosynthesis or combined chemical and biosynthesis receiving special notation (*).

The utility of biosynthetic approaches depends on the biosynthetic system employed. This determines whether a single product or a multiplicity of products are produced and also determines the ease and speed with which single, pure product, free from macromolecular contamination, can be isolated. The complexity of the reaction mixture is especially critical with ^{13}N because of its short half-life.

Thus far some of the biosynthetic approaches used with short-lived nuclides include photosynthetic systems using plant material, purified and

partially purified enzymes including immobilized enzymes, and rat liver microsomes. These systems have been used to synthesize molecules and, in some cases, to resolve optical isomers by reacting selectively with one enantiomer. In some cases, a combination of synthetic and biosynthetic schemes have been used to synthesize the desired radiotracer.

The photosynthetic production of ^{11}C-glucose is a modification of a method used for preparing ^{14}C-glucose (398) and was first reported in 1971 (267-268). The approach involves the recirculation of $^{11}CO_2$ around fresh (light starved) Swiss Chard leaves in the presence of incandescent light. The crude unhydrolyzed reaction mixture contains ^{11}C-sucrose and ^{11}C-sugar phosphates. After hydrolysis, the labeled free sugars glucose and fructose and sugar phosphates are present.

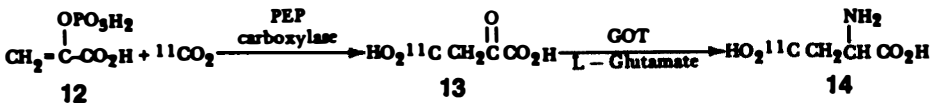
$$^{11}CO_2 + \text{Starved Swiss Chard Leaves} \xrightarrow[\text{2. Alcohol extraction}]{\text{1. Photosynthesis}} \left.\begin{matrix} ^{11}\text{C-Glucose} \\ ^{11}\text{C-Fructose} \\ ^{11}\text{C-Sucrose} \end{matrix}\right\} + \text{Phosphates}$$

$$\xrightarrow[\text{2. Neutralize}]{\text{1. } H^+} \begin{matrix} ^{11}\text{C-Glucose} \\ ^{11}\text{C-Fructose} \end{matrix} \xrightarrow{\text{HPLC}} {}^{11}\text{C-Glucose}$$

The separation of sugar phosphates from ^{11}C-glucose and fructose is accomplished by ion exchange chromatography after which ^{11}C-glucose is separated from ^{11}C-fructose by high pressure liquid chromatography (269-270). Since intact plants are used in this synthesis, a multiplicity of products are produced necessitating an involved workup and purification scheme. Nonetheless, the simplicity of the photosynthetic system makes this a very attractive synthesis and the separation of pure ^{11}C-labeled glucose from this complex reaction mixture of labeled compounds and plant materials in an overall time of 75 minutes is worthy of comment. More recently this general method has been modified to use the green alga Scenedesmus obtusiusculus Chod as the plant material and $H^{11}CO_3^-$ as the feed material (271). Since the $H^{11}CO_3^-$ can be easily shielded and transported to a chemistry facility, this method offers an alternative when the photosynthesis cannot be carried out adjacent to the cyclotron. ^{11}C-Glucose is of special interest as a radiotracer for quantitating brain glucose metabolism and the mathematical models for extracting regional metabolic rates from emission tomographic data have been developed (3).

The enzymatic synthesis of ^{11}C-amino acids from $^{11}CO_2$ has been applied to L-aspartic acid using a crude extract of chicken liver acetone powder with the conditions for the reaction being optimized with carbon-14 (199). A

refinement of this approach to L-[4-^{14}C]aspartic acid has been recently reported using immobilized phosphoenolpyruvate (PEP) carboxylase to catalyze



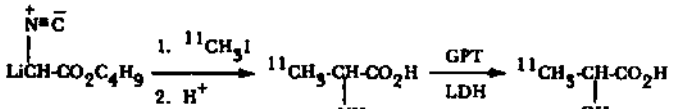
12 13 14

the reaction between phosphoenolpyruvic acid 12 and $^{11}CO_2$ to form [4-^{11}C]-oxaloacetate 13 followed by immobilized glutamate/oxaloacetic acid transaminase (GOT) to transform ^{11}C-oxaloacetic acid into aspartic acid 14. The use of immobilized enzymes allowed the production of pharmaceutical quality L-aspartic acid in 15-25 minutes after $^{11}CO_2$ production with sufficient quantities being produced to allow its evaluation as a tracer for local myocardial metabolism (200).

A two-step enzymatic synthesis of ^{11}C-L-lactic acid has been developed and consists of 1) production of C-11 pyruvate from $^{11}CO_2$ and acetyl CoA in the presence of an enzyme extracted from Clostridium acidi urici and 2) conversion of C-11 pyruvate to ^{11}C-lactic acid by lactic dehydrogenase in a yield of 3-5%. ^{11}C-L-alanine is produced from ^{11}C-pyruvic acid using glutamic-pyruvic transaminase (181-182).

Isolated enzymes have been used to synthesize L-amino acids using ^{13}N-ammonia. In contrast to the ^{11}C-glucose synthesis, these systems yield single labeled products when incubated with ^{13}N-ammonia (see Nitrogen-13 section). Sequential enzymatic syntheses have also been used. Briefly, the procedure involves incubation followed by purification by ion exchange chromatography, which gives a radiochemically pure product frequently contaminated by potentially pyrogenic macromolecular materials. The use of immobilized enzymes, however, yields pharmaceutical quality materials. Although many of the enzymes which have been used are obtained from commercial sources in some cases, enzyme isolation as well as immobilization may be necessary.

Another attractive tactic combines synthetic and biosynthetic techniques. For example, the conversion of ^{11}C-alanine (15) to 3-^{11}-C-lactic (16) has been accomplished and involves the synthesis of ^{11}C-alanine by a

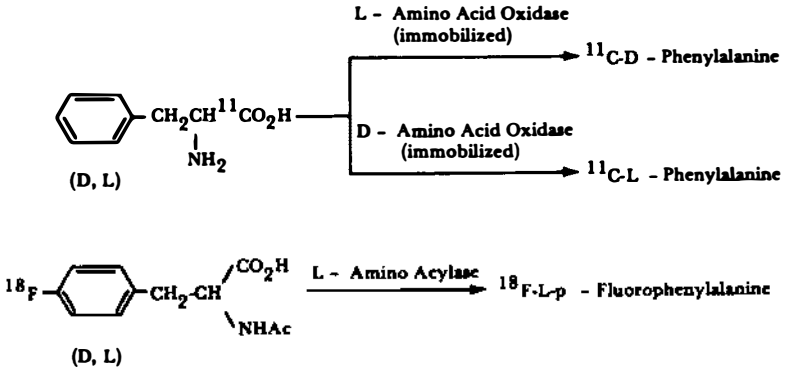


15 16

synthetic route followed by the enzymatic (glutamate pyruvate transaminase, GTP) conversion to lactic acid in the presence of α-ketoglutarate and lactic

dehydrogenase (LDH). The enzymatic synthesis, uses only the L-isomer of alanine, thereby reducing the radiochemical yield (183). Asymmetric induction has since been used to enrich the L-alanine in the mixture (178).

In another similar combination of techniques, enzymes have been used to resolve D,L-mixtures of labeled amino acids. This has been applied to



^{11}C-labeled amino acids (176) and ^{18}F-labeled amino acids (307-308). These enzymatic resolution methods along with the chromatographic resolution of amino acids (195,198) offer the possibility of doing studies on amino acid metabolism using the physiologically active L-isomer thus reducing background activity as well as the radiation dose resulting from the D-isomer.

Another approach which has only been explored briefly, but which could probably be exploited to a greater extent is the use of mitochondria to carry out synthetic transformations. In the one example reported ^{11}C-hippuric acid was prepared from ^{11}C-benzoic acid and glycine using rat liver mitochondria (221).

These examples were chosen to illustrate the potential advantages and problems associated with biosynthesis. The application of a combination of synthetic and biosynthetic techniques allows maximum flexibility and provides an attractive alternative to the use of a single approach. Advances in enzyme technology as well as chromatographic techniques can be expected to contribute significantly to future developments in the biosynthetic approach to short-lived radiotracers.

Radiotracer Purification and Quality Control

Assuming the absence of radionuclidic impurities, there are three requirements which radiotracers must meet. The first two are that the product

be chemically and radiochemically pure and the third is that the material be sterile and pyrogen free if it is to be used in human studies. These standards must be met and verified while working within a restricted time scale.

The synthesis of short-lived positron emitting radiotracers generally gives a crude reaction mixture containing the desired labeled product, labeled and unlabeled side products, and excess reagents and substrates. Frequently it is possible to purify an acidic or basic compound by extraction as exemplified by the synthesis of ^{11}C-alkylamines (41,255) and ^{11}C-palmitic acid (211). When more complex separations are encountered, however, other strategies must be used. The choice of separation method, of course, depends on the composition of the reaction mixture.

The use of chromatographic materials of small particle size in conjunction with high, and medium pressure liquid chromatography (HPLC and MPLC) has revolutionized the separation of compounds which differ only slightly in their structures. An essential feature of these separations is their speed and high resolution. This technology has been applied to normal and reverse phase as well as ion exchange separations and has wide application in the purification and analysis of short-lived radiotracers.

A review covering the literature on ion exchange and liquid chromatography for 1978 and 1979 provides an excellent survey of recent developments (399) and a guide to books and review articles appearing during this time period. In addition the Journal of Chromatography provides a yearly bibliography on gas chromatography, liquid chromatography and thin layer chromatography (400). An excellent text on the fundamentals and applications of chromatography is also recommended (401).

Ion exchange chromatography is frequently effective in the purification of amphoteric, acidic and basic compounds as well as sugars. It can be used to remove metal ions from reaction mixtures as in the synthesis of ^{11}C-2-deoxyglucose, and to simply immobilize the desired product while undesired components of the reaction mixture are removed as in the synthesis of ^{11}C-labeled catecholamines (251-253). The above two applications simply involve rapid filtration of the crude reaction mixture through the appropriate resin rather than effecting a separation through the amplification of subtle differences in acidity or basicity. In contrast, the separation of sugars having only slight structural differences is rapidly accomplished by the use of micro-particulate cation exchange resins and HPLC examples being the purification of ^{11}C-glucose (269-270), the purification of ^{11}C-mannitol (266) produced by photosynthesis, or the chromatography of (^{18}F)-2-deoxy-2-fluoro-D-glucose (402).

Normal phase chromatography over silica gel is a classical separation method which has recently been improved through the use of small particle size silica gel and HPLC and MPLC techniques. This has allowed rapid separations to be effected. The HPLC technique usually involves the frequent monitoring of the resolving power of the column. This also applies to reverse phase chromatography and procedures for regenerating these expensive columns which have lost their resolving power can often be obtained from the manufacturer. Frequently, the reversal of the elution patterns for compounds on a reverse phase compared to a normal phase column can be used to advantage. For example, it is desirable, in separating two compounds with only slightly different retention times, to have the desired product elute first to avoid contamination by tailing. The use of HPLC (403) as well as incorporation of HPLC into an automated synthesis system has been reported for the routine and frequent synthesis ^{11}C-labeled imipramine at high activity levels and an automated remote injection system has also been described (185,230,403-405). Here reverse phase chromatography is used to effect the rapid separation of ^{11}C-labeled imipramine from desmethylimipramine, the starting material.

An option of HPLC for normal phase separations requiring medium resolution ($\Delta R_f > 0.15$) is flash chromatography. Flash chromatography is an air pressure driven hybrid of medium pressure and short column chromatography (406). The advantage of this method is not only its simplicity and reliability, but also that the solvent system used to separate a given mixture on Merck tlc plates (No. 5775) can be used with the silica gel columns (Merck No. 9385) with similar results. This permits a rapid exploration and optimization of column conditions. The use of fresh silica get for each separation ensures the reproducibility of the separation. The average separation requires five minutes and when elution volumes are determined in advance a simple column design involving two fractions can be used (Figure 2). This technique is routinely and reliably used in our labroatory in the synthesis of ^{18}F-2-deoxy-2-fluoro-D-glucose (349), ^{11}C-2-deoxy-D-glucose (277) and ^{11}C-spiroperidol (304). Figure 2 also shows the separations achieved by comparing radio thin layer chromatograms of the crude reaction mixture (a) forecut (b) and product fractions (c) after separation. Another alternative to common chromatographic techniques is vacuum liquid chromatography which also features good resolution in short times (407).

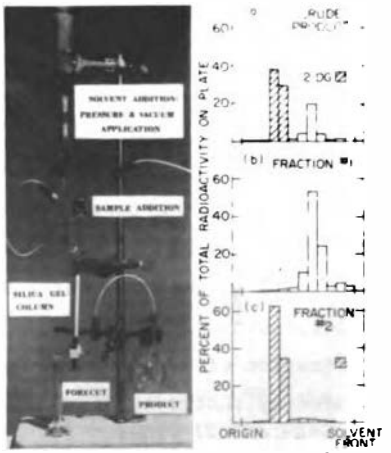


Fig. 2 Purification of ^{11}C-2DG by flash chromatography

Thin layer chromatography (TLC), HPLC, and gas liquid chromatography (GLC) are commonly used methods for determining radiochemical purity of short lived radiotracers. The adequacy of an analytical method depends on the chromatographic similarities of impurities. Guidance on the selection of adsorbants, solvents and detection systems can often be obtained by consulting compilations of chromatographic data in various sources (399-400,408). For most routine applications TLC is a simple rapid method for determining radiochemical purity especially if the product is chromatographed in a number of solvent systems. The use of plastic back tlc sheets allows the simple accurate determination of the distribution of radioactivity by cutting the sheets into strips and counting the strips in an automatic or manual well counter. Alternatively TLC scanners or autoradiography can be used (408a). Many TLC systems require only 5-10 minutes for development and are therefore suitable for use with short half-life tracers. Frequently the addition of inactive carrier compound to a sample of the radioactive compound is required for the analysis since the mass of compound produced in a high specific activity or no carrier added synthesis is below detectable limits. It is not unusual to encounter TLC artifacts with acidic or basic compounds, especially when small amounts of acid or base are present in the spotting medium and one should be aware of this as well as radiochemical impurities as a possible cause for unusual activity distribution (409-411). Applications laboratories associated with commercial producers of liquid chromatography equipment and columns are a frequently good source of information on the choice of HPLC columns and solvent systems for particular applications.

