CHAPTER 9

Uses of Radioactive Tracers

Contents

In this chapter some of the ways in which radiochemistry has aided research in various areas of chemistry and related sciences are reviewed.

The first experiments with radioactive tracers were conducted in 1913 by de Hevesy and Paneth who determined the solubility of lead salts by using one of the naturally occurring radioactive isotopes of lead. Later, after discovery of induced radioactivity, de Hevesy and Chiewitz in 1935 synthesized ^{32}P (β^- $t_{½}$ 14.3 d) and used this tracer in biological studies. In the same year de Hevesy and co-workers also carried out activation analyses on rare

earths. Despite the demonstration of the value of the tracer technique by these early studies the technique did not come into common use until after World War II when relatively large amounts of cheap radionuclides became available through the use of nuclear reactors.

While it is not necessary to use radioactive isotopes for tracer studies, in general, the use of radioactivity is simpler and less expensive than the use of stable isotopes. Research with the latter requires rather sophisticated and expensive measuring devices such as mass spectrometers, cf. §2.3.2. We restrict our discussion to the use of radioactive tracers.

Among the advantages of using radiotracers we can list the following: (a) radiotracers are easy to detect and measure with high precision to sensitivities of 10^{-16} to 10^{-6} g; (b) the radioactivity is independent of pressure, temperature, chemical and physical state; (c) radiotracers do not affect the system and can be used in nondestructive techniques; (d) if the tracer is radiochemically pure, interference from other elements is of no concern (common in ordinary chemical analyses); (e) for most radioisotopes the radiation can be measured independently of the matrix, eliminating the need for calibration curves.

9.1. Basic assumptions for tracer use

In some experiments answers to scientific questions which require knowledge of the presence and concentration of a specific element or compound at a certain place and at a certain time can be obtained only through the use of a radioactive tracer. For example, self diffusion of metal ions in solutions of their salts cannot easily be studied by any other technique. However, in other cases the use of radioactive tracers is not necessary in principle but is justified by the greater convenience. In either type of investigation there are two assumptions implicit in such uses.

The primary assumption is that radioactive isotopes are chemically identical with stable isotopes of the same element, i.e. the substitution of ^{14}C for ^{12}C in a compound of carbon does not change the type or strength of the chemical bonds nor does it affect the physical properties of the compound. The validity of this assumption depends on the precision of measurement of the chemical and physical properties. The difference in mass between the various isotopes does cause some change in these properties (§2.5) but even in the case of ^{14}C and ^{12}C, with a mass difference of approximately 15%, the isotope effect is rather small and difficult to detect. Normally only for systems involving hydrogen-deuterium-tritium substitution must isotope effects be considered. For heavier elements it can be neglected in almost every situation.

The second assumption in the use of tracer techniques is that the radioactive nature of the isotope does not change the chemical and physical properties. Until the moment of its disintegration the radioactive atom is indistinguishable from its stable isotope except for the isotopic mass difference. When the radioactive disintegration of the atom has been observed ("counted"), the decay product is normally a different element and its subsequent chemical behavior is usually of no interest. If the disintegration rate is very high, the energy released by the radioactive decay can cause observable secondary radiolytic effects (Ch. 7). However, in well-designed tracer experiments the level of radioactivity is high enough to provide accurate data but normally small enough not to produce noticeable chemical effects.

While the radioactivity of the tracers is assumed not to affect the chemical systems, the parent-daughter relationship of radioactive nuclides needs special consideration. For

example, since strontium and yttrium are not chemically identical, a gross β-count of strontium samples including ^{90}Sr may include an unknown fraction of ^{90}Y activity present from ^{90}Sr decay because or the relationship

$$^{90}Sr(\beta^-,\ t_{½}\ 28.5\ y)\ ^{90}Y(\beta^-\gamma,\ t_{½}\ 2.671\ d)\ ^{90}Zr(stable)$$

Beta-absorption, and β- or γ-scintillation techniques which use energy discrimination, are frequently useful in such parent-daughter cases. If equilibrium is rapidly established between the parent and daughter activities it is usually simpler to count the samples after sufficient time for this to occur, the contribution to the observed count rate by the daughter is then proportional to the amount of mother in the sample. In the case of ^{90}Sr-^{90}Y, radioactive equilibrium is established in about 25 d. If ^{137}Cs ($\beta^-\gamma$, $t_{½}$ 30.0 y) is being used to study cesium chemistry it is necessary to wait only 15 – 20 min after sampling until counting as the daughter ^{137m}Ba (IT, $t_{½}$ 2.55 min) reaches an equilibrium level within that time. Since the ratio of the ^{137m}Ba and the ^{137}Cs activity is the same in all samples at equilibrium, the total count rate before and after a chemical step is then a true measure of the behavior of cesium alone. If radioactive equilibrium is not re-established in a convenient time, it may be necessary to either discriminate against the activity not involved in the chemical system, to take into account its contributions to the net count rate, or to remove it immediately before counting.

