H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac															

Chemistry for Nuclear Medicine

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CHEMISTRY FOR NUCLEAR MEDICINE

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CHEMISTRY FOR NUCLEAR MEDICINE

To my wife,
Darlene Billinghurst

To my wife,
Lisbeth Fritzberg
and my parents,
William and *Evelyn Fritzberg*

PREFACE

Radiopharmaceuticals play a central role in nuclear medicine. A broad understanding of their development and preparation requires a knowledge of chemistry, ranging from general chemistry to inorganic, organic, and analytical chemistry, while an understanding of their behavior in vivo requires a knowledge of biochemistry and physiological chemistry. Our involvement with chemistry and radiopharmacy courses for nuclear medicine technologists, pharmacists, and medical physics graduate students has indicated that there is no single chemistry text that covers these areas in a manner relevant to nuclear medicine. This book was written to meet these needs.

The organization of the text is based on the Canadian nuclear medicine technologist syllabus. Specifically, the text is written to provide basic principles that explain the chemical properties and reactions of radiopharmaceuticals. Basic biochemistry is presented as it serves to explain the in vivo behavior of radiopharmaceuticals and the interactions involved in competitive protein-binding assays. Chromatographic methods as well as basic laboratory techniques used in the nuclear medicine laboratory are also discussed.

The text should be useful to students who do not have broad chemistry backgrounds, such as nuclear medicine technologists and medical physics graduate students, as well as to pharmacists and radiologists who work with radiopharmaceuticals and find a review of pertinent chemistry helpful.

CONTENTS

chapter 1

INTRODUCTION

An accurate definition of chemistry would require considerable space because the scope of chemistry extends into the borders of physics, biology, medicine, and engineering. At its core, however, chemistry is the study of the composition of substances and their interactions with each other. It is the study of the way in which the component parts of substances are put together, their disassembly, and their reassembly so that rare and complex naturally occurring compounds can be prepared from readily available starting materials and thus made more available. It involves the design and preparation of compounds that do not exist in nature but that may be of use to man. Thus, we may conclude that chemistry is a vast field of endeavor. In this textbook, it is not our purpose to cover the whole study of chemistry or to select one specific area or subsection and to treat it in depth, but rather to provide a broad background of those fundamental concepts of chemistry that are prerequisites to the study of nuclear medicine. Since nuclear medicine itself is a very broad subject, ranging from the chemical physics aspects associated with liquid scintillation detection of β particles, to the biochemical aspects of radioimmunoassay, to the analytical aspects of radiopharmaceutical quality control, the scope of this textbook must have considerable breadth. Fortunately, because the purpose is to provide a basis on which to build other knowledge, in-depth understanding of all aspects is not required. As much as possible, where it serves the overall purpose, the classical approach to teaching chemistry has been discarded in favor of placing greater emphasis on those aspects that relate directly to nuclear medicine.

Characterization of matter

Since chemistry is the study of substances, it is necessary to classify these substances. The basic classifications are mixtures, solutions, pure substances, compounds, and elements. We will outline these in order of increasing degree of order.

Homogeneous *mixtures* or *solutions* are mixtures of substances in which there is no physical boundary or physical distinction between the two components. The most common examples are the aqueous solutions formed when a substance such as sugar dissolves in water. No chemical reaction takes place. Both water molecules and sugar molecules continue to exist as such, but they cannot be separated by any mechanical means; that is, they cannot be separated visually even under a microscope nor can they be separated by filtration or centrifugation. Separation can be accomplished only by means such as distillation or crystallization. The term *solution* is not restricted to the aqueous phase or even to liquids, however. All gases are completely *miscible* (able to dissolve in one another in all proportions) and are gaseous solutions, whereas alloys are solutions of one metal in another and, of course, are solids at room temperatures.