Gas liquid chromatography is also a useful reliable method of determining radiochemical and chemical purity. Its use frequently requires the derivatization of the product to increase its volatility and procedures for forming derivatives are well established. GLC also is a powerful tool in the determination of target gas composition, an application which may be necessary for development work and in tracing the cause of difficulties encountered in precursor production. An automatic gas liquid chromatography apparatus for the analysis of organic compounds labeled with short-lived radioisotopes has been described (411a and references therein).

The production of a sterile, pyrogen free radiotracer for human use requires the establishment of a procedure which has been proven to yield a pharmaceutical quality product, and then strictly adhering to the protocol. After-the-fact testing for sterility and apyrogenicity is carried out at frequent intervals.

CARBON-11

Carbon-11 as a Label for Radiotracers

Carbon and hydrogen are the most ubiquitous of elements present in the biomolecules of life. Carbon, as is the case with hydrogen, exists in both stable and radioactive forms but only carbon has radionuclides which are positron emitters and which can be used to provide body penetrating radiation for monitoring dynamic processes in animals and humans. The most well known of carbon tracers are carbon-14, a long lived β-emitter and carbon-13, a stable isotope. Other radioactive forms of carbon include carbon 9 ($t_{1/2}$ 0.13s) carbon-10 ($t_{1/2}$ 19.4s) and carbon-11 ($t_{1/2}$ 20.3m) but, of these, only carbon-11 has been used extensively in biological and medical research. It is a positron emitter with a small (~ 0.19%) electron capture component and decays to a stable isotope, boron-11. It is quite possibly the first positron emitter that was used in biochemical and medical research (217,412). Because of the short half life its popularity dwindled as a tracer for chemical and many biochemical studies when carbon-14 became available in the late 1940's (217). Nevertheless its unique physical properties, particularly the body penetrating photons resulting from positron annihilation in the host have regenerated increasing active interest in its use in the past ten years. In addition, its 20.4 minute half-life is particularly suited for serial studies of the dynamics of ^{11}C-labeled radiotracers in a single human or animal subject at short time intervals.

The chemical properties of carbon-11 are indistinguishable from those of carbon-12 and thus it is the ideal label for biomolecules and drugs where metabolism or catabolism does not destroy its effectiveness as a tracer. The maximum kinetic isotope effect which can result from cleavage of a carbon-11 to carbon-12 bond is of the order of 6-8%. This can usually be neglected since its use as a tracer in-vivo rarely reflects this difference and carbon-carbon bond breakage in a biomechanistically significant step is usually not involved. In any event, precision measurements in in-vivo tracer applications are such that an isotope effect of 1-4% (the most commonly observed range) would not be detected. However, if degradative procedures are used to verify label positions then the isotope effect must be taken into account if precise label concentrations are to be determined. Fortunately, an abundant theoretical and experimental literature exists for carbon-14 and carbon-13 (413) and thus precise estimates for carbon-11 effects can be addressed.

Because of the short half life of carbon-11, production of large quantities of the isotope is mandatory if the final product is to be made

available in sufficient quantity for biological and medical studies which require more than a few minutes for data acquisition. One must draw a distinction at this point between tracers such as ^{11}CO and $^{11}CO_2$ which can be made available at EOB in near quantitative yield and tracers requiring more extensive synthetic work with concomitant decay during synthesis non-quantitative chemical yields and losses during purification. Fortunately, carbon-11 is one of the most easily prepared radionuclides with a variety of nuclear reactions being available utilizing targets that are not isotopic with the product. Although choice of production methods do depend on available charged particles e.g. protons and/or deuterons and whether or not external beams are available, for the great majority of applications the simple and reliable nitrogen gas target utilizing the $^{14}N(p\alpha)^{11}C$ reaction is in use in most laboratories doing extensive synthetic work (89). A useful alternative is the boron oxide target which can be used to advantage in the $^{11}B(p,n)^{11}C$ reaction or the $^{10}B(d,n)^{11}C$ reactions depending on particle availability (see 164 and references therein). Although the use of the enriched boron isotope can enhance the carbon-11 yield, acceptable quantities can be obtained from the natural abundance compound. Targetry for the boron system is somewhat more cumbersome and target reprocessing or "throw-away" targets are necessary.

Simple Carbon-11 Compounds and Other Precursors Used as Radiotracers (see Table 2)

Synthesis of organic compounds containing carbon-11 has as its major constraint the time available between acquisition of the radionuclide and delivery of the compound to the user. While this may seem obvious, the literature contains synthetic procedures involving carbon-11 which are in no sense practical with regard to biological research to say nothing of application in humans. Problems involving loss of the radionuclide and/or intermediate due to surface to volume effects and adsorption properties of vessels, substrates used for purification etc. are very much more prominent in carbon-11 syntheses than in carbon-14 syntheses. This is not surprising when one considers the fact that a millicurie of carbon-14 contains 9.59×10^{18} atoms, equal to a weight of 0.22 milligrams, whereas a millicurie of carbon-11 contains 6.53×10^{10} atoms equal to a weight of 1.5 picograms. Another problem which is peculiar to syntheses with carbon, very much more so than with other elements because of chemical factors and the fact that carbon is ubiquitous in nature, is the danger of dilution with carbon-12 resulting in reduction of specific activity below that of the specific activity of the starting precursor. The preparation of a truly carrier free compound (remembering that in this case of carbon one applies the term carrier free to

a specific carbon position in the molecule) is highly improbable. Nevertheless dilutions in the range of 100 times greater than CF should be possible as the technology of carbon-11 precursor production advances. The possibility of labeling more than one position in a single molecule of more than two or three carbon atoms as has been accomplished with carbon-14 substitution is extremely remote with carbon-11. Here again the level of sophistication reached in in-vivo experiments with carbon-11 do not at present demand attempts to prepare such compounds. At least one advantage presents itself in carbon-11 synthesis. Appreciable self radiolysis in preparation are precluded even at the 100 mCi level when one considers the very small amounts involved and the radial range of the positron (414) (see Table 1).

There are only three widely used simple precursors for synthesis with carbon-11, $^{11}CO_2$, $^{11}CN^-$, and $H^{11}CHO$. However, this does not mean that, as the field grows, greater use will not be made of some of the other readily available simple compounds. This should be particularly true of carbonylation reactions utilizing ^{11}CO.

The preparation of $^{11}CO_2$ in up to Curie quantities from a nitrogen gas target is simple and straightforward. The nitrogen gas target must contain a few ppm of oxygen but that is usually the case for most commercial sources of purified nitrogen gas. The tank gas should, however, always be analyzed by gas chromatography before being attached to the production line to be sure that carbon containing impurities are absent or present at acceptable levels. The presence of impurities such as CO, CO_2, CH_4 etc. will serve to materially reduce the specific activity of the $^{11}CO_2$ produced. Levels of these impurities can be reduced cryogenically and/or by using suitable adsorbents. Suitable simple target systems can be found in the literature (89). Preparation from B_2O_3 poses similar problems in that the B_2O_3 can contain carbon impurities. However, the sweep gas, usually He, can also introduce carbon impurities and this should be kept in mind during production. The major product from these targets is $^{11}CO_2$. If the ^{11}CO contaminant is of no consequence in the synthesis, the gas mixture can be used directly in the first step of synthesis. However, if it is necessary to optimize the $^{11}CO_2$ yield the gas can be passed over CuO to insure near quantitative conversion to $^{11}CO_2$. Care must again be taken not to introduce trace quantities of carbon at this point. Carbon monoxide can also be produced directly by increasing the oxygen content of the target gas to a few percent. However, at high production levels the oxides of nitrogen produced in the target system make the isolation of the ^{11}CO more difficult. It is more generally useful to pass the effluent purified nitrogen target gas over CuO for $^{11}CO_2$ production and over metallic zinc for ^{11}CO production. This adds a few minutes to the

production of these two precursors after EOB. The complex chemistry occurring in the target should be kept in mind since the yields are a function of both dose and dose rate (415).

At the present time remote systems which deliver ^{11}CO and $^{11}CO_2$ reliably can be purchased from cyclotron manufacturers but as yet no simplified computer controlled (i.e. truly automatic) system is commercially available. In any event, construction of a reliable ^{11}CO and $^{11}CO_2$ production system is well within the capability of any chemistry facility associated with a cyclotron complex.

The preparation of $H^{11}CN$ and $H^{11}CHO$ are most effectively carried out by on-line systems connected to the target systems. While direct production of $H^{11}CN$ is possible using a N_2-H_2 target (92), reliability and high yield are best served by using a combination of target chemistry and subsequent chemical processing (89,415). The N_2-H_2 target is run at high beam current so that the $H^{11}CN$ initially produced is radiolytically reduced to $^{11}CH_4$ *in situ*. Small amounts of NH_3 are produced in the target gas mixture concomitantly with the $^{11}CH_4$ and this mixture of $^{11}CH_4$ and NH_3 is passed over Pt wool at 1000°C converting it to $H^{11}CN$ which can then be used for synthetic purposes. It should be emphasized that this is an "on-line" procedure with $H^{11}CN$ being available for organic synthesis at the end of bombardment with no manipulation required.

Procedures for production of $H^{11}CHO$ are less satisfactory in that they must be performed after cyclotron bombardment, are time consuming and are not quantitative. The reduction of ^{11}CO or $^{11}CO_2$ to $^{11}CH_3OH$ with $LiAlH_4$ in THF is followed by catalytic oxidation using ferric molybdenum oxide (100) or silver wool (98,101) Nevertheless, millicurie quantities of $H^{11}CHO$ in 10 to 20 min EOB are readily obtained.

In addition to $H^{11}CHO$, $^{11}CH_3I$ which is also of considerable utility can be obtained via rapid synthetic procedures (97-99). These methods all depend on the conversion of $^{11}CH_3OH$ prepared in the conventional manner, to $^{11}CH_3I$ usually using hydroiodic acid although other iodinating agents have been reported. Recently the production of $^{11}CH_3I$ by direct recoil synthesis in a N_2-HI flow target system was reported (96).

A number of other one and two carbon intermediates for synthesis such as cyanate, phosgene, acetylene, 1 or 2 labeled ethanol, acetic acid, and acetone have been described (see Tables 2,3).

While the appearance of novel or completely new synthetic procedures is unlikely in the development of labeling methods with carbon-11, the adaptation and modification of known procedures to allow rapid preparation of needed

compounds at high specific activity presents a challenge to the synthetic organic chemist as great as can be found in the syntheses of new and ever more complex organic structures. The challenge is clearly apparent in the "rule of thumb" for organic synthesis with short lived radionuclide in that the time for preparation from EOB to EOS should not exceed 3 x $t_{1/2}$ for the element in question.

Major advances in years to come will also depend on true automation of syntheses of needed precursors so that $^{11}CO_2$, $H^{11}CN$, $H^{11}CHO$ and $^{11}CH_3I$ will be available as usable reagents at EOB or near EOB without operator intervention. Their ready availability as reagents will greatly facilitate the synthetic work which will follow.

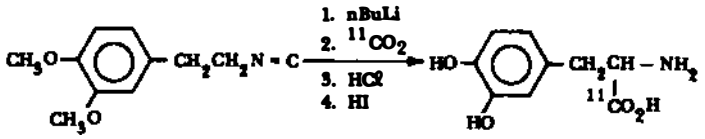
Synthesis with Carbon-11 Labeled Precursors

The many different compounds which can be produced using carbon-11 labeled precursors are apparent from the listings in Table 3 which is arranged according to compound type and includes labeled precursor, labeling reagent and reference. The introduction of carbon-11 in a complex molecule in the great majority of cases depends on the formation of a new carbon-carbon or carbon nitrogen bond. In that the limitations of time are met, reactions which involve powerful nucleophiles such as compounds containing carbon to metal bonds or substitution reactions in which solvent conditions are chosen to enhance the nucleophilic character of the labeling anion are usually chosen. Condensation reactions have been exploited to a lesser degree because of their generally slower reaction velocities.

One of the most facile reactions for carbon carbon-bond formation is the carboxylation of a Grignard reagent or other organometallic reagents such as

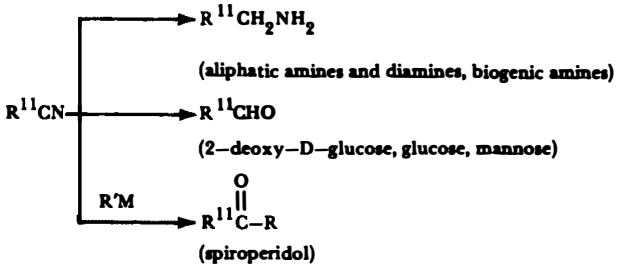
$$RMgX + {}^{11}CO_2 \longrightarrow R{}^{11}CO_2MgX \longrightarrow R{}^{11}CO_2H$$

organolithium reagents. For example α-lithioisonitriles have been carboxylated to produce ^{11}C-labeled amino acids such as α-phenylglycine, α-phenylalanine and L-DOPA (see Table 3 for examples)



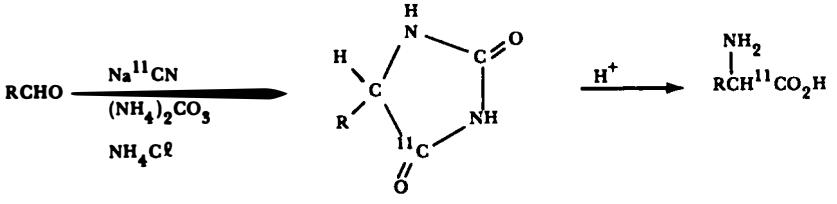
One of the earliest synthesis with carbon-11 was the preparation of 1-^{11}-C-acetic acid from CH_3MgI and $^{11}CO_2$ (217). The carboxylation of a Grignard reagent has been extensively used (see Table 3 for examples). There are two approaches. One can condense the $^{11}CO_2$ into reaction vessel and subsequently add the Grignard or other organometallic reagent. The organometallic reagent can be used most efficiently in this way and solvent volumes can be kept to a minimum. Alternatively the $^{11}CO_2$ can be swept through the solution organometallic reagent slowly over a period of 15-30 minutes. Subsequent work-up follows normal synthetic procedures. This reaction lends itself readily to remote operation and should be simple to automate. Great care must, however, be taken in carrying out this type of reaction if the specific activity of the product is to be kept high. Not only will the $^{11}CO_2$ be diluted with some amount of carrier depending on the method of production and transport but the strongly basic substrate solution will actively react with any contaminant source of $^{12}CO_2$ in the system. Grignard machines for this purpose should be set up with a minimum number of joints and transfer lines. Solvents should be degassed and reagents kept free of exposure to air or other sources of $^{12}CO_2$. Inert gas for transfer or as a blanket for the reaction mixture should be dry and scrubbed cryogenically and chemically to remove all trace of $^{12}CO_2$. Yields are frequently very high and a carboxylic acid can be prepared in under 40 minutes from EOB. Synthesis time can be materially shortened by using an on line flow system and trapping the $^{11}CO_2$ as it is being produced. Hundreds of millicuries of carboxyl labeled acids can be produced in this way.