It may be necessary or expedient to use a radioactive nuclide which can undergo significant decay during the chemical investigation. In these cases, in order to compare results at different points in the process, it is necessary to correct all counts to the same time (usually starting time of the experiment).

9.2. Chemistry of trace concentrations

Consider a sample containing a pure radionuclide with a disintegration rate of 10^7 dpm. For a $t_{½}$ of 1 h the number of atoms is (§4.11) 8.7×10^8; for a $t_{½}$ of 1 y it is 7.6×10^{12}. If such a sample is dissolved in one liter of solution, the respective concentrations would be 1.4×10^{-15} M and 1.3×10^{-11} M. At such concentrations the chemical behavior may be quite different than it is at higher concentrations. Addition of macroscopic amounts (e.g. at the gram level) of non-radioactive (isotopic) atoms of the element results in concentrations of 10^{-3} to 10^{-1} M. The non-radioactive component is called a *carrier* as it "carries" the radioactive and ensures normal chemical behavior. Many applications of radiotracers involve mixing the tracer atoms with a much larger amount of nonradioactive isotopic atoms prior to use.

If a radionuclide is to follow the chemical properties of an isotopic carrier it is necessary that the radionuclide and the carrier undergo *isotopic exchange*. If it is not known a priori that such exchange takes place between two compounds with a common element this must be determined by experimentation before it can be assumed that the tracer and the carrier would act similarly in a chemical system. This consideration must be particularly borne in mind if the radioactive tracer and the inert carrier are in different oxidation states when mixed.

In the remainder of this paragraph we discuss the behavior of trace level concentrations as it is desirable in some applications to use very low concentrations of radiotracers with no carrier.

9.2.1. *Adsorption*

Solutes in contact with surfaces have a tendency to be adsorbed on the surface. In order to cover the glass surface of a one liter vessel with a monomolecular layer of a hydrated cation only 10^{-7} - 10^{-8} moles are required. As indicated in the previous paragraph, the amount of radionuclide in the solution may be less than this and, in principle, all the radioactive atoms could be adsorbed on the walls of the vessel. The *Paneth and Fajans rule* for tracer adsorption states that: "a micro component is adsorbed on a solid macro component or precipitated together with it if it forms an insoluble compound with a counter ion of the macro component".

The amount of radionuclide that is adsorbed on the walls of the container depends on the concentration, on the chemical state of the radionuclide and on the nature of the container material. Figure 9.1 shows the variation of the adsorption of thorium on the walls of glass and polyethylene containers as a function of concentration and pH. In case (a) the sorption time is that of pipetting (of an aqueous Th-complex), in case (b) it is that for equilibrium. The variation of adsorption with pH reflects the adsorption of various hydrolytic species formed by thorium as the pH is increased. Curve (a) shows that sorption can be neglected at concentrations $> 10^{-4}$ M in this system.

In general adsorption of cations increases with ionic charge in the order $M^{+} < M^{2+} < M^{3+} < M^{4+}$. The importance of the nature of the surface is obvious in Figure 9.1.b. Adsorption of Pm(III) ions have been shown to increase in the order platinum < silver < stainless steel < polyvinyl chloride. Addition of isotopic carrier dilutes the radiotracer and a smaller fraction of tracer is adsorbed (Fig. 9.1.a). Unfortunately, such isotopic dilution results in a decrease in the specific activity of the trace element, which can be disadvantageous in certain types of experiments. In some cases it is possible to avoid