Pure substances consist of a single component, either an element or a compound. Such pure substances are characterized by a single discrete boiling point/liquefaction point (that is, if the substance as a liquid is slowly heated, it will all boil to a vapor at a single discrete temperature, and if that vapor is then cooled, it will all liquefy at the same discrete temperature at which it boiled) and a single discrete freezing point/melting point. There are thousands of known pure substances and new ones are constantly being prepared. All new substances, however, are composed of only about 104 currently known elements. Pure substances are either one of these 104 elements or chemical compounds composed of more than one element.

Chemical *compounds* are the products of the chemical combination of several elements in definite proportions to form a compound that has discrete properties of its own. Usually these properties have no relationship to the properties of the elements of which the compound is composed; in fact, any similarities that occur on occasion are purely fortuitous.

Elements are the basic building blocks of all compounds, the simplest units of the pure substances. Elements cannot be broken down into component parts by any physical or chemical means. Division of a "lump" of an element results in only smaller pieces of that same element until the ultimate unit size is reached. This is the atom, and it is indivisible by any chemical or physical means.

Atoms

Atoms are the basic building blocks of chemistry. Chemical reactions take place between atoms of different elements to form molecules of compounds. Although atoms are indivisible by any chemical or physical means, nuclear physics has allowed us to take them apart, and we now know that atoms consist of a nucleus, which is positively charged, and electrons, which are negatively charged. The electrons, each carrying unit negative charge, move around the nucleus in orbits, which can be crudely conceived of as being like the orbits of the planets around the sun. These electrons are known to possess very little mass; nearly all the mass of the atom is concentrated in the nucleus. Nuclear physics has also allowed us to take the nucleus apart, and it is made up of several different components in various proportions. Only two of these have any real significance in chemistry; they are the proton and the neutron.

The proton is positively charged. In any atom, the number of protons in the nucleus is equal to the number of electrons orbiting the nucleus, so that the atom as a whole is electrically neutral. However, unlike the electron, the proton has significant mass; in fact, it is 1,837 times the mass of an electron. The mass of the proton is defined as unit atomic mass or 1 atomic mass unit; thus, the mass of an electron is 1/1,837 of an atomic mass unit.

The neutron, as its name implies, is electrically neutral. Its mass is essentially the same as that of a proton. Thus, the atomic mass, *A*, of one atom is the sum of the number of protons and the number of neutrons in the nucleus of that atom. The atomic number, *Z*, of any atom is equal to the number of protons in the nucleus of that atom, or to the number of electrons surrounding the nucleus. Therefore, the number of neutrons equals $A - Z$. Any atom may be completely defined by specifying the atomic mass and the atomic number, since the atomic number defines the nuclear charge (the number of protons in the nucleus and the number of orbiting electrons), while the atomic mass defines the total mass of the atom (the sum of the number of protons and the number of neutrons). The accepted way of writing this information is to precede the symbol for the element with a superscript specifying the atomic mass and a subscript specifying the atomic number—i.e., ${}^{A}_{Z}X$. For example, ${}^{99}_{42}Mo$ indicates that the atomic number of molybdenum is 42; that is, molybdenum has 42 electrons surrounding the nucleus and 42 protons in the nucleus, which results in a nucleus with a positive charge of 42 electrostatic units. The atomic mass of the isotope of molybdenum that is referred to is 99, indicating that the number of neutrons in the nucleus is 99 − 42, or 57.

Isotopes

Definition

Since chemical properties are the result of interactions between atoms and it is the electrons that envelop the atoms, chemical interactions involve the electrons and chemical properties are determined by the electrons. Thus, atoms that have the same number of electrons—that is, atoms that have the same atomic number—behave in a chemically identical manner and are said to be atoms of the same element irrespective of the number of neutrons in the nucleus. That is to say that atoms of the same element have the same atomic number but need not have the same atomic mass. Atoms that have the same atomic number but different atomic masses are *isotopes* of the same element. Different isotopes of the same element behave in a chemically identical manner and cannot be separated by any chemical means; that is, they are chemically identical. The only way isotopes can be separated is by physical methods of separation based on the weight of the atom—e.g., mass spectroscopy and differential diffusion.