Carbon-11 labeled hydrogen cyanide is of considerable value as a labeled precursor for two reasons. Firstly, it is available at end of cyclotron bombardment with no operator intervention (89). Secondly, it is readily used in displacement and addition reactions which proceed rapidly to produce ^{11}C-labeled nitriles or cyanohydrins. These are valuable intermediates in the synthesis of a wide variety of ^{11}C-labeled compounds which are of use in radiotracer research. These reactions are shown in generalized form below.



The use of H^{11}CN in ^{11}C-dopamine synthesis involves the preparation of the cyanohydrin which is prepared from the bisulfite addition product of 3,4-dihydroxybenzaldehyde is readily reduced to 1-^{11}C-dopamine hydrochloride using Pd/C and H_2 in acidic solution (251). Alternatively the cyanohydrin can be reduced with BH_3 and then purified to yield 1-^{11}C-norepinephrine hydrochloride (253). Alkyl nitriles are readily prepared by $^{11}CN^-$ displacement on an alkyl halide in DMSO or DMF (for examples see Table 3, [cyano-^{11}C]nitriles). These can be rapidly reduced directly to the amine (with $LiAlH_4$ or other suitable reducing agent). Sugars and deoxysugars (Table 3) labeled at C-1 also readily accessible by extension of chain length with $^{11}CN^-$ displacement on carbon attached to a suitable leaving group, for example triflate, mesylate or iodide. Judicious choice of leaving group can be critical. For example, a blocked arabinitol triflate is converted to the nitrile only after several days at 25° in DMF as solvent whereas conversion of the same arabinitol triflate to the nitrile takes place in a few minutes at 25° in DMF (277) (see Substrate, Structure, Reducing Agents, Protective Groups and Solvents).

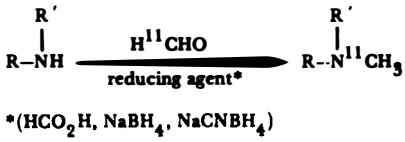
The preparation of a number of amino acids labeled in the carboxyl group can be accomplished by using a modification of the Bucherer-Strecker synthesis (see 175 and examples in Table 3). The appropriate aldehyde or ketone is mixed with $(NH_4)_2CO_3$, NH_4Cl, and aqueous Na^{11}CN and heated to



between 210 and 240° in a sealed metal reaction vessel for 5-10 minutes. The vessel is opened, NaOH solution added, and resealed and heated for another 10 minutes to accomplish hydrolysis of the intermediate hydantoin. The resulting

^{11}C-labeled D,L-amino acid mixture can be resolved to give the natural L-amino acid using enzymatic techniques (176), HPLC with chiral column materials (195) or selective binding to albumin (198).

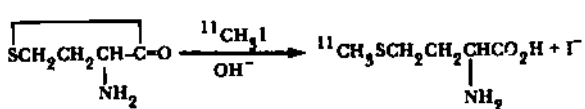
Introduction of a methyl group in such diverse compounds as proteins, antidepressants and naturally occurring polyamines e.g. putrescine and spermine has been accomplished by reductive formylation. Formic acid



(Eschweiler-Clarke reaction), sodium borohydride, sodium cyanoborohydride or other suitable reducing agents can be used. Both albumin and fibrinogen have been conveniently labeled by combining a buffered solution of the protein with a basic solution containing the H^{11}CHO, equilibrating for a few minutes and then adding a basic and buffered solution of the sodium borohydride (238). The methylated protein (i.e. RNH^{11}CH$_3$) is then isolated and purified. Methylation of desmethylimipramine is accomplished by first forming the imine in acid solution containing H^{11}CHO folowed by reduction of the imine with NaCNBH$_3$. In this way chlorpromazine, imipramine and nicotine are readily labeled (see Table 3).

Methylation with ^{11}C-methyl iodide is also conveniently carried out. There is frequently a choice to be made between reductive formylation and displacement on methyl iodide. Compare, for example, the preparation of [N-methyl-^{11}C]morphine with CH_3I (226) and H^{11}CHO (227)

Carbon-11 labeled L-methionine 17 has been prepared by allowing L-homocystein thiolactone 18 to react with $^{11}CH_3I$ in basic acetone containing solution. The yields are high and the purified product is



18 17

obtained in 30 min from EOB (185). Other routes to ^{11}C-methionine appear in Table 3 as well as numerous other examples of methylation with $^{11}CH_3I$.

A potentially useful reaction for preparing carbon-11 labeled compounds is carbonylation by insertion of ^{11}CO into a carbon-boron bond. For example [1-^{11}C] octanal 19 was prepared by allowing ^{11}CO to react with n-heptyl-9-borabicyclo-[3.3.1]nonane and $(CH_3O)_3LiAlH$. The adduct was then oxidatively hydrolyzed (291). Reactions of this type (for versatility see

$$\text{B-heptyl-9-BBN} + (CH_3O)_3HLiAl + {}^{11}CO \xrightarrow[H_2O_2(30\%)]{\text{hydrolysis (pH=7)}} C_7H_{15}{}^{11}CHO \quad \mathbf{19}$$

416-418) can make use of the readily available precursor ^{11}CO and simplify access to carbon-11 labeled compounds such as aldehydes.

While the above examples serve to provide a measure of the synthetic versatility of the most easily available precursors it is clear that many other types of compounds are accessible from these precursors as from some of the less readily available one two and three carbon precursors listed above and in Table 2.

Conclusion

Many classes of compounds can be prepared from carbon-11 labeled precursors. Some of these syntheses are simple and straightforward such as carbonation of a Grignard and some very much more complex such as amino acid syntheses, neuroleptic syntheses and sugar syntheses. It is important to reiterate one of the peculiarities of synthesis with carbon-11 and that is the problem of carbon-12 carrier. Wherever possible a direct measure of specific activity of the precursor or compound should be made. For example the Nash assay or derivatization procedure can be used for formaldehyde (419). Extremely sensitive methods (to within a factor of 10^3 of carrier free) exist for the assay of cyanide (420-421). Compound assay in some special cases is also possible via radio-receptor procedures (422). Unfortunately, no reliable and simple method has yet been devised for assay of dilution by factors of 10 or 100. The assay of CO_2 and compounds derived therefrom is particularly problematical. The term CF, NCA, and CA (see Specific Activity and Stoichiometry) should be used in the strictest sense in order to remove the confusion about carrier state introduced by virtually all groups working in the field up to about 1979 (303,389).

The decay of carbon-11 leaves behind a boron-11 atom which is multiply charged and which leaves the site originally binding the carbon-11 precursor. The molecular "debris" left behind by this decay event can be in the form of a totally fragmented molecule or a highly excited molecular species which can then form a new molecule which may or may not influence its surroundings in a deleterious way. While the chemical and biological consequences of β-decay have been reviewed in detail (423). biological consequences of B^+ decay have

just begun to receive attention (424). As the use of B^+ emitter proliferates in medical procedures, this area must receive attention. This is particularly apparent when one considers the fact that sites connected with compounds labeled with positron emitters can include receptors, nuclear material, and other physiologically active areas, to which damage could lead to irreversible changes.

Much can be learned and applied from the many techniques developed in connection with tritium and carbon-14 syntheses (see Appendix 2). This is especially true with regard to vacuum line and micromanipulation methods. Nevertheless the use of positron emitters present their own unique and new problems and much remains to be learned.

Labeling with elements which are positron emitters, especially carbon-11 and nitrogen-13, because of their multiple valency, present challenges to the synthetic organic chemist which require innovation and sophistication and which should provide a stimulus to those who are entering this rediscovered and burgeoning field.

FLUORINE-18

Fluorine-18 as a Label for Radiotracers

In a number of ways, fluorine-18 is the most attractive nuclide for positron emission tomography. The average range of fluorine-18's relatively low energy positron is 2.4 mm before annihilation occurs (Table I). This short range before annihilation will become increasingly important as the resolution of positron emission tomographs improves. In addition the 110 minute half-life allows a comparatively long synthesis and the transportation of the radiotracer over moderate distances, as well as, the study of relatively slow biological processes.

In addition to the decay characteristics of fluorine-18, the physical properties of the fluorine atom itself and the characteristics of the C-F bond also contributes to its popularity as a label for radiotracers. For example, fluorine has a similar van der Waal's radius to hydrogen (425) and its substitution for hydrogen causes little steric perturbation compared to substitution with other halogens (426). Its electronegativity, however, is far greater than that of the other halogens and the carbon-fluorine bond energy is very high (425). Thus the chemical and biochemical properties of an organofluorine compound could be drastically altered with respect to the unsubstituted analog.

Although fluorine, in chemical combination with carbon, occurs only rarely in nature, the development of synthetic approaches for its substitution for hydrogen or other functional groups in organic molecules has often resulted in molecules with intriguing biological properties. Frequently, the alteration of chemical properties brought about by fluorine substitution provides information about biochemical processes and the study of the behavior of the carbon-fluorine bond in living systems as an active area of research 426-430).

General Comments on the Preparation of ^{18}F-Labeled Radiotracers

The synthesis of ^{18}F-labeled organic compounds (165,431-433) and ^{18}F-labeled inorganic compounds (167) has been reviewed and a listing of ^{18}F-labeled precursors and radiotracers and is given in Tables 2 and 4 respectively. The extension of the synthetic methodology of organofluorine chemistry to the synthesis of ^{18}F-labeled tracers is frequently hampered by the many anomalies and experimental difficulties associated with C-F bond formation. Usually, the development of a practical route to an ^{18}F-labeled radiotracer involves the initial development of a synthesis to the unlabeled molecule which can then be applied the synthesis of the radiotracer. Along

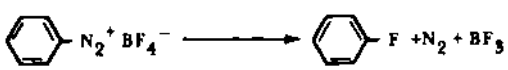
these lines, the use of fluorine-18 as a tracer can add a new dimension for exploring the kinetics and mechanism of C-F bond formation in organic synthesis (327).

Frequently fluorination reagents are highly reactive molecules such as F_2, CF_3OF, ClO_3F, XeF_2 and HF and their safe effective use requires special handling. When high specific activity radiotracers are required, the normally encountered problems of chemical reactivity are amplified due to high ratio's of substrate to ^{18}F-labeled precursors and contaminants which can deactivate the fluorination reagent. In the following sections, references to general articles containing information on experimental techniques will be given.

This monograph will deal with three categories of fluorination reaction, namely, aromatic fluorination, substitutions by fluoride on aliphatic compounds and electrophilic fluorination. Although examples involving fluorine-18 will be emphasized, general reactions which are of preparative value in organofluorine chemistry, especially recent work will also be mentioned. These reactions which are tabulated in the following sections may or may not be useful to labeling with ^{18}F and are intended as a guide as a stimulus for exploring new ways of introducing fluorine-18 into organic molecules. Factors which need to be explored before applying any new fluorination procedure to radiotracer synthesis with F-18 are the time scale of the reaction, whether the appropriate precursor forms of ^{18}F could be prepared and whether the reaction stoichiometry would accommodate the use of high specific activity ^{18}F-labeled precursors.

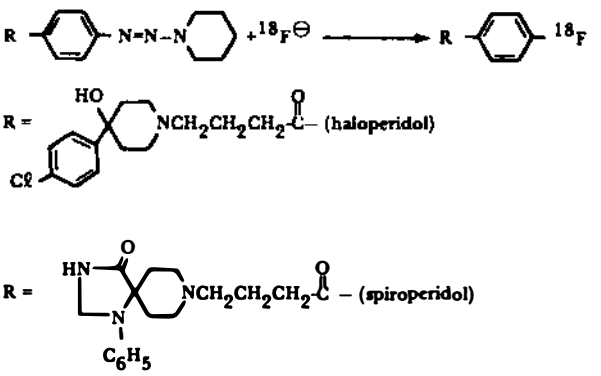
^{18}F-Labeled Aryl Fluorides

The most generally useful method for the introduction of fluorine into an aromatic ring is the Balz-Schiemann reaction first described in the late nineteenth century (433a). This reaction was also one of the first methods of



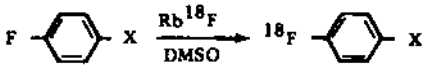
synthesis of ^{18}F-labeled aryl fluorides. The source of ^{18}F in these syntheses was either ^{18}F-labeled fluoride from the water target (309), $HB^{18}F_4$ (310), $LiB^{18}F_4$ (306), or an unidentified ^{18}F-species from the recirculating neon target (136,308). Since the specific activity as well as the total activity which could be produced by this route was low due to isotope dilution, other methods for ^{18}F-labeling of aromatics were sought. This resulted in the successful application of another reaction which was first described in the late 19th century (434), namely the decomposition of aryl triazenes by $H^{18}F$

(324,435-437). Although this resulted in the production of carrier free or near carrier-free ^{18}F labeled radiotracers such as haloperidol and spiroperidol the radiochemical yields of these reaction are very low. The scope and conditions for triazene reactions have been studied (321,323,323a,437) from the standpoint of solvents and substrate complexity.



Thus far this reaction has used ^{18}F in the form of anhydrous $Cs^{18}F$ which is obtained via anhydrous $H^{18}F$ from the H_2/Ne target. While the low yield and lack of reproducibility of the triazene decomposition as well as target delivery of $H^{18}F$ are presently drawbacks to the use of this method, it's development represents a improvement over the Schiemann reaction both in terms of the stability of the triazene and increasing specific activity. The need for an efficient synthesis for aryl fluorides should provide the stimulus for identifying the factors which are important to high radiochemical yields and reproducible delivery of $H^{18}F$ from the target.

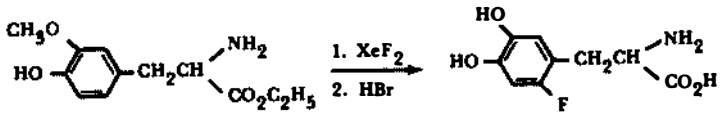
The use of nucleophilic aromatic substitution as a route to aryl fluorides was explored with a view to applying this reaction to ^{18}F-labeling. In one such study of the displacement by fluoride of a sulfonate leaving group as a route to fluoroaromatics, it was found that fluoride attack occurred at sulfur rather than at carbon resulting in the ultimate production of diaryl ethers and demonstrating that this particular leaving group was not useful in effecting the desired transformation (438). In contrast, nucleophilic aromatic substitution of activated fluoride by [^{18}F]fluoride proved to be quite a facile reaction and in effect an ^{18}F for ^{19}F exchange reaction took place. Although the use of an isotope exchange reaction precludes the synthesis of NCA tracers it has been possible to achieve reasonably high specific activity [^{18}F]-aryl fluorides using this method (328). The possibilities for applying this facile reaction to radiotracer synthesis are



X = CN, NO_2

many when one considers the potential functionality which can be derived from the cyano and nitro groups.