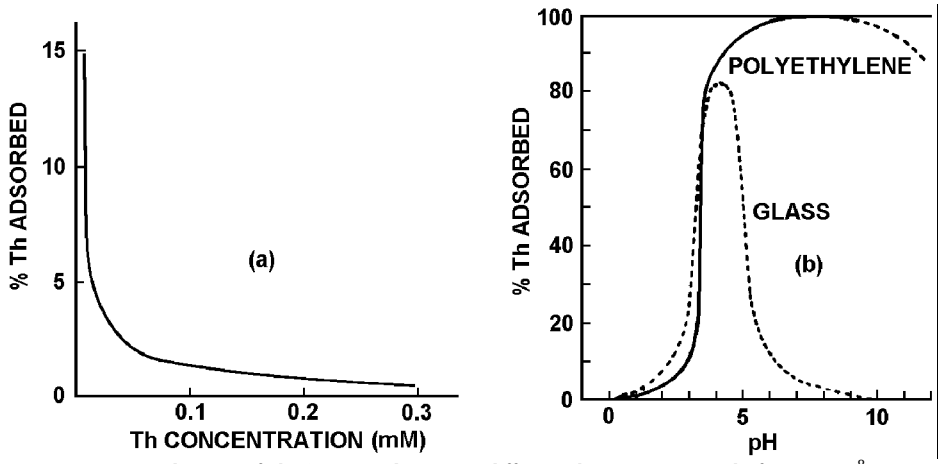

FIG. 9.1. Adsorption of Th (a) in a 10 ml pipette at different Th concentrations, (b) from 2×10^{-8} M $Th(ClO_4)_4$ solution on different surfaces and pH's. (From Rydberg and Rydberg.)

decreasing the specific activity by adding macro amounts of a nonisotopic element which is easily adsorbed and may block the available surfaces from adsorbing the tracer.

In addition to adsorption on the walls of the container, radioactive species frequently adsorb on precipitates present in the system. The nature of the precipitate as well as its mode of precipitation are major factors in the amount of adsorption. If silver iodide is precipitated in an excess of silver ion the precipitate has a positive surface layer due to the excess concentration of silver ions on the surface. By contrast if the precipitation occurs in excess iodide, there is a negative surface charge due to the excess iodide on the surface. When trace amounts of radioactive lead ions are added to a suspension of two such precipitates in water, the precipitate with the negative surface charge adsorbs > 70% of the tracer lead ions from the solution, while the precipitate with the positive surface charge adsorbs < 5%. The amount of adsorption increases with the ionic charge of the radioactive tracer, e.g. it has been found that with a precipitate of Ag_2S about 7% of Ra^{2+}, 75% of Ac^{3+} and 100% of Th^{4+} is adsorbed.

The adsorption properties of trace elements have been used to advantage for the isolation of the trace elements as well as for the separation of different trace elements with different adsorption properties.

9.2.2. *Radiocolloids*

Radioactive tracers adsorb not only on solid container surfaces and precipitates but on any kind of solid material suspended or in contact with the solution. Dust, cellulose fibers, glass fragments, organic materials, etc., are examples of substances that readily adsorb radioactive tracers from solution. If the solution contains large molecules as, for example, polymeric metal hydrolysis products, these also tend to adsorb trace elements. In addition to sorption, the presence of such material in the solution can lead to the phenomenon of radiocolloid formation, which is the attachment of radionuclides to semicolloidal aggregates in solution. If the solution is kept at sufficiently low pH and extremely free from foreign particles, sorption and radiocolloid formation are usually avoided as major problems.

9.2.3. *Equilibrium reactions*

The low concentration of radioactive tracers can lead to the formation of solute species that are not observed at equilibrium with macro amounts. For example, the hydrolysis of uranyl ions corresponds to the equilibrium

$$m\ UO_2^{2+} + p\ H_2O \rightleftarrows (UO_2)_m(OH)_p^{2m-p} + p\ H^+$$

With macro concentrations of uranium this equilibrium is shifted to the right with the observation of polymers with properties rather different than that of the uranyl ion. At a uranium concentration of approximately 0.001 M, more than 50% of the uranium is polymerized at pH 6, while for uranium concentrations less than 10^{-6} M the polymerization is negligible. This condition can be used to advantage: trace metal concentrations can be used if one wishes to study the properties of a metal ion at relatively high pH's without

interference of polymerization reactions. However, one then must be aware of the adsorption risks.