All atoms have atomic masses that are whole numbers because there must be a whole number of neutrons and a whole number of protons in the nucleus and each of these subatomic particles has unit mass (other subatomic particles have negligible mass). However, many elements appear to have fractional atomic weights. This is not a contradiction but happens because elements may contain a variety of isotopes, and in most cases these occur as a mixture of the stable isotopes of that element in constant proportions. Relatively few elements are *monoisotopic*—that is, have only one stable or nonradioactive isotope. Iodine is one such element, and it has an atomic weight very close to 127. A more common situation is that of tin, which has an atomic weight of 118.70 and is composed of $^{112}_{50}Sn$ (0.96%), $^{114}_{50}Sn$ (0.66%), $^{115}_{50}Sn$ (0.35%), $^{116}_{50}Sn$ (14.30%), $^{117}_{50}Sn$ (7.61%), $^{118}_{50}Sn$ (24.03%), $^{119}_{50}Sn$ (8.58%), $^{120}_{50}Sn$ (32.85%), $^{122}_{50}Sn$ (4.72%), and $^{124}_{50}Sn$ (5.94%). All these isotopes of tin are stable isotopes; that is, they are not radioactive. In addition to these isotopes, many other isotopes of tin are known. In fact, an isotope of every mass number from 108 to 132 is known for tin; however, all those not listed above are radioactive. They are artificially produced as a result of nuclear reactions and exist for only a finite time.

Radioactive isotopes

In some cases, the particular combination of protons and neutrons that make up the nucleus of a given isotope is unstable and undergoes spontaneous change to form a more stable arrangement. Such spontaneous changes are associated with the emission of energy and, in many cases, subatomic particles by the nucleus. Such isotopes are said to be *radioactive*, or *radioisotopes*, and the emission of energy and subatomic particles is referred to as *radioactive decay*. Since these radioactive isotopes undergo spontaneous change to other isotopes of the same element or a different element depending on the type of decay, the chemical quantity of the radioactive isotope does not remain constant but is continually decreasing, unless it is being concurrently formed by the decay of another radioactive isotope. Most elements with atomic numbers up to and including 82 (i.e., lead) have at least one stable isotope as well as a number of radioactive isotopes. However, all elements with atomic numbers greater than 82 have no stable isotope and occur only as various radioactive isotopes, many of which occur naturally. For example, uranium with an atomic number of 92 has three isotopes that occur naturally: $^{238}_{92}U$, approximately 99.27% abundant; $^{235}_{92}U$, approximately 0.72% abundant; and $^{234}_{92}U$, approximately 0.006% abundant. Although some radioisotopes of the heavier elements occur naturally, the radioisotopes of the lighter elements are artificially produced by the bombardment of the element or one of its relatively close neighbors with various subatomic particles.

Symbols

Since the repeated writing of full names of various elements is time-consuming, chemists very early on sought an acceptable uniform shorthand that would cross the language barriers, and a group of universally accepted symbols was developed. In some cases, these symbols are obvious to the modern English-speaking student—e.g., O for oxygen, P for phosphorus, and N for nitrogen—and require no memorization. Others, such as Sn for tin, Fe for iron, and Au for gold, appear to be irrational and must be memorized. It is probably of little consolation to the student trying to learn these symbols that they are derived from Latin; stannum is Latin for tin, ferrum for iron, and aurum for gold. Table 1–1 lists all the ele-

TABLE 1–1.—CHEMICAL ELEMENTS

ATOMIC NUMBER	ELEMENT	SYMBOL	ATOMIC WEIGHT
1	Hydrogen	H	1.008
2	Helium	He	4.003
3	Lithium	Li	6.941
4	Beryllium	Be	9.012
5	Boron	B	10.81
6	Carbon	C	12.011
7	Nitrogen	N	14.067
8	Oxygen	O	15.999
9	Fluorine	F	18.998
10	Neon	Ne	20.179
11	Sodium	Na	22.99
12	Magnesium	Mg	24.305
13	Aluminum	Al	26.982