In another recent development L-3-methoxy-4-hydroxyphenylalanine 20 was fluorinated directly with XeF_2 to give L-6-fluorodopa 21 after hydrolysis (316). This synthesis represents a significant improvement over the Schiemann reaction which was previously used for the preparation of the 5-fluoro isomer



(L-isomer) **20** (L-isomer) **21**

and which yielded the D,L-mixture (308,312-314). When this reaction is carried out in the presence of ^{18}F-labeled tetrabutylammonium fluoride a low yield of ^{18}F-labeled L-6-fluorodopa is produced (315). More recently the synthesis of $[^{18}F]XeF_2$ from XeF_2 and $H^{18}F$ in 31% radiochemical yield has been reported thus extending the utility of this reagent in ^{18}F-labeling (143). The availability of other ^{18}F-labeled forms of electrophilic fluorine such as $[^{18}F]F_2$ (130) and $CH_3CO_2{}^{18}F$ (139) make this a promising approach for fluorinating electron rich aromatic rings in applications where carrier free radiotracers are not required.

Some other recent examples of aromatic fluorination with inactive fluorine have been described and although they are not of general use, they may be useful in the fluorination of certain molecules. For example, F_2 (327,439), AgF_2 (440), XeF_2 (441-442) and $CsSO_4F$ (443) have all been reported to be of limited utility in the monofluorination of certain aromatics and may be of use in certain applications where carrier fluorine can be tolerated. The electrophilic reagent CF_3OF has been used to fluorinate certain aromatic molecules (444) but again it would not be possible to synthesize carrier-free radiotracers using this reagent. Phenyl azide and phenylhydroxylamine have both been shown to react with HF to give p-fluoroaniline (445-446) and since these reactions use HF they may be of use in the synthesis of carrier free compounds. The aryl azide decomposition has been studied with a view to ^{18}F-labeling and it was found that oxygen or large alkyl groups ortho to the azide function interfered with the fluorination (437). Fluoroaromatics without nitrogen or oxygen substituents have been prepared by thallation followed by fluoride introduction but extension of this reaction to ^{18}F-labeling would require addition of carrier fluorine (447).

Since these examples from the recent chemical literature were not developed with a view of ^{18}F-labeling, their potential use in ^{18}F-labeling must be considered in the light of the many pitfalls and restraints which half-life, precursor availability, stoichiometry and specific activity requirements impose. As can be seen, the need for a general synthetic route to NCA [^{18}F]-aryl fluorides which gives a high radiochemical yield still remains one of the many challenges in this field.

Substitution by Fluoride (^{18}F-Labeled Aliphatic Compounds)

A detailed review has been published on the synthesis of monofluoro aliphatic compounds (448). It covers the substitution reactions of fluoride along with the addition and substitution reactions of HF and includes discussion of the scope and mechanistic aspects of these reactions. This along with textbooks on organic fluorine chemistry provides a reasonably up to date survey on the progress of organofluorine chemistry as well as practical details on the use of fluorination reagents such as HF, CF_3OF and ClO_3F (439,449). This chapter as well as a recent review article provide considerable information on preparing anhydrous fluoride salts (450). When HF is required for small scale exploratory work, it can be conveniently and safely generated by the thermal decomposition of $NaHF_2$ (451).

Although the formation of carbon-fluorine bonds by the nucleophilic displacement of an appropriate leaving group is formally a simple reaction, in practice, this is often not the case. A major problem is the lack of reactivity of fluoride in the presence of water due to its high solvation energy (439). Solutions of fluoride salts with large cations in aprotic solvents are a good source of fluoride which is unsolvated and therefore highly nucleophilic (448). Unfortunately, fluoride in this medium is also highly basic causing a competition between displacement and elimination

$$R\text{-}CH_2CH_2\text{-}X + F^- \longrightarrow RCH_2CH_2\text{-}F + RCH=CH_2$$

reactions. This is exemplified by the widespread use of fluoride ion as a base in many synthetic applications (450).

These problems of competing reactions and fluoride solvation are magnified in the labeling of organic molecules with fluorine-18 especially when high specific activity products are required and little or no carrier fluoride is used. At these levels, minute tracers of water can completely solvate the fluoride ion rendering it unreactive in displacement reactions.

A number of methods have been used to increase the reactivity of fluoride in nucleophilic displacement reactions. For example, the use of crown ethers,

bulky cations, large polarizable alkali metals and dipolar aprotic solvents have all met with some success (448). (See Table 4).

Several of these approaches have been applied to labeling with ^{18}F. In syntheses using $^{18}F^-$ from the water target, the reactivity of the ^{18}F-fluoride (after careful drying) is increased by using bulky cations or by using crown ethers. For example, ^{18}F-6-deoxy-6-fluoro-D-galactopyranose has been prepared using tetraethylammonium [^{18}F]fluoride in acetonitrile (342). The use of $K^{18}F$ and 18-crown-6 has been applied to the synthesis of ^{18}F-21-fluoroprogesterone, and 21-fluoropregnenolone-3-acetate (335-337) as well as to the ^{18}F for F exchange on benzotrifluoride (358). ^{18}F-labeled α-D-glucosyl fluoride has been prepared by the reaction of tetra-O-acetyl-α-D-glucosyl bromide with $Ag^{18}F$ in acetonitrile (343).

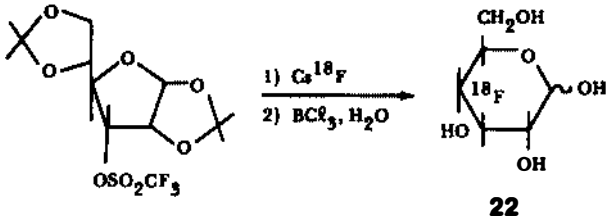
The conversion of aqueous $H^{18}F$ from the water target to a useful nucleophilic form of ^{18}F for labeling continues to be a challenge. The problems center around the difficulty of dissolving the ^{18}F in an appropriate reaction medium, after the water has been removed. A model synthesis, the nucleophilic displacement of the mesylate of 21-hydroxypregn-4-ene-20-dione by ^{18}F-fluoride (NCA) was chosen to explore this problem. It was found that ^{18}F-trapped in potassium hydroxide and evaporated to dryness in a teflon vessel could be solubilized in a chloroform/crown ether system. Using these conditions it was possible to obtain 21-[^{18}F]fluoroprogesterone (NCA) (335-336). The ^{18}F for F exchange on benzotrifluoride has been investigated as a function of carrier concentration (358). Again the major problem was removal of the ^{18}F from the glass vessel walls. Another approach to the solubilization of anhydrous carrier-free ^{18}F from the water target is to convert it to $H^{18}F$ (anhydrous) which is distilled into an appropriate reaction medium (135).

The problems of ^{18}F-labeling at low carrier concentrations are well illustrated by a study of the F for Br exchange labeling of long chain fatty acids with ^{18}F in molten acetamide (332). It was found that at carrier

$$K^{18}F + BrCH_2(CH_2)_{15}CH_2CO_2CH_3 \xrightarrow[150^\circ]{CH_3CONH_2} {}^{18}F\text{-}CH_2(CH_2)_{15}CH_2CO_2CH_3$$

concentrations less than 1 mg of KF, the yield dropped drastically indicating that this reaction would not be applicable to the carrier free state.

No carrier added displacements have been carried out using anhydrous $H^{18}F$ from the Ne/H_2 target. The $H^{18}F$ is trapped on CsOH or Cs_2CO_3 which is then added to an appropriate reaction mixture. Using this method, ^{18}F-labeled



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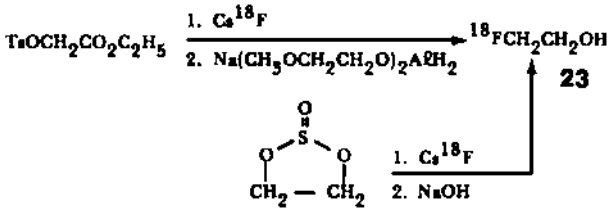

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3-deoxy-3-fluoro-D-glucose 22 (124) and 2-fluoroethanol 23 (363) as well as 7-fluoropalmitic (334) acid have been synthesized at NCA levels.

The combination of leaving group, fluoride ion source, solvent and reaction conditions to effect a given transformation is not presently predictable often necessitating a trial and error approach. In one study, using the synthesis of ^{18}F-3-deoxy-3-fluoro-D-glucose as a model, the effects of solvent, temperature, ions, leaving groups and water on the displacement reaction were investigated (352). This study was done with a view to obtaining useful information for making rational choices of reaction parameters and was done with fluoride carrier added.

Some examples of fluoride displacement reactions were selected from the recent literature (Table 7) to update the excellent treatment of this subject which has already appeared (439,448-449,452-453). These references are to unlabeled fluoride and serve as a guide to combinations of fluoride salts and solvents used in various applications with a caution to the difficulties encountered with ^{18}F at low carrier concentrations. This is an especially important consideration in reactions where HF is used as a solvent or in large excess.

Table 7. Some examples of substitution by fluoride

Substrate	Fluorination Reagent	Product	Reference
RX[a]	KF/CH_3CN/polyethylene glycol[b]	RF	454
RX	F^-/anion exchange resin	RF	455
RNH_2	2,4,6-triphenylpyrilium fluoride	RF	456
ROH	R_2NSF_3	RF	457
ROH	SF_4	RF	429
R-SH	F_2, CF_3OF, Cl_2 or N-chlorosuccinimide in HF solvent[d]	RF	429,458
$R-OSO_2CH_3$	$Bu_4N^-F^+$/THF	RF	459
epoxides ()	KHF_2/ethylene glycol	α-fluorohydrins	460-461
1-azirenes ()	pyridinium poly (hydrogen fluoride)[c]	β,β-difluoroamines	462-463
aziridines ()	"	fluoroamines	464
various substrates[e]	"	fluorocompounds	462

a. RX = ArCOCl, RCOCl, $ArSO_2Cl$, $ArCH_2Br$, cyclo-$C_6H_{11}Br$, 2,4-$(NO_2)_2C_6H_3Cl$.

b. Phase transfer catalyst.

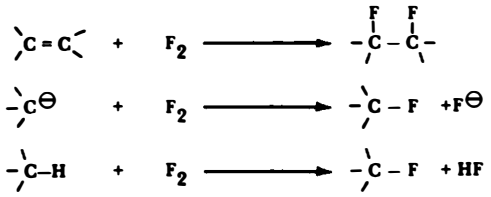
c. Pyridinium poly (hydrogen fluoride) is a convenient source of HF which effects a large number of addition and substitution reactions. Isotope dilution would limit its use in radiotracer synthesis.

d. HF solvent is the source of fluorine, and the dilution of isotope would lead to exceedingly low specific activity products.

e. Olefins, amino acids, aminoarenes, carbamates, geminal dihalides,

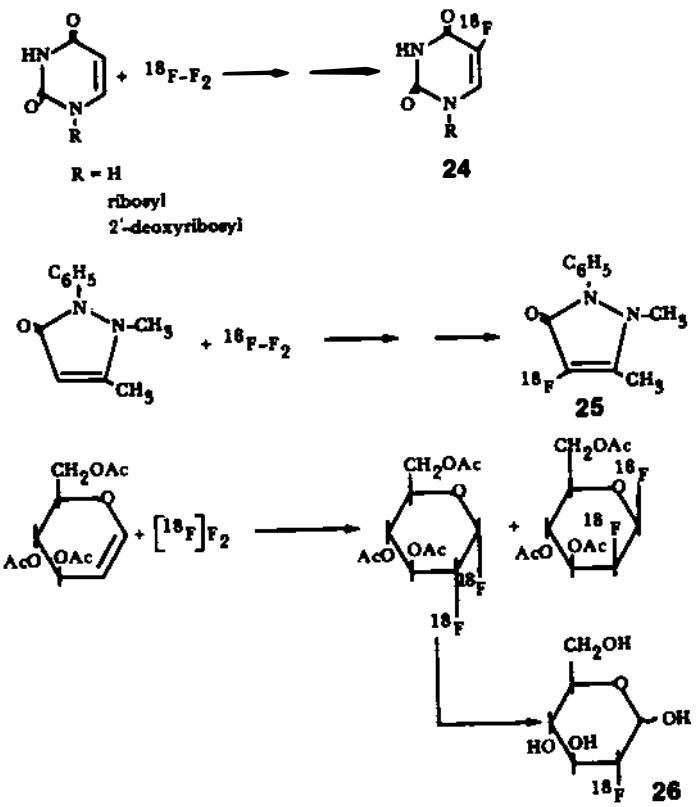
Electrophilic Fluorination as a Route to ^{18}F-Labeled Compounds

The formation of carbon fluoride bonds by electrophilic fluorine (formally F^+) usually involves the reaction of a molecule which is polarized so that fluorine is electrophilic (for example CF_3OF, F_2, ClO_3F, XeF_2 or CH_3CO_2F or possibly NOF) and an electron rich substrate such as an unsaturated molecule, a carbanion and in some cases a carbon-hydrogen single bond. Using F_2 as the source of electrophilic fluorine, these reactions can be formally represented as follows:



Although in organofluorine chemistry, CF_3OF is used more frequently as a source of electrophilic fluorine, the use of F_2 frequently gives very similar results. Traditionally, the use of F_2 in organic synthesis has been avoided due to its high reactivity and reputation for extensively degrading organic molecules (439). Recently, however, techniques for moderating its reactivity have been worked out allowing its use in organic synthesis to be explored. It has been found that esters, nitrates, 3^o alcohols, epoxides, ketones and chlorine are stable to F_2 while bromine, olefins and esters are reactive (465). The moderation of the reactivity of F_2 is achieved by diluting it with an inert gas and carrying out reactions at low temperatures (465) and references therein). Furthermore, it is not necessary to handle pure fluorine since mixtures of F_2 in an inert gas and gas regulators and other equipment required for handling F_2 are commercially available (Matheson Company, Inc. Rutherford, N. J.). Unlike HF, the reactions of elemental fluorine can be carried out in glass vessels and the diluted gas is conveniently transported in stainless steel or monel manifolds using valves of the same materials. Since elemental fluorine is a highly toxic and reactive gas, the reader is directed to sources of information on its safe handling (449,466-467).