An additional complication can arise in solution if the radioactive species in trace amounts react with trace concentrations of impurities. For example, in an investigation of the properties of pentavalent protactinium, Pa(V), it was found that the protactinium was extracted into pure xylene from 1 M $HClO_4$ solutions. Further experimentation showed that this extraction was due to the presence in the xylene of organic impurities at concentrations below the detectable limit of 0.01%. Support for this interpretation was provided when the solution was made 10^{-4} M in thorium, which was expected to form complexes with the probable impurity, thereby preventing the reaction with the protactinium. In fact, no protactinium was extracted into xylene from this solution. The thorium in this case acts as a *hold-back carrier*.

9.2.4. *Precipitation and crystallization*

Due to the low concentration of radioactive tracers in solution the solubility product for an "insoluble" salt is not always exceeded upon the addition of macro concentrations of a *counter ion*. Let us as example take the insoluble lanthanum hydroxides. The solubility product for the reaction $La(OH)_3$ (s) $\rightleftarrows$ La^{3+} + 3 OH^- is $K_{s0} \approx 10^{-19}$; in 1 mM NaOH the concentration of La^{3+} in the solution is only 10^{-10} M in equilibrium with the $La(OH)_3$ precipitate. If 100 MBq (2.7 mCi) ^{140}La, obtained as a fission product or by milking from ^{140}Ba (Table 4.1), is dissolved in 1 l, the solution will have $[La^{3+}] \approx 3.5 \times 10^{-11}$ M. In this case the solubility product is not exceeded in 1 mM NaOH. To precipitate the $La(OH)_3$ quantitatively the NaOH concentration must be raised to 10 - 100 mM; however, at these concentrations the precipitate is formed as a colloid in solution and even upon centrifugation the amount of precipitate is so small as to be unweighable by present techniques. With the addition of a *carrier* for ^{140}La, the precipitation can be carried out without any difficulty.

It is possible to remove ions at tracer level concentrations from solutions by precipitation using adsorption or coprecipitation. *Coprecipitation* occurs if the compound of the tracer and the oppositely charged ion of the precipitate is isomorphous with the precipitate. In these cases the active ion may be included in the crystal lattice of the precipitate at a lattice point, particularly if the tracer ion is close in size to the ion which it displaces. However, at trace level concentrations exceptions are found to this requirement of similarity in size as well as to the requirement of isomorphism. When the distribution of the tracer is found to be uniform throughout the precipitate it can be described by the *Berthelot-Nernst homogeneous distribution law* which is expressed as

$$x/y = D' (a - x)/(b - y) \qquad (9.1)$$

where x and y are the amounts of A^{z+} and B^{z+} in the precipitate, a and b are the initial amounts of these ions, and D' is the "distribution coefficient". A more "true" distribution constant (D = concentration of tracer in solid/concentration of tracer in solution) can be obtained by using a conversion factor, e.g. C = gram solute per ml of saturated carrier solution divided by the density of the solid

$$D' = D\,C \tag{9.2}$$

The entire precipitate is in equilibrium with solution in this system.

If only the freshly forming surface of the growing crystal is in equilibrium with the solution phase, a nonuniform distribution is observed. In these cases the system is described by a logarithmic (according to Doerner and Hoskins) distribution law, which has the form

$$\ln[a/(a - x)] = \lambda' \ln[b/(b - y)] \tag{9.3}$$

where λ' is the *logarithmic distribution coefficient*, a constant characteristic of the system (Fig. 9.2).

The importance of isomorphism can be illustrated by the coprecipitation of Ra^{2+} in trace quantities with Sr^{2+} in strontium nitrate. If the precipitation is carried out at 34°C, the radium coprecipitates since at this temperature the strontium precipitates as $Sr(NO_3)_2$ with which radium nitrate is isomorphous. However, if the precipitation occurs at 4°C, the strontium crystallizes as $Sr(NO_3)_2{\cdot}4H_2O$ and is no longer isomorphous with $Ra(NO_3)_2$. Due to the lack of isomorphism the radium is not coprecipitated at 4°C.