(Continued)

TABLE 1-1. *(cont.)*

ATOMIC NUMBER	ELEMENT	SYMBOL	ATOMIC WEIGHT
14	Silicon	Si	28.086
15	Phosphorus	P	30.974
16	Sulfur	S	32.06
17	Chlorine	Cl	35.453
18	Argon	Ar	39.948
19	Potassium	K	39.102
20	Calcium	Ca	40.08
21	Scandium	Sc	44.956
22	Titanium	Ti	47.90
23	Vanadium	V	50.941
24	Chromium	Cr	51.996
25	Manganese	Mn	54.938
26	Iron	Fe	55.847
27	Cobalt	Co	58.933
28	Nickel	Ni	58.70
29	Copper	Cu	63.546
30	Zinc	Zn	65.38
31	Gallium	Ga	69.72
32	Germanium	Ge	72.59
33	Arsenic	As	74.922
34	Selenium	Se	78.96
35	Bromine	Br	79.904
36	Krypton	Kr	83.80
37	Rubidium	Rb	85.468
38	Strontium	Sr	87.62
39	Yttrium	Y	88.906
40	Zirconium	Zr	91.22
41	Niobium	Nb	92.906
42	Molybdenum	Mo	95.94
43	Technetium	Tc	98.906
44	Ruthenium	Ru	101.07
45	Rhodium	Rh	102.906
46	Palladium	Pd	106.4
47	Silver	Ag	107.67
48	Cadmium	Cd	112.40
49	Indium	In	114.82
50	Tin	Sn	118.69
51	Antimony	Sb	121.75
52	Tellurium	Te	127.60
53	Iodine	I	126.90
54	Xenon	Xe	131.30
55	Cesium	Cs	132.905
56	Barium	Ba	137.34
57	Lanthanum	La	138.906
58	Cerium	Ce	140.12
59	Praseodymium	Pr	140.908
60	Neodymium	Nd	144.24
61	Promethium	Pm	–
62	Samarium	Sm	150.4
63	Europium	Eu	151.96

TABLE 1-1. *(cont.)*

ATOMIC NUMBER	ELEMENT	SYMBOL	ATOMIC WEIGHT
64	Gadolinium	Gd	157.25
65	Terbium	Tb	158.925
66	Dysprosium	Dy	162.50
67	Holmium	Ho	164.93
68	Erbium	Er	167.26
69	Thulium	Tm	168.934
70	Ytterbium	Yb	173.04
71	Lutetium	Lu	174.97
72	Hafnium	Hs	178.49
73	Tantalum	Ta	180.948
74	Tungsten	W	183.85
75	Rhenium	Re	186.202
76	Osmium	Os	190.2
77	Iridium	Ir	192.22
78	Platinum	Pt	195.09
79	Gold	Au	196.9665
80	Mercury	Hg	200.59
81	Thallium	Tl	204.37
82	Lead	Pb	207.2
83	Bismuth	Bi	208.98
84	Polonium	Po	–
85	Astatine	At	–
86	Radon	Rn	–
87	Francium	Fr	–
88	Radium	Ra	226.025
89	Actinium	Ac	–
90	Thorium	Th	232.038
91	Protactinium	Pa	231.036
92	Uranium	U	–
93	Neptunium	Np	–
94	Plutonium	Pu	–
95	Americium	Am	–
96	Curium	Cm	–
97	Berkelium	Bk	–
98	Californium	Cf	–
99	Einsteinium	Es	–
100	Fermium	Fm	–
101	Mendelevium	Md	–
102	Nobelium	No	–

ments, their symbols, and their atomic numbers and atomic weights. Although it is not necessary to memorize the atomic numbers and atomic weights, it is necessary to recognize the element to which each symbol corresponds. There should be no exceptions to this for elements with atomic numbers below 56; however, for those with atomic numbers greater than 56, the student should recognize all those with which he or she comes into contact.