A number of ^{18}F-labeled elecrophilic fluorination reagents which have been prepared including $NO^{18}F$, $^{18}F\text{-}CF_3OF$, $[^{18}F]XeF_2$, $[^{18}F]F_2$ and $CH_3CO_2{}^{18}F$ (see Table 2). Of these, only $^{18}F\text{-}F_2$ has been used extensively in the synthesis of radiotracers. The targetry for routinely delivering large quantities of $[^{18}F]F_2$ has been described in detail along with some of the factors influencing its recovery from the target. Although it is not possible to produce $^{18}F\text{-}F_2$ carrier free, it is possible to obtain high recoveries from the (Ne/F_2) target with as little as 20 μmol of F_2 carrier. A number of ^{18}F-labeled radiotracers have been synthesized using $[^{18}F]F_2$ including ^{18}F-labeled 5-fluorouracil 24 (353-354),

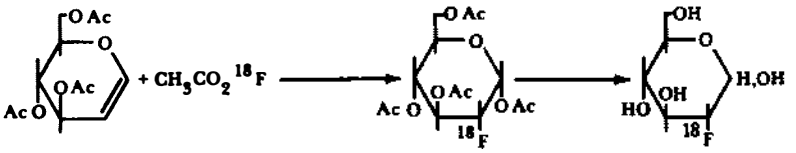


5-fluorouridine (357), 5-fluoro-2'-deoxyuridine (355), 4-fluoroantipyrine 25 (366), and 2-deoxy-2-fluoro-D-glucose 26 (344-346) and fluorobenzene (326). Interestingly, most of these reactions have also been reported using CF_3OF supporting the similarity in the reactions of CF_3OF and F_2.

Acetyl hypofluorite, which was recently synthesized from the reaction of sodium acetate and F_2 (468), has been labeled with fluorine-18 by simply purging $[^{18}F]F_2$ from the Ne/F_2 target through a solution of ammonium acetate in acetic acid (139). The resulting solution of $CH_3CO_2{}^{18}F$ has been used in

$$[^{18}F]F_2 + CH_3CO_2NH_4 \xrightarrow{CH_3CO_2H} CH_3CO_2{}^{18}F + NH_4{}^{18}F$$

the synthesis of 2-deoxy-2-$[^{18}F]$-fluoro-D-glucose (349). This development



represents a significant improvement over the synthesis described above using F_2 because only one adduct is formed, the experimental setup is simplified and the yield is increased (see Experimental Design-Examples).

The synthesis of monofluoroaliphatic compounds has been reviewed and many examples tabulated, including the reactions of CF_3OF, ClO_3F and NOF and experimental procedures for handling these highly reactive gases (448). In addition, there are some interesting new developments in the use of these reagents as well as the *in situ* synthesis of novel electrophilic reagents and their use in organic synthesis. Some examples from the recent literature have been tabulated to illustrate the diverse structures which can be obtained using electrophilic fluorination reagents (see Table 8). The extension of some of these reactions to ^{18}F-labeling may be possible.

Table 8. Some examples of electrophilic fluorination reactions

Substrate	Fluorination Reagent	Product	Reference
stilbenes and diphenylacetylene	CF_3COOF[a]	α-fluorohydrins	469
enol-acetates	CF_3CF_2OF[b]	α-fluoroketones	470-471
enol-acetates	XeF_2/HF	α-fluoro-ketones	472
α-diazoketones	CF_3OF or F_2	α,α-difluoroketones	473-474
silyl enol ethers	CF_3OF	α-fluoro carbonyl compounds	475
R_3CH	CF_3OF or F_2	R_3C-F	476-479
olefins and aromatics	CF_3OF	mono and difluoro compounds	444
olefins, acetylenes and aromatics	XeF_2	mono and difluoro compounds	442,480
RH	CF_3OF/h [c]	R-F	429
R-X[d]	F_2	R-F	481
olefins and aromatics	CH_3CO_2F	fluoroacetoxy compounds and aryl fluorides	468,482
aromatic compounds	F_2	aryl fluorides	483

a. Generated *in situ* from $CF_3CO_2Na + F_2$ with traces of H_2O or HF.

b. Generated *in situ* from $CF_3CO_2Na + F_2$ (anhydrous conditions).

c. Reaction mechanism may involve radical formation.

d. Bromo and iodoadamantanes.

Statistical Factors and Radiochemical Yield

The theoretical upper limit of the radiochemical yield of a reaction is variable depending on stoichiometry. For example in the case of a fluoride displacement reaction the theoretical maximum radiochemical yield is 100%. However, in the synthesis of

$$R - X + {}^{18}F^- \longrightarrow R\text{-}{}^{18}F + X^-$$

^{18}F-acetyl hypofluorite ($CH_3CO_2{}^{18}F$) from $[^{18}F]F_2$ (139) the maximum radiochemical yield is 50% because only one fluorine atom in the fluorine molecule is radioactive and there is an equal probability that the fluorine

$$2\,{}^{18}F\text{-}F + 2CH_3CO_2NH_4 \longrightarrow CH_3CO_2F + CH_3CO_2{}^{18}F + NH_4F + NH_4{}^{18}F$$

atom which reacts with acetate ion is unlabeled. Therefore for each 2 molecules of ^{18}F-F, only one molecule of labeled acetyl hypofluorite is produced along with one molecule of $NH_4{}^{18}F$, giving a radiochemical yield of 50%. The upper limit of the radiochemical yield is even less in the case of the pyrolysis of an ^{18}F-labeled diazonium fluoroborate salt to produce an aryl fluoride. Here only one fluorine atom in four is labeled and therefore the

$$4\,ArN_2^+\,F\text{—}\underset{\displaystyle F}{\overset{\displaystyle F}{\underset{|}{\overset{|}{B}}}}\text{—}{}^{18}F \longrightarrow Ar{}^{18}F + 3\,ArF + BF_3 + 3BF_3{}^{18}F + 4N_2$$

maximum radiochemical yield obtainable from a specifically labeled diazonium fluoroborate salt is 25%.

Special Problems with ^{18}F-Precursor Production and Radiotracer Development

The high reactivity of fluorine and its compounds presents a particular challenge to the exploration of the nuclear reactions and target chemistry which will provide useful ^{18}F-labeled precursors reproducibly and in high yield. The broad spectrum of accelerators (including relatively low energy medical cyclotrons) which are currently in use for radiotracer research has required that the production of useful precursors as well as radiotracer be approached by different routes so that their availability for biomedical studies is maximized. For example, while the targetry for the routine production of large quantities of $[^{18}F]F_2$ on cyclotrons having high energy deuterons (> 15 mev) is well worked out, targets designed for the production of large quantities of $[^{18}F]F_2$ on medical cyclotrons having ~ 8 mev deuterons and high currents has not yet been demonstrated. An alternative reaction for

producing ^{18}F in large yields on medical cyclotrons is the $^{18}O(p,n)^{18}F$ reaction (484). Along this line some of the challenging problems in the production of ^{18}F-labeled tracers are summarized below:

(1) Developing targets which can be used with 8 mev deuterons at high currents so that useful quantities of $[^{18}F]F_2$ and $H^{18}F$ can be produced on medical cyclotrons via the $^{20}Ne(d,\alpha)^{18}F$ reaction.

(2) Determining the target chemistry for the $^{18}O(p,n)^{18}F$ reaction so that high yields of synthetically useful ^{18}F-labeled precursors such as $H^{18}F$ (anhydrous) and $[^{18}F]F_2$ can be produced on medical cyclotrons.

(3) Obtaining $^{18}F^-$ in nucleophilic form at high specific activity.

(4) Developing and optimizing high yield synthetic routes to high specific activity ^{18}F labeled tracers which are of interest in the biomedical studies so that availability is maximized.

The importance of all of these problems is well illustrated when one considers that presently 2-deoxy-2[^{18}F] fluoro-D-glucose (^{18}FDG), a tracer which is in high demand from the biomedical community can only be produced at a few centers which have cyclotrons with the sufficiently high deuteron energies for producing the requisite amount of precursor $[^{18}F]F_2$ for human studies. The development of the targetry which could compensate the low deuteron energies of medical cyclotrons by taking advantage of the high currents available could impact significantly on the availability of ^{18}FDG. Similarly, development of the appropriate target chemistry for the $^{18}O(p,n)^{18}F$ reaction may represent another solution to this problem. Of equal importance to the exploration new methods of ^{18}F-precursor production should be the continued pursuit of alternate higher yield synthetic routes to such tracers as 2-deoxy-2[^{18}F]fluoro-D-glucose, thereby more efficiently using the isotope which is produced.

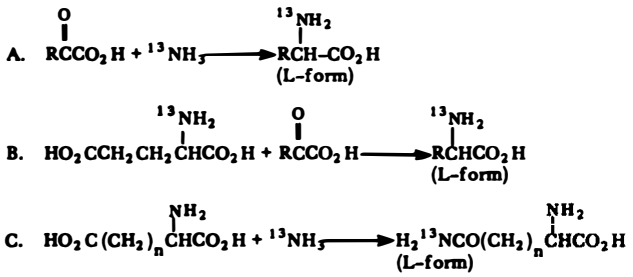
NITROGEN-13

The ten minute half-life of nitrogen-13 presents an unusual challenge for the development of rapid methods for its incorporation into organic molecules. Because of its short half-life and potentially high specific activity, nitrogen-13, unlike nitrogen-15 can be used to study the metabolic fate of nitrogen in various systems at true tracer levels and with high sensitivity (397). It is therefore unique in its ability to act as a tracer for stable nitrogen, a factor which compensates for the inconvenience of the 10 minute half-life and the requirement for on-site accelerator and related facilities and expertise. For example, the metabolic fate as well as the transport of ^{13}N-ammonia in the rat brain has been determined at sub-physiological ammonia doses (370). In contrast, the study of ammonia metabolism using ^{15}N-ammonia required that this tracer be used in toxic doses to compensate for the low sensitivity of the detection technique (485). In another example, with $^{13}NO_3^-$, it has been possible to measure denitrification rates in soils from flooded rice fields at true tracer levels (145) and ^{13}N labeled nitrogen, ammonia and nitrate have been used to probe nitrogen fixation and metabolism in bacteria (393-396). The unique applications of ^{13}N as a tracer for the metabolic fate of various nitrogen containing functional groups in organic and inorganic molecules has been recently reviewed (397).

A listing of ^{13}N-labeled precursors with selected references appears in Table 2. ^{13}N-Ammonia is the most widely used ^{13}N-labeled precursor for radiotracer synthesis although $^{13}NO_3^-$, $^{13}NO_2^-$ and ^{13}NO have also been used. The most commonly used nuclear reactions are the deuteron bombardment of methane ($^{12}C(d,n)^{13}N$) or the proton bombardment of water ($^{16}O(p,\alpha)^{13}N$). The deuteron bombardment of methane yields $^{13}NH_3$ directly but also produces impurities which must be removed by distillation (150-152). The water target yields ^{13}N-labled nitrates and nitrites which can be reduced to ^{13}N-ammonia and is presently the method of choice (146,149,153-157). The production of ^{13}N-precursors using various nuclear reactions and targetry as well as the chemical form of N-13 produced in various nuclear reactions and chemical environments have been discussed (168-169,486-487).

The enzyme systems which are responsible for ammonia metabolism in living systems have been exploited for the rapid, stereospecific synthesis of ^{13}N-labeled amino acids (392,488). The general reactions (A, B and C) which have been used are summarized below: In the general reaction A, glutamic acid dehydrogenase (GAD), catalyzes the formation of ^{13}N-L-amino acids from $^{13}NH_3$ and an α-keto acid. Although α-ketoglutaric acid is the natural substrate for

GAD, certain other α-ketoacids also serve as substrates for this enzyme and have been used to prepare other ^{13}N-L-amino acids (see Table 5). In example B, ^{13}N-L-glutamic acid is synthesized and the ^{13}N is transferred to an α-keto acid in a reaction catalyzed by glutamate-pyruvate or glutamate-oxalacetate



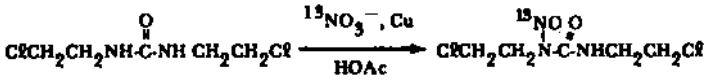
transferase. In reaction C, an ^{13}N-amide is synthesized via the glutamine or aspargine synthetase catalyzed reaction of $^{13}NH_3$ and the amino acid. Examples of ^{13}N-L-amino acids synthesized via these various routes are summarized in Table 5.

The number of enzymatically synthesized ^{13}N-L-amino acids has been largely limited to those reactions which can be carried out with commercially available enzymes. Recently the reactivity of a variety of substrates (α-ketoacids) with GAD has been studied with a view to expanding the number of ^{13}N-L-amino acids available for research (373). The production of pharmaceutical quality ^{13}N-labeled compounds which are free from pyrogenic macromolecular contamination which is present in enzyme catalyzed reactions can be overcome in some cases by the synthetic attachment of the enzyme to a solid support. The purification of the ^{13}N-amino acids is generally accomplished by ion exchange chromatography.

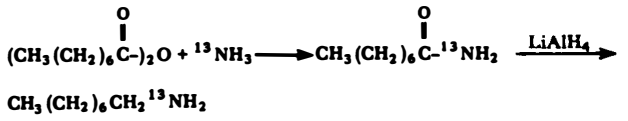
In addition to biosynthetic approaches, classical organic synthetic approaches to ^{13}N-labeled radiotracers have been developed (see Table 6). For example ^{13}N-asparagine has been synthesized enzymatically from aspartic acid (380-381), $^{13}NH_3$ and aspargine synthetase which is not commercially available. Since this enzymatic synthesis gives a low yield and the enzyme cannot be immobilized due to its instability, a rapid and efficient chemical synthesis was developed. It involves the reaction of α-N-t-Boc-t-Bu-aspartate (activated with N-hydroxysuccinimide) with $^{13}NH_3$ and yields ^{13}N-L-asparagine in 30-40% yield (384).

The synthesis of ^{13}N-N-nitrosoureas using $^{13}NO_3^-$ obtained directly from the water target and reduced <u>in situ</u> to $^{13}NO_2^-$ has been described (159). This

is an improvement of a previously described procedure which used $^{13}NH_3$



as an isotopic precursor and required its oxidation to ^{13}NO and $^{13}NO_2$ (158). ^{13}N-labeled streptozotocin and nitrosocarbaryl have been synthesized using similar reactions (382). A synthesis of ^{13}N-labeled octylamine (385) from



$^{13}NH_3$ and octanoic anhydride followed by reduction has been developed as has the preparation of ^{13}N-urea (383). In addition the recent report of the synthesis of nitrogen-15-labeled primary amines via organoboranes has potential application to ^{13}N-amine synthesis (489).