9.2.5. *Electrochemical properties*

For the redox equilibrium

$$M^{z+} + ne^- \rightleftarrows M^{z-n} \quad (n \geq 1)$$

where M^{z+} and M^{z-n} are the oxidized and reduced states of a chemical species, the *Nernst equation* is valid, i.e.

$$E = E^0 - \{\mathbf{R}T/(n\mathbf{F})\} \ln([M^{z-n}]/[M^{z+}]) \tag{9.4}$$

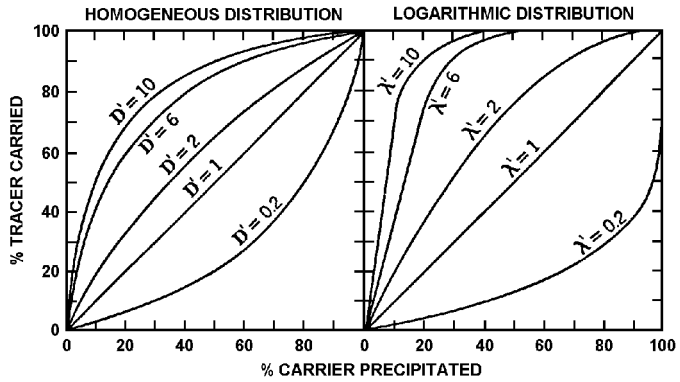

FIG. 9.2. Efficiency with which the tracer is carried for various values of the distribution coefficients D' and λ'. (From Wahl and Bonner.)

In this equation E^0 is the potential for a standard state of 1 M concentration; the species in brackets relates to the chemical activities in the particular solution phase. This relationship indicates that the redox potential E of a solution is independent of the total concentration of the species and depends only on the ratio of the oxidized and reduced forms. This has been confirmed since concentrations of trace amounts of ions show the same redox behavior as macro concentrations. Reduction and oxidation reactions can, therefore, be carried out in solutions with trace amounts of radioactive species.

Electrolysis of solutions can be used for electrodeposition of a trace metal on an electrode. The selectivity and efficiency which would be present for electrolytic deposition of macro amounts of ions at a controlled potential is not present, however, for trace amounts. The activity of trace amounts of the species is an unknown quantity even if the concentration is known, since the activity coefficient is dependent upon the behavior of the mixed electrolyte system. Moreover, the concentration of the tracer in solution may not be known accurately since there is always the possibility of some loss through adsorption, complex formation with impurities, etc. Nevertheless, despite these uncertainties it has been found that the Nernst equation can be used, with some caution, for calculating the conditions necessary for electrolytic deposition of trace metals.

It is also possible to precipitate insoluble species on electrodes. For example, if a fluorosilicate solution is electrolyzed, thereby freeing a high concentration of fluoride ion at the electrode, a thin uniform layer of UF_4, can be deposited. Similarly, trace amounts of elements which form insoluble hydroxides can be deposited from solutions in which water is being electrolyzed as a region of extremely high pH is present at the cathode.

9.2.6. *Tracer separation methods*

All the analytical techniques used in conventional chemistry may be used for the separation and isolation of radioactive elements and compounds in macro or trace concentrations. The precipitation method was amply demonstrated by the early radio-chemists M. Curie, Debierne, Rutherford, Hahn, etc., for the separation, concentration and identification of the naturally occurring radioactive elements. However, in §§9.2.1-9.2.4 we have pointed out the many pitfalls in working with tracer concentrations in solutions containing precipitates, etc, as well as in the use of electrochemical methods (§9.2.5).

Normally these separation methods require the addition of a macro amount of isotopic carrier. However, in some cases analytical procedures are available for separation and isolation of carrier free radiotracer concentrations. *Solvent extraction* (see §9.4.3 and App. A), and various forms of *partition chromatography* (§9.4.1), methods have been found to be particularly advantageous in this connection since they are selective, simple, and fast.

Liquid-liquid (or *solvent*) *extraction* is a technique for selectively transferring a species between an aqueous solution and an organic phase (e.g. kerosene, benzene, chloroform, etc) by equilibrating the aqueous phase with an organic solvent. Usually the organic phase contains a reagent A (*extractant*) which forms a neutral compound MA_N with the species M to be transferred between the phases. The number of extractants applied are numerous and the literature must be consulted to determine the most suitable ones for the system of interest; typical extractants are organophosphates, amines and metal chelating agents (usually weak organic acids). The fraction extracted at equal phase volumes is

$$E\ \% = 100\ D/(D + 1) \tag{9.5}$$

where D is the *distribution ratio* of the radioactivity between the two phases

$$D = R_{org}/R_{aq} = \psi_{org}A_{org}/\psi_{aq}A_{aq} \approx N_{org}/N_{aq} = [M]_{org}/[M]_{aq} \tag{9.6}$$

The last equality requires that the radioactive measurements R are carried out on equal phase volumes (eventually evaporated to dryness) and that $\psi_{org} = \psi_{aq}$, a requirement easily met by proper choice of radiometric equipment. Thus the D-value directly reflects the concentration ratio of the radioactive species. Figure 9.3 shows as an example how the extraction of a number of metals from an aqueous into an organic solution varies with pH. Such curves are used to select optimal separation conditions: in the Figure at pH < 3.5, Pd, Fe and Ni are extracted to 100% into chloroform, while all the Co and Mn stays in the aqueous phase, thus facilitating an easy separation of these two groups of metals.