The use of an ^{13}N-labeled radiotracer requires that the biological process under investigation is sufficiently rapid to be traced with this short-lived nuclide and necessitates the development of rapid assay systems for the ^{13}N-labeled tracer and its labeled metabolites in order to determine the factors responsible for its biodistribution. In spite of the short half-life of ^{13}N, rapid analytical methods have been developed for its study (397). For example, in the study of the metabolic fate of ammonia in rat brain it has been found that 5 seconds after injection of ^{13}N-ammonia, ~ 60% of the label recovered in the brain had already been incorporated into glutamine emphasizing the importance of glutamine synthetase as a metabolic trap for blood borne ammonia (370).

EXPERIMENTAL DESIGN AND RELATED TECHNOLOGY

The application of positron emitting radiotracers to the study of metabolism and function using PETT requires that the chemistry laboratory adjacent to the cyclotron be designed to accommodate and manipulate Curie levels of short-lived nuclides. This section will deal with some of the important aspects of laboratory design including radioactivity monitoring and routine production of radiotracers. Experimental details for the synthesis of three radiotracers (^{11}C-imipramine, ^{11}C-palmitic acid and ^{18}F-2-deoxy-2-fluoro-D-glucose) which are currently in routine use at different institutions will also be used to illustrate these points.

Radioactivity Assay

The detection and measurement of radioactivity both in the microcurie range and in the hundreds of millicuries - Curie range is required in the development of rapid synthesis for short-lived radiotracers and also in their routine production for clinical studies. In each case an appreciation for the limitations of the various methods for assaying radioactivity is important as is an accurate calibration of the detector or counter. The reader is referred to an excellent text on radiation detection and measurement for a detailed treatment of the subject (490) and to an article on the criteria which should be applied in choosing the appropriate assay method (491). In this section, a limited amount of practical information on the use and calibration of ion chambers and well counters and monitoring radioactivity during radiotracer synthesis, will be presented.

Ion Chamber and Well Counter Calibration: Where activity levels in excess of a total of roughly 5 μCi must be determined in one entity, the ion chamber is the only practical method to be used. This is the detection method employed in all so-called dose calibrators. The current measured by the ion chamber is linearly dependent on the amount of ionization taking place in the filling gas of the chamber, and this in turn is directly dependent on the amount and energy of each component of the decay scheme of the nuclide being used. Therefore, in order to obtain accurate values with these instruments it is necessary to know the decay scheme of the nuclide accurately and to be able to relate these parameters correctly to the inherent properties of the measuring device and its electronics. This is usually done by the manufacturer, but there have been many documented cases where this has not been done in a satisfactory manner.

In certain cases it is possible to calibrate these instruments very accurately. For all work in this field, a well-calibrated crystal well

counter is needed. Such counters are relatively insensitive to variations in the energy of the photons being detected, at least over a reasonable range, and they are rather insensitive to lower energy x-rays (around 30-40 keV). This is an energy range to which ion-chambers are particularly sensitive, and this is a major contributor to their lack of precision without very careful calibration. If, however, a source of protons with an energy of at least 20 MeV is available, one can irradiate a thin piece of polyethylene for a few seconds, and by means of the $^{12}C(p,pn)^{11}C$ reaction produce polyethylene containing several mCi of ^{11}C in a small piece of foil. This foil is then placed in position in the ion chamber and readings are taken at the manufacturer's recommended setting and at a number of other settings on either side of it. The precise time at which each reading is taken must be noted, so that all readings can be decay-corrected to a common time. After allowing the foil to decay for 4-5 half lives, it can be counted in the well counter (again at a known time). If the count rate is still such that a dead-time correction should be applied, this should be done or it should be allowed to decay further. If the well counter has already been calibrated properly, one can now simply determine which of the dose-calibrator settings was giving the correct reading.

If the well-counter is not properly calibrated, at this point one can place a small amount of glass wool in the bottom of a standard liquid scintillation vial, load the vial with a pure toluene or xylene-based scintillator, and place the foil in the solution. If the sample is counted in the ^{32}P channel, or in a channel with no upper discriminator setting, it has been shown by the method described below that the efficiency for the ^{11}C positron is identical to that for the ^{14}C beta particle under such non-quenching conditions. Therefore an absolute determination can be made of either the total or the specific activity of the foil, and this can be decay corrected to the standard time to calculate the true activity in the foil at any desired time when the previous determinations were made.

For a precise calibration of the well counters, the weighed, activated piece of polyethylene is combusted to carbon dioxide on a system designed for the purpose, and the $^{11}CO_2$ is introduced into an internal gas proportional counter (492), after all other counting has been completed. The efficiency of such counters is known to ± 1% by both theoretical calculations and comparison with the NBS standards. After equilibration of the gas mixture in the tubes for 20-30 minutes, they can be counted and the specific activity of the $^{11}CO_2$, and thus the polyethylene foil, can be calculated to ± 2%. The efficiency of the well-counter can then be calculated to the same accuracy, and this

efficiency is valid for any "pure" positron emitter (e.g. ^{18}F, ^{13}N, or ^{15}O). Numerous comparisons of such measurements with the liquid scintillation technique described above has shown that the latter is entirely valid when used as described.

Radioactivity Monitoring During a Synthesis: Monitoring the amount of radioactive precursor delivered from a target to the synthesis area is conveniently carried out using an ionization chamber with a digital readout in a fixed geometry relative to other components in the synthesis system. These detectors operate in the range of 10 μCi to > 2 Ci (for example Capintec Inc., Mt. Vernon, N. Y.) Such a detector can be calibrated to give an estimate of the accumulated amount of radioactivity at any time during activity transfer. Furthermore, although not highly accurate, changes in ionization chamber readings during various transfers are useful monitors during synthetic manipulations and provide an instantaneous indication of problem areas. This requires, of course, that the geometry of all components of the system remain fixed relative to the probe from one run to the next.

Monitoring the distribution of radioactivity among the components of a synthesis either during a synthesis or after the synthesis is an essential step in trouble shooting a system and assessing the various factors responsible for yield losses. It can be done conveniently during the synthesis or after completion of the synthesis using a shielded ionization chamber with a large (~ 2-7/8 in.) diameter well (for example, Capintec Inc., Mt. Vernon, New York). It is useful to design the size of various system components to fit into the chamber. For assaying lower levels of activity (< 5 μCi) a calibrated well counter, is required. Automated gamma counters are useful for assaying a number of samples as, for example, in the quantitation of the distribution of radioactivity from fractions on a chromatogram or assaying tissue samples. An important consideration in the specifications for an automatic gamma counter for use with short-lived nuclides is that there is considerable advantage in a rapid sample changing mechanism. This is of overriding importance when using ^{15}O or even ^{13}N.

The design of laboratory space ideally should allow low level analytical work and high level synthesis to be accomplished simultaneously. This requires that sensitive counting equipment be located away from high level areas and/or be well shielded from high background radiation levels. This design is also compatible with avoiding contamination problems. Many problems can also be avoided if long-lived radionuclides are excluded from the short-lived synthesis laboratory.

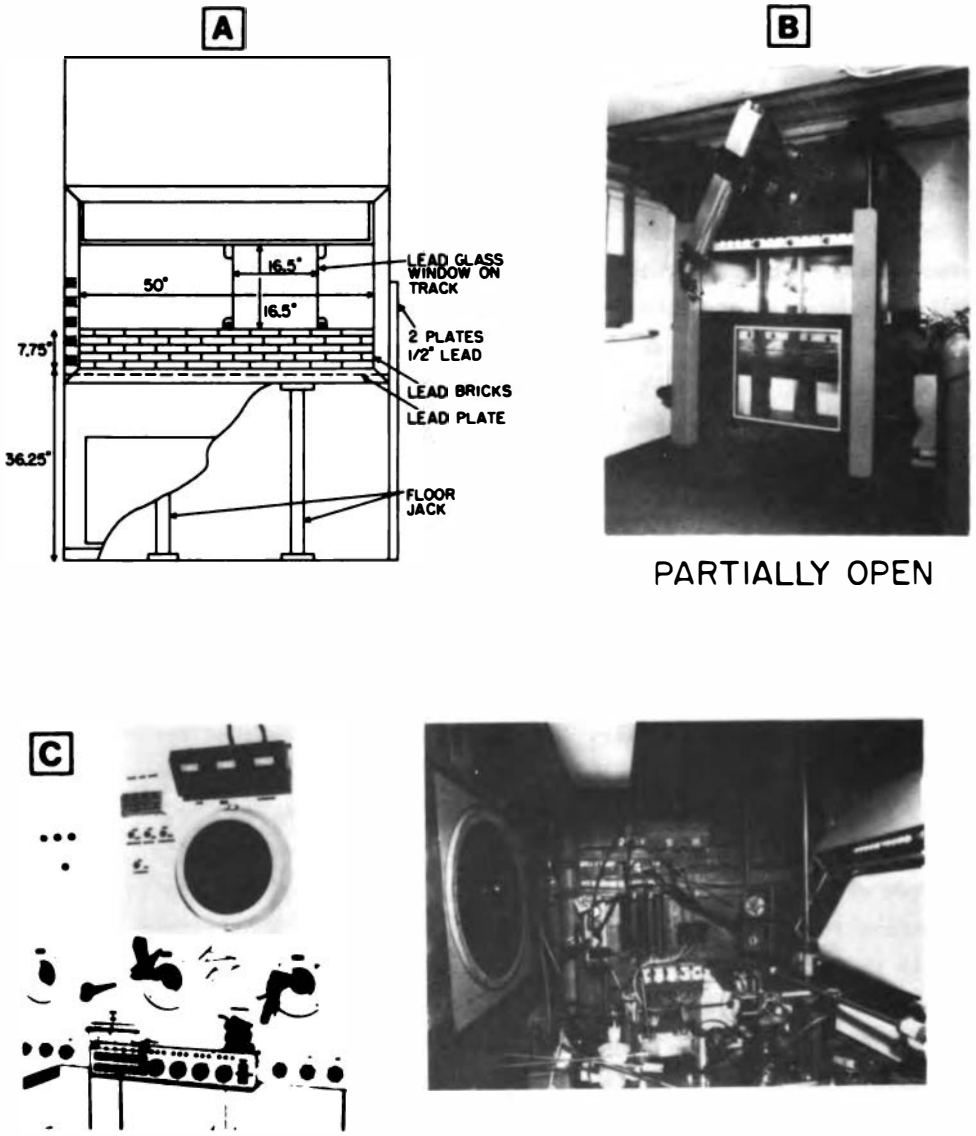


Fig. 3 Shielded work areas. A. Shielded commercial hood. B. Shielded synthesis box for use with high levels of radioactivity. C. Hot cell for remote synthesis of radiotracers (photograph provided by D. Comar).

Shielded Work Areas

An area in which the synthesis of short-lived positron emitting tracers can be safely carried out can take many forms. Three examples, varying in cost and construction complexity will be illustrated here keeping in mind that many different individual designs have been developed on the basis of individual needs.

The simplest shielded work area involves modification of a commercially available laboratory hood and is illustrated in figure 3A. Basically, its fabrication involves providing structural support of the floor of the hood (floor jacks) and placing a lead plate on the hood floor. Along the entire front face of the hood, a short wall of lead bricks is built. On the top of this wall a high density (6.2 gm/cc) lead glass window (16.5 in high x 16.5 in wide) is installed on a track so that it slides across the front face of the hood and can be used to shield different areas as the radioactivity is moved to different areas within the hood. This provides a reasonably well shielded work area for use with moderate levels of radioactivity, especially when modular shielding is used within the hood. For example, lead shielding of various vessels in which the nuclide is trapped as well as small lead shields for various reaction vessels and columns, when used inside the modified commercial hood provides reasonably inexpensive and effective protection for manipulations which need to be carried out during a synthesis. However, when large quantities of radiotracer are required on a regular basis, the need for more shielding escalates. This need has been met by two systems described below.

Another design appears in figure 3B. Basically it is a shielded box with complete access to the front area by mechanically lowering a large lead glass window mounted in steel frame. Behind this is a small lead glass window on a horizontal track. The large window can be used in any position and in the fully open position gives complete access for experimental setup. Used in the partially open configuration (shown in figure 3B) in conjunction with the smaller window, this shielded box can be used for lower level exploratory work where a completely remote or automated system has not been developed. A master-slave manipulator is also an essential feature of this system (493).

A closed shielded hood has been described for the synthesis of ^{11}C-labeled radiotracers at the ~ 100 mCi (product at end of synthesis) level (185). The experimental setup has been integrated into the shielded hot cell and has been completely automated so that the ^{11}C can be incorporated without manual intervention at no radiation risk to personnel involved in the synthesis. This hot cell which in routine use is shown in figure 3C.

Routine Production of Radiotracers for Clinical Studies

The initial development of the synthetic approach itself as well as preparing the tracer for evaluation in small animals requires working with relatively low levels of radioactivity. In contrast, the extension of these low level studies to the use of the radiotracer in humans on a regular basis using PETT usually requires the repetitive handling of large quantities of radioactivity. For example, to produce 20 mCi of an ^{18}F-labeled tracer at the end of a 60 min synthesis requires starting with ~ 300 mCi of ^{18}F if the radiochemical yield is 10%. Since this quantity of ^{18}F as a point source delivers 0.45 mR/sec at 1 cm, heavily shielded work areas and an experimental setup which is compatible with such a shielded work area are essential features of the process. Thus the technical aspects of refining the experimental design of the synthetic approach so that the labeling can be accomplished reliably and remotely becomes important at this stage of the development of the radiotracer.

Experimental Design - Examples

The integration of an experimental setup into a shielded work area requires defining the essential features of a synthetic approach, incorporating them into an experimental setup which minimizes operator intervention and discarding non-essential transfers, and intermediate purification steps whenever possible. Frequently micro-scale reactions are used and therefore the glassware and other components of the synthesis system must be designed and fabricated on a micro-scale to minimize losses which occur on transfer and manipulation. This has been accomplished by different groups using different approaches (99,185,211,230,345,405,494-496). Frequently the designation of essential vs. non-essential steps in a procedure requires a considerable amount of experimental work. Coincident with this streamlining process, yield improvements are usually made because the procedure is made faster by eliminating cumbersome transfers and manipulations. The goal in the setup of a routine system is the evolution of the simplest possible experimental system which involves a minumum number of manipulations. This sequence can then be automated or integrated into a manual/remote system or an automatic/remote system, using extension tools and/or manipulators and remotely controlled valves. One concept which can be applied to all experimental approaches is that all components of the system which do not come into contact with the radioactivity or where low levels of radioactivity is involved be set up outside of the shielded area.

To illustrate the different approaches to carrying out the routine synthesis remotely, examples of the experimental design and procedures for

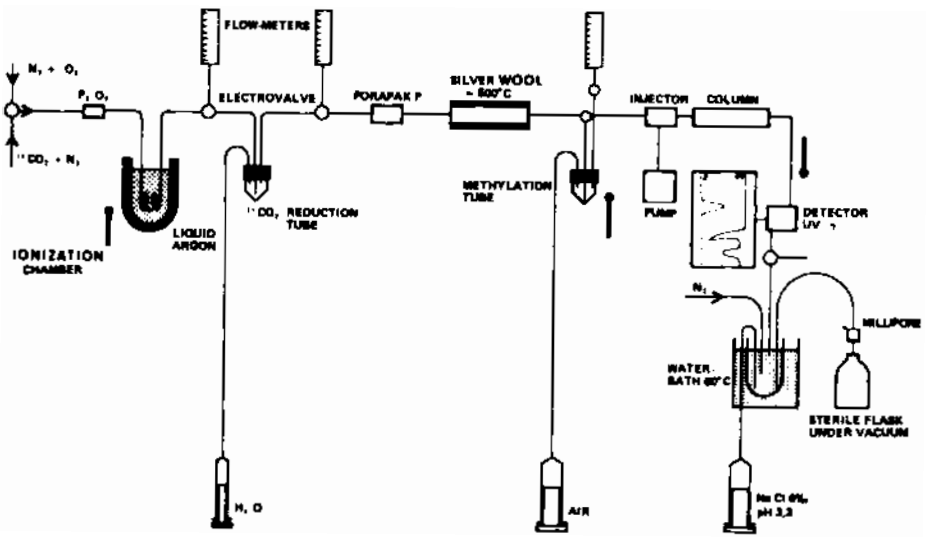


Fig. 4 Experimental setup for ^{11}C-imipramine synthesis (photograph provided by D. Comar).

producing positron emitting radiotracers which are routinely used are presented. These tracers are ^{11}C-labeled imipramine, ^{11}C-labeled palmitic acid and ^{18}F-2-deoxy-2-fluoro-D-glucose and demand for them at the institution where they were developed as well as at collaborating institutions has necessitated devising the shielded experimental setups for their frequent and routine production. Further increases in demand for short-lived radiotracers will require more sophisticated approaches. For example, the concept of programmable unit process automation which consists of a central processing unit (computer) which senses certain experimental parameters, regulated events related to these parameters and logs events for future reference would possess distinct advantages over the hard-wire automated systems which are in use today. For example, changes could be effected by reprogramming rather than rewiring and individual programs could be generalized and applied to any number of production and synthesis systems. Thus total automation of all aspects of short-lived radiotracer synthesis for routine use is a goal which should free scientists for creative efforts in the development of new radiotracers for application in biology and medicine.

^{11}C-Imipramine (185): A schematic diagram of the synthesis apparatus is shown in figure 4. It is housed in the closed shielded hood shown in figure 3C. Carbon-11 labeled CO_2 produced by the irradiation of a static nitrogen target $^{14}N(p,\alpha)^{11}C$ is purged with a stream of nitrogen through a P_2O_5 trap to remove water and trapped in a metal capillary at - 185°C (ARGON). The trap is warmed to 20°C and the $^{11}CO_2$ is purged (carrier gas: N_2 + 2% O_2) through a solution of 50 µl of THF (anhyd) and 4-8 µmol of $LiAlH_4$ at - 5° to - 10°. The THF is evaporated by heating the tube at 130°, while bubbling a current of nitrogen, then cooled and 50 µl of water is added. ^{11}C-labeled methanol is distilled off by heating the vessel to 130° and is carried through a Porapak P trap size (0.3 x 10 cm) to remove THF and through a silver wool furnace (0.3 x 7 cm) at about 500° to give ^{11}C-formaldehyde.

The ^{11}C-formaldehyde is purged through a solution of 1 µmol of norimipramine (PERTOFRAN) 1 µmol $NaCNBH_3$, 2 µl of acetic acid, 50 µl of H_2O and 200 µl acetonitrile and the mixture is heated to 50° for 7 min.

The mixture is then injected into a 50 cm Partisil Magnum 9 column eluting with a mixture of 97% chloroform, 3% ethanol (containing 2% ethylamine and 2% water). The fraction containing the appropriate chromatogram peak is collected in a heated container and the solvent (5-10 ml) evaporated by a stream of nitrogen. The labeled product is redissolved in 5 ml of physiological serum buffered to pH 3.3 by sodium phosphate (2.5×10^{-3}M),

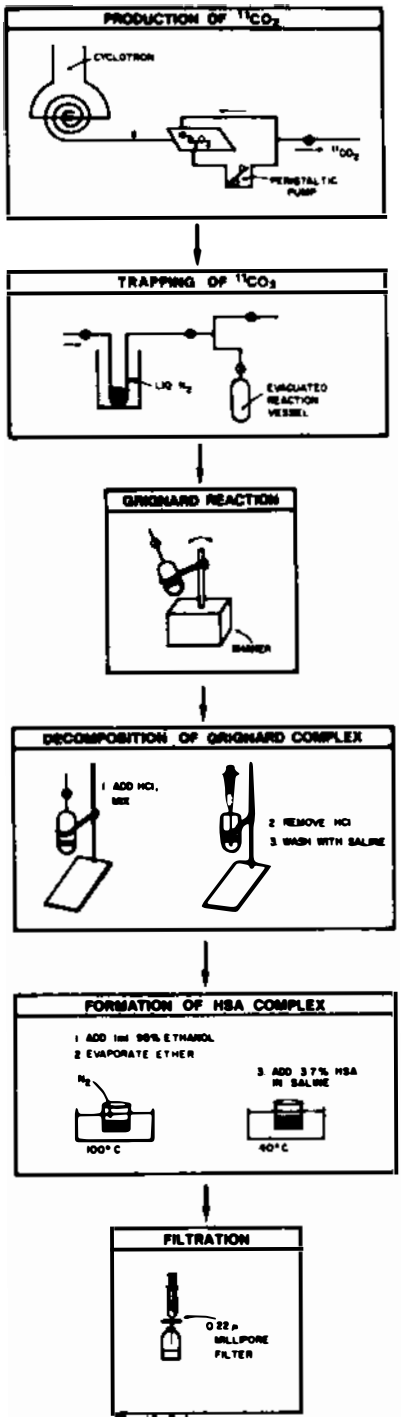


Fig. 5 Experimental setup for ^{11}C-palmitic acid synthesis (photograph provided by K. McElvaney and M. Welch).

followed by sterilization by filtration through a 0.22 μm Millipore filter connected by a sterile needle to an evacuated sterile vial.

This method results in the preparation of 50-80 mCi ^{11}C-imipramine with a specific activity of ~ 500 mCi/μmol starting with 500 mCi - 1 Ci of $^{11}CO_2$. The synthesis time is 25 min. The material is chromatographically pure, sterile and apyrogenic. The completely enclosed design results in no radiation risk to personnel involved in the synthesis.

^{11}C-Palmitic Acid (211): The $^{11}CO_2$ is produced *in situ* at the Washington University Medical School Cyclotron (Allis Chalmers) by the $^{10}B(d,n)^{11}C$ reaction. The $^{11}CO_2$ is swept from the target with a carrier gas mixture of helium:oxygen (98:2), yielding > 95% of the isotope in the desired $^{11}CO_2$ form. The $^{11}CO_2$ is trapped in a coiled glass tube containing a plug of glass wool and immersed in liquid nitrogen. (See figure 5 for experimental setup).

After warming the trap in a water bath, the $^{11}CO_2$ is quickly transferred to an evacuated vessel using a flow of helium. Two ml of the Grignard solution are added and the vessel is shaken for about 3 to 4 minutes. The palmitic acid-MgBr complex is decomposed with 2 ml of 1 N HCl while shaking the vessel to clarify the ether layer. The contents are transferred to a 1.5 x 12 cm test tube, the acidic layer removed by means of a syringe, and ether freed of any traces of acid by washing twice with 2 ml portions of normal saline solution (0.9% NaCl). The ethereal solution is then transferred to a 50 ml beaker, 1 ml 95% ethanol is added, and the ether is evaporated in a hot water bath under N_2 to yield a final volume of ~ 1 ml. The resulting solution is warmed to 40° C and combined with about 8 ml of 3.7% human serum albumin in normal saline, also at 40° C. After warming for about 3 minutes to allow for binding of the palmitic acid to the albumin, the mixture is filtered through a 0.45 μ Millipore filter, and the filter and beaker are rinsed with ~ 1 ml of saline. The solution is finally passed through a 0.22 μ disposable Millipore filter and the activity measured prior to injection. The total preparation time, including the initial trapping of $^{11}CO_2$, is about 15-20 minutes.

In order to verify the formation of ^{11}C-palmitic acid and detect any pentadecane or other impurities which may be present, the final solution is analyzed by high pressure liquid chromatography under the following conditions:

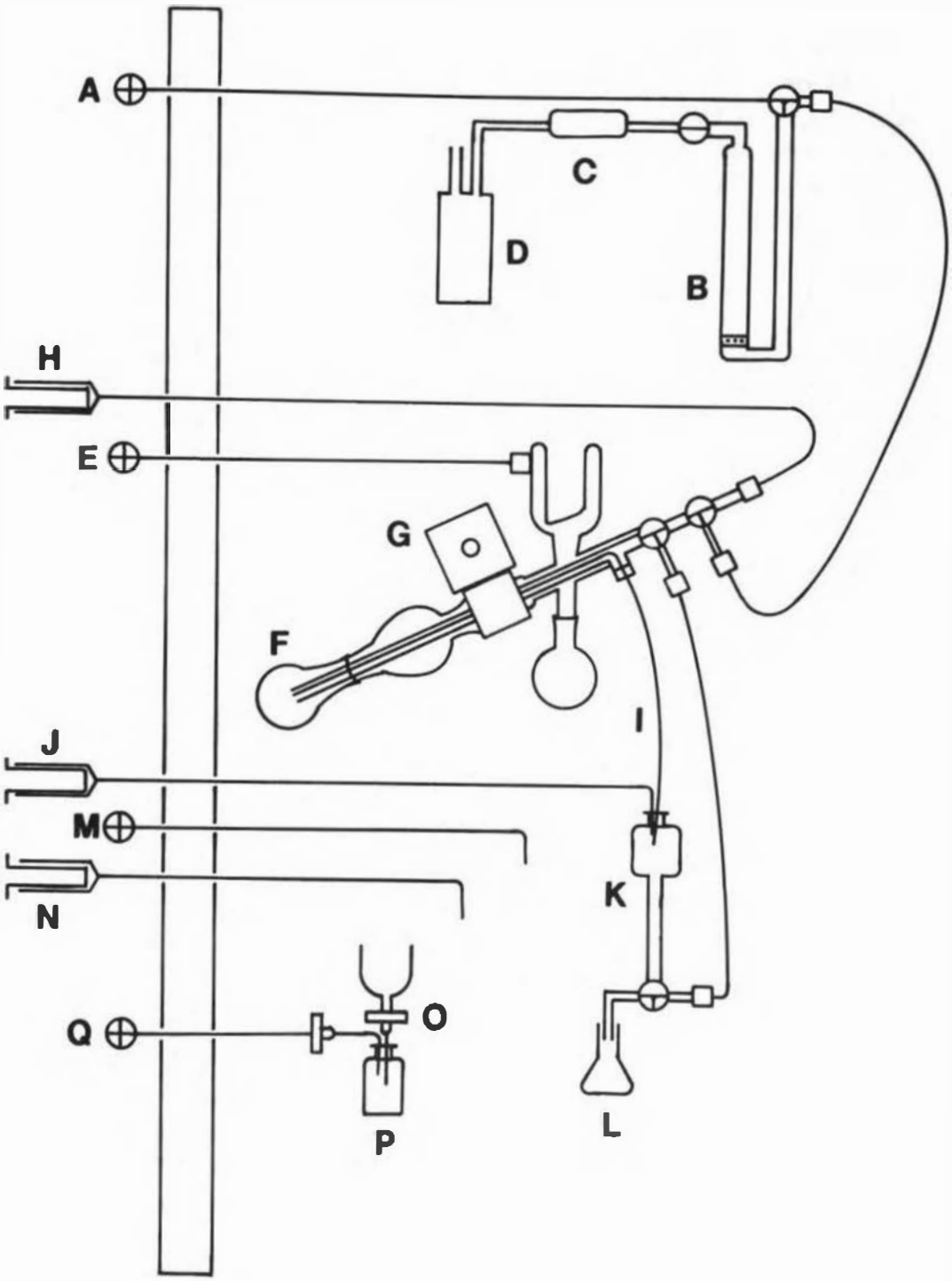


Fig. 6 Experimental setup for 2-deoxy-2[18]fluoro-D-glucose synthesis.

Instrument: Waters LC; M-6000 solvent delivery system
Column: Fatty acid analysis column, 10 micron particle size; 3.9 mm I.D. x 30 cm long
Solvent: THF:CH_3CN:H_2O:(35:30:40, v:v)
Flow Rate: 2 ml/min(~ 2300 psi)
Refractive Index and NaI(Tl) Detectors

^{11}C-Palmitic acid elutes at about 5.0 min, and the hydrocarbon at about 10.0 min. Analyses of ^{11}C-palmitic acid preparations, as expected, have not shown a mass peak corresponding to the pentadecane, which precipitates out in the alcoholic solution upon evaporation of ether, and is later filtered out of the final preparation. Radiochromatograms consistently show a single peak with a retention corresponding to that time of unlabeled palmitic acid; the radiochemical purity is calculated to be higher than 99%.

2-Deoxy-2-[^{18}F]-Fluoro-D-Glucose (^{18}FDG) from $CH_3CO_2{}^{18}F$ (349): The ^{18}FDG synthesis system is shown in figure 6 with letters referring to various components. Prior to the run, all of the components are assembled in the shielded synthesis hood (figure 3B) with 1/8" O.D. teflon tubing and Swagelock fittings.