This technique has a number of applications, i.e.

- on a large scale for the production of valuable metals, such as U, described in §5.5.3,
- for reprocessing spent nuclear fuels as described in Ch. 21,
- at trace metal concentrations for determining equilibrium constants as described in §9.4.3,
- for separation and identification of short lived radionuclides as described in §15.7.

Solid organic resin *ion exchangers* consist of organic polymeric networks containing basic or acidic groups attached to the organic framework. Analogous to (9.6) a distribution ratio D_{iex} is defined as

$$D_{iex} = [M]_{resin}/[M]_{sol} \tag{9.7}$$

for the distribution of a (e.g radioactive) metal between the solid resin and the aqueous solution. D_{iex} depends on resin properties and on solution parameters such as the nature of the metal ion, ionic strength of the solution, temperature, etc. The basic equilibria are discussed in §9.4.3. Because the sorption in the resin phase increases with the valency of the cation, multivalent ions are absorbed more strongly (i.e. have larger D_{iex} values) than divalent or monovalent ions. Most commonly ion exchange columns are used for metal ion separations. In this case, the radioactivity is sorbed in the top layer of a column of the wet

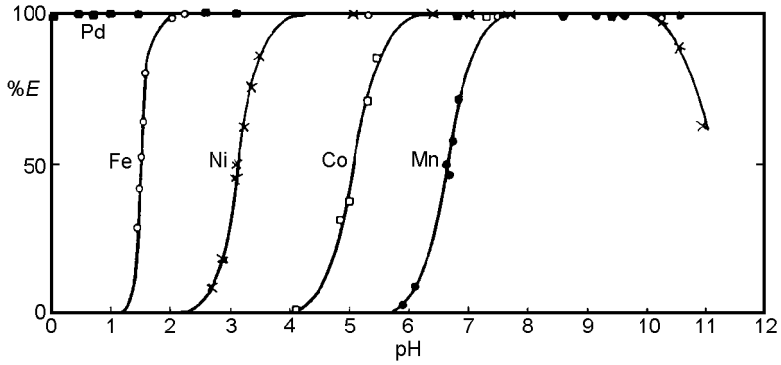

FIG. 9.3. Effect of pH on the extraction of some divalent metals from aqueous solution into chloroform by 0.01M 8-hydroxyquinoline (oxine).

ion exchange resin. Following sorption (e.g. of M^+), the metal is eluted from the resin bed by passage of a solution (eluant) through the column. The eluant may contain a complexing anion or another metal ion (e.g. M^{3+}) which displaces M^+ through competition with it for positions on the resin. The metals are eluted by complexing agents in an order depending on their complex formation properties, as e.g. is illustrated for the lanthanides and actinides in Chapter 16 (Fig. 16.7).

In principle, *liquid partition chromatography* (LPC) is a liquid-liquid extraction where one of the liquid phases is stationary and attached to a supporting material, and the other liquid phase is mobile. It can be carried out with either the aqueous or the organic phase stationary; in the latter case the technique is referred to as reversed phase LPC. The aqueous phase can be made stationary by adsorption on silica gel, cellulose powder, etc. In order to make the organic phase stationary, beads (usually 50 - 200 μm) of PVC, teflon, Kel-F, etc., are being used.

Reversed phase LPC has been useful in radiochemistry for separating individual elements, e.g. lanthanides or actinides. It has also been used for separation of macro amounts of actinides. Instead of using columns in partition chromatography, a sheet of paper may be used to hold the stationary phase (*paper chromatography*) or an adsorbent coated on a glass plate (*thin-layer chromatography*). This technique has an advantage over column separations because the positions of the radioactive species are easily identified on the sheet, either simply by autoradiography (§9.4.4) or by scanning instruments. Paper chromatography is further described in an example in §9.4.1 and illustrated by Figures 9.7 and 9.8.