The contents of the irradiated Ne/F_2 target containing [^{18}F]F_2 in neon (~ 40 μmol F_2) was purged (needle valve A) through a vessel (B) containing a solution of ammonium hydroxide (0.010 ml) in glacial acetic acid (15 ml). The gas exiting the reaction vessel is passed through a soda lime trap (C) and a charcoal (6-8 mesh) trap (D) at -78°C. Purging of the target (26.5 atm → 1 atm) requires 25 minutes after which the acetic acid solution is transferred by vacuum (E) into the flask (F) of a rotary evaporator (G, Brinkman Model M). Flask F contains 25 mg of 3,4,6-tri-O-acetyl glucal (Aldrich Chemical Co., no purification required). After transfer the acetic acid is evaporated to dryness, 3 ml of 2 N HCl is added (syringe H) and the mixture heated at 130-135°C for 12 min while rotating the flask. Charcoal (USP, 15 mg/1.0 ml H_2O) is added (syringe H) and heating is continued for 3 minutes after which the solution is evaporated to dryness. To the residue is added (syringe H) 2 ml of aqueous acetonitrile (0.3 ml H_2O/100 ml CH_3CN). This is evaporated to dryness, an additional 3 ml of aqueous acetonitrile is added and the mixture transferred from flask F via teflon tube (I) and syringe vacuum (J) onto a flash chromatrography column (K, 0.75 cm x 10 cm) packed dry with silica gel 60 (Merck No. 9385) and rinsing with 2 ml of the aqueous acetonitrile. Syringe J is then used to apply pressure to the column and force the acetonitrile solution onto the packing after which 20 ml of

aqueous acetonitrile is added and elution is begun. A forecut (7-8 ml) is collected (L) after which the flow is directed into the rotary evaporator and the remaining solvent is eluted into the rotary evaporator to which a clean flask has been attached. The solvent is evaporated and 1 ml of water is added and evaporated. The flask is removed from the evaporator, a stream of nitrogen (M) is purged through it for 2 min to remove all traces of solvent. Saline (8 ml) is added via syringe N and the solution is passed through a millipore filter O into an evacuated (vacuum Q) multi-injection vial P. This procedure typically produces 1.5-2.0 mg of ^{18}FDG in a synthesis time of 70 minutes from EOB. The radiochemical yield is 20% and the purity is 97% as determined by thin layer chromatography. Thus from 350 mCi of ^{18}F one obtains 45 mCi of FDG at end of synthesis (EOS, 70 min).

Appendix 1. A Guide to the Literature of Organic Synthesis

This appendix is intended to serve as a guide to the chemical literature emphasizing works which are of particular value to designing practical synthetic approaches to organic molecules. The vast body of documentation in organic synthesis appearing in the form of text books, monographs, reviews and journal articles precludes all but a superficial treatment here. However within the selected references the reader can be guided through many aspects of the designing, refining and implementation of a synthetic approach which is compatible with the restraints imposed by short-lived nuclides. Along these lines the brief description of a selected number of leading works on the following topics will be covered:

A. Searching the literature for a particular organic molecule
B. Works of synthetic organic chemistry
C. Special topics
D. Review articles

A. Searching the literature for a particular organic compound:

A search of the literature serves to reveal the preparation, physical and chemical properties, and uses of an organic molecule. Frequently, a number of synthetic routes to the unlabeled molecule can be found in the literature and one or more of these can be adapted to the rapid labeling with a positron emitter. The following is suggested as a rapid stepwise approach to searching the literature.

1. Determine the molecular formula for the compounds, and name the molecule.
2. Locate the formula in Beilstein (described below) and differentiate among structural isomers by the name. References listed in Beilstein (first and second supplements) cover the literature through 1929.
3. Consult Chemical Abstracts (described below) collective formula index for the years 1920-1946, and the cumulative indices for the following years (1947-1956, 1957-1961, 1962-1966, 1967-1971, 1972-1976) and yearly indices thereafter.

Beilstein (in German): Although a book has been written on the use of Beilstein (A Brief Introduction to the Use of Beilstein's Handbuch der Organischen Chemie, E. H. Huntress, John Wiley and Sons, Inc., New York, 1938), a brief guide to its uses usually suffices to provide a rapid overview of the literature through 1929. The simplest method involves the use of the cumulative formula indices. The compound is located based on its formula and name, after which will appear volume and page references to the main series

(the literature through 1909) and the first supplementary series (1909-1919) and the second supplementary series (1919-1929). For example, the Beilstein entry in the formula index for formaldehyde (molecular formula CH_2O) appears:

CH_2O Formaldehyde 1, 558, I289, II615; 6II 1244.

This refers to volume 1 page 558 of the main series.
volume 1 page 289 of the first supplement
(Erstes Erganzungswerk) and
volume 1 page 615 of the second supplement
(Zweites Erganzungwserk) 6II 1244 refers to
volume 6 page 1244 of the second supplement

Chemical Abstracts: The American Chemical Society publishes chemical abstracts which summarizes all original articles on chemistry that appear in journals. It is published twice a month. Yearly indices of formulae, authors and subjects appear along with the cumulative indices described above.

B. Works of Synthetic Organic Chemistry

D. Barton and W. D. Ollis, Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds, J. F. Stoddard ed., (Pergamon Press, Oxford, 1979). Six volumes give emphasis to the properties and reactions of all the important classes of organic compounds. Volume 6 is an extensive index according to formula, subject, author, reaction and reagents. The reaction index is especially useful since part of the listings under each reaction is compilation of pertinent references (mainly reviews). The reagent index lists over 2500 organic and inorganic compounds which are used in organic synthesis and gives specific reactions performed by the reagent followed by a list of compounds which undergo that particular reaction with the reagent. This index is cross referenced with volume 1-5.

Organic Reactions: (John Wiley and Sons, New York) A series of volumes from 1942 to present containing chapters devoted to specific reactions and contains experimental procedures and tables detailing every case of use of the reaction at the time of writing.

Houben-Weyl, "Methoden der Organischen Chemie," E. Muller, ed., Theime Verlag, 4th Ed., 1952-present. A compilation of synthetic methods and references, primarily arranged by functional group including many experimental procedures. In German.

L. F. Fieser and M. Fieser, Reagents for Organic Synthesis, Vol. I-VII, (John Wiley and Sons, Inc., New York) A series of volumes having an alphabetical arrangement of reagents with their synthetic applications. References to original literature and review articles with extensive indices.

C. A. Buehler and D. E. Pearson, Survey of Organic Syntheses, Second Edition, (W. A. Benjamin Inc., California, 1972) A survey of selected synthetic methods including formation of carbon-carbon bonds, reductions and oxidations.

C. Special Topics

J. Mathieu and J. Weill-Raynal, Formation of C-C Bonds (George Thieme Publishers, Stuttgard, 1973) in three volumes; contains formula schemes and tables; volume 1 describes reactions which involve the introduction of one carbon atom bearing a functional group into the carbon skeleton (i.e. hydroxymethylation, the Mannich reaction, formylation, carboxylation and cyanation) and is of particular value to surveying possible routes for incorporation of one-carbon precursors of ^{11}C into complex molecules.

M. R. C. Gerstenberger and A. Haas. Methods of fluorination in organic chemistry. Angew. Chem. Int. Ed. Engl. 20, 647-667, 1981.

Protective Groups in Organic Synthesis T. W. Greene (John Wiley and Sons, New York, 1981). This book presents information on the synthetically useful protective groups (~ 500) for five major functional groups: -OH, -NH, -SH, $-CO_2H$ and $\rangle C{=}O$. References through 1979, the best method(s) of formation and cleavage, and some information on the scope and limitations of each protective group are given.

Protective Groups in Organic Chemistry J. F. W. McOmie, Ed. (Plenum Press, London, 1973) There is a chapter devoted to each of the functional groups commonly in need of protection. See also Chemistry and Industry (No. 18), Sept. 1979 pp. 603-604 for articles on recent developments on protective groups and E. Haslam, Recent developments in methods for the esterification and protection of the carboxyl group. Tetrahedron 36,2409-2433, 1980.

W. A. Sheppard and C. M. Sharts, Organic Fluorine Chemistry (W. A. Benjamin, Inc., New York, 1969) A critical look at the literature through 1968 includes discussions of mechanisms, synthetic methods and extensive tables; see also C. M. Sharts and W. A. Sheppard, "Methods to Prepare Monofluoroaliphatic Compounds", in Organic Reactions Vol. 21 (John Wiley and Sons, New York, 1974) pp. 125-406.

M. Hudlicky, Chemistry of Organic Fluorine Compounds, 2nd edition, (Halsted Press, a Division of John Wiley and Sons, New York, 1976). Contains extensive material on the synthesis and reactions of organic fluorine compounds with extensive references, examples of experimental procedures and techniques for handling fluorination reagents.

M. F. A. Dove, The Halogens and Hydrogen. Coordination Chemistry Reviews 30, 351-378, 1979. A review focussing on recent developments on the synthesis of novel fluorine containing compounds.

R. Rylander, Catalytic Hydrogenation in Organic Syntheses (Academic Press, New York, 1979); a guide to catalyst selection and reaction conditions arranged according to the functional group undergoing reduction.

E. R. H. Walker, The functional group selectivity of complex hydride reducing agents, Chem. Rev. 5,22-50, 1976.

A. J. Gordon and R. A. Ford, The Chemist's Companion (John Wiley and Sons, Inc., New York, 1972) A handbook of practical data, techniques and references.

IUPAC Commission on the Nomenclature of Organic Chemistry (CNOC), Nomenclature of Organic Chemistry Section H: Isotopically Modified Compounds. Eur. J. Biochem. 86, 9-25, 1978.

IUPAC Commission on the Nomenclature of Inorganic Chemistry. Nomenclature of Inorganic Chemistry 12. Isotopically Modified Compounds. Pure and Appl. Chem. 51,1981-1994, 1979. See also Pure and Appl. Chem. 53, 1887-1900, 1981.

D. Review Articles: Recent indices to review articles on topics related to synthetic methodology can be rapidly located by consulting the following sources:

D. Barton and W. D. Ollis. Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds (see description above).

J. Org. Chem. 43, 3085, 1978. Recent Reviews 1, covers the 1977 literature.

J. Org. Chem. 43, 4397, 1978. Recent Reviews 2, covers the first part of the 1978 literature.

J. Org. Chem. 44, 1752, 1978. Recent Reviews 3, covers the second part of the 1978 literature.

J. Org. Chem. 44, 4016, 1979. RecentReviews 4, covers the first part of the 1979 literature.

J. Org. Chem. 45, 1728, 1980. Recent Reviews 5, covers the second half of the 1979 literature.

Index of Biochemical Reviews, 1980 (compiled by R. E. Arnstein, M. Harvey and H. R. V. Arnstein, FEBS Letters, 131, Suppl., August, 1981.

Appendix 2. A Guide to the Literature on Organic Synthesis with Isotopes Especially Positron Emitters.

General References

A. Murray and D. L. Williams, Organic Synthesis with Isotopes, Parts I and II (Interscience Publishers, Inc., New York, 1958). An encyclopedic source of methods of isotopic synthesis with detailed experimental procedures covering the literature through 1955. The synthetic routes used for the preparation of ^{14}C-labeled compounds may, in some cases be generalized to ^{11}C keeping in mind the significant differences between labeling with ^{14}C and ^{11}C.

H. E. Mertel, "Synthesis of Isotopically Labeled Compounds" in Drug Fate and Metabolism, Vol. 3, E. R. Garrett and J. L. Hirtz (Marcel Dekker, Inc., New York, 1979). This chapter includes sections on synthetic and analytical methods.

D. R. Christman and K. I. Karlstrom, Accelerator Produced Nuclides for Use in Biology and Medicine - A Bibliography, Vol. I (1939-1973) and Vol. II (January 1974 - June 1976) (Brookhaven National Laboratory, Associated Universities Inc., BNL No. 50448). This bibliography focusses on charged particle accelerators, their use for nuclide production, the synthesis of compounds in research and application in nuclear medicine; includes subject, nuclide and author indices.

A. P. Wolf, D. R. Christman, J. S. Fowler and R. M. Lambrecht, "Synthesis of Radiopharmaceuticals and Labeled Compounds Utilizing Short Lived Isotopes" in Radiopharmaceuticals and Labelled Compounds, Vol. I, (IAEA, Vienna (1973), IAEA-SM-171/30) p. 345.

N. D. Heindel, H. D. Burns, T. Honda and L. W. Brady, eds. The Chemistry of Radiopharmaceuticals (Masson Publishing U.S.A., Inc., 1978) Contains chapters on radiopharmaceutical design, quality control and positron emitting radiopharmaceuticals.

J. C. Clark and P. D. Buckingham, Short-Lived Radioactive Gases for Clinical Use (Butterworths, London and Boston, 1975). A practical handbook concerned with the production of short-lived radioactive gases (^{11}C, ^{13}N, ^{15}O).

D. J. Silvester, Preparation of Radiopharmaceuticals and Labeled Compounds Using Short-Lived Radionuclides, Radiochemistry, Vol. 3, The Chemical Society, Burlington House, London, 1976, p. 73-107.

L. Kronrad, K. Mudra and J. Marek, Preparation of Organic Compounds Labeled With Short-Lived Radioisotopes, Radioisotopy, 17, p. 155-249, 1976.

G. Subramanian, B. A. Rhodes, J. F. Cooper and V. J. Sodd, Eds., Radiopharmaceuticals, Proceedings of the First International Symposium on Radiopharmaceuticals, (The Society of Nuclear Medicine, Inc., New York, 1975). Contains chapters on the halogens, cyclotron products and quality control.

J. A. Sorenson, book coordinator, Radiopharmaceuticals II, Proceedings of the 2nd International Symposium on Radiopharmaceuticals, (The Society of Nuclear Medicine Inc., New York, 1975). Contains chapters on organic radiopharmaceuticals and radionuclide production.

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M. G. Straatmann, "A look at ^{13}N and ^{15}O in radiopharmaceuticals," pp. 21-24.

A. P. Wolf and C. S. Redvanly, "Carbon-11 and Radiopharmaceuticals," pp. 29-48.

C. Mazarano, M. Maziere, G. Berger and D. Comar, "Synthesis of methyl iodide-^{11}C and formaldehyde-^{11}C, pp. 49-52.

A. J. Palmer, J. C. Clark and R. W. Goulding, "The preparation of fluorine-18 labeled radiopharmaceuticals," pp. 53-65.

K. A. Krohn and A. L. Jansholt, "Radiochemical quality control of short-lived radiopharmaceuticals," pp. 213-227.

Journals (covering various aspects of radiotracer development)

Journal of Labelled Compounds and Radiopharmaceuticals (Vol. XVII (No. 4) is a compound index for Vol. I-XVI).

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