9.3. Analytical chemistry

9.3.1. *Radiometric analysis*

The term radiometric analysis is often used in a broad sense to include all methods of determination of concentrations using radioactive tracers. In a more restricted sense it refers to a specific analytical method which is based on a two-phase titration in the presence of a radioactive isotope. The endpoint of the titration is indicated by the disappearance of the radioisotope from one of the phases. Figure 9.4 illustrates two cases, (a) the determination of Ag^+ in a solution by titration with NaI solution containing $^{129}I^-$ ($\beta^-\gamma$ $t_{½}$ 1.57×10^7 y),and (b) the determination of Fe^{2+} in an aqueous solution, to which trace amounts of radioactive $^{55}Fe^{2+}$ (EC $t_{½}$ 2.73 y) has been added. In case (a) the AgI precipitate is radioactive but the solution has little radioactivity until all the Ag^+ has been precipitated. The activity of the solution is measured by a liquid flow GM-detector (Ch. 8). In the latter case (b) a two-phase liquid-liquid analytical technique is used (§9.2.6); the titrant contains a substance (oxine) which extracts Fe(II) from the aqueous to the chloroform phase. The radioactivity of the organic phase is followed by liquid scintillation (sampling) to determine the end point of the titration.

Radiometric analysis is simple and rapid. Nevertheless, it is rarely used in analytical routine work, as a large number of multiple-element "instrumental" techniques are readily available (though the instruments usually are more expensive). Its most extensive use is for calibration of other techniques, and in analytical comparative techniques (e.g. environmental

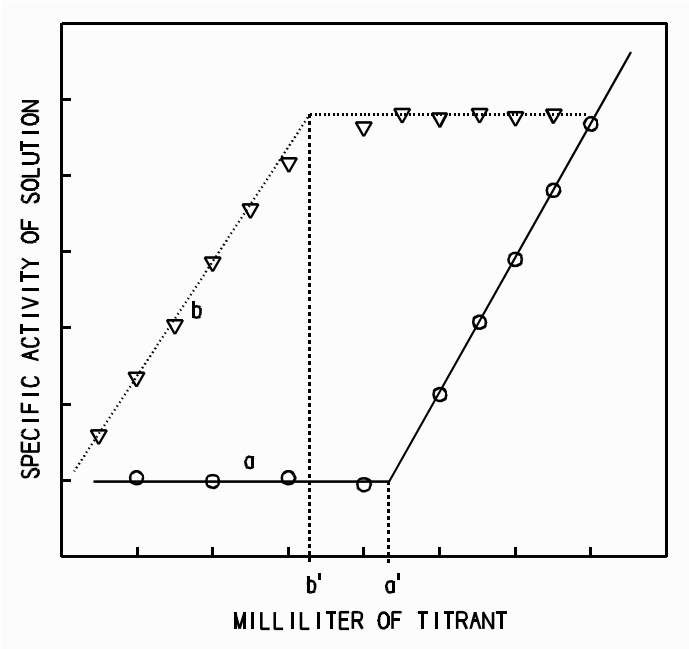

FIG. 9.4. Radiometric titration curves.

samples). In some cases results from different laboratories on common samples using various analytical techniques have differed by factors of 10^3 to 10^5 ! Because the radioactive tracer can be proven to be "atomically pure" (i.e. the radiation given off is unique for the radioisotope and element), it offers an absolute standard.

9.3.2. *Isotope dilution analysis using radiotracers*

In complex mixtures of compounds (for example, in organic synthesis or biochemical systems) it may be quite difficult to ascertain the exact amount of a specific component. A widely used technique of considerable value is *isotope dilution analysis*. This can be applied either with stable isotopes, in which case the detector is a mass spectrometer, or with radioactive isotopes, using measuring techniques presented in Chapter 8. The use of stable isotopes is usually limited to geologic samples, as described in §2.3, but may be applied to biological samples using highly enriched ^{13}C, ^{15}N or ^{18}O. However, the technique with radiotracers is more common due to its simplicity and lower cost.

A small radiochemically pure amount (w_0 g) of the selected compound ("reference") is added to the complex sample containing the unknown amount (w_u g) of the same compound. The reference may be either an element or a labeled compound, whose specific activity is known (S_0 Bq/g). After intimate mixing, the selected compound is isolated in high purity but not necessarily in high yield. The separated compound is weighed (w_m, g) and counted (R_m Bq) so that its specific activity (S_m, Bq/g) can be calculated. The method is pictured schematically in Figure 9.5. The weight, w_u, of the selected compound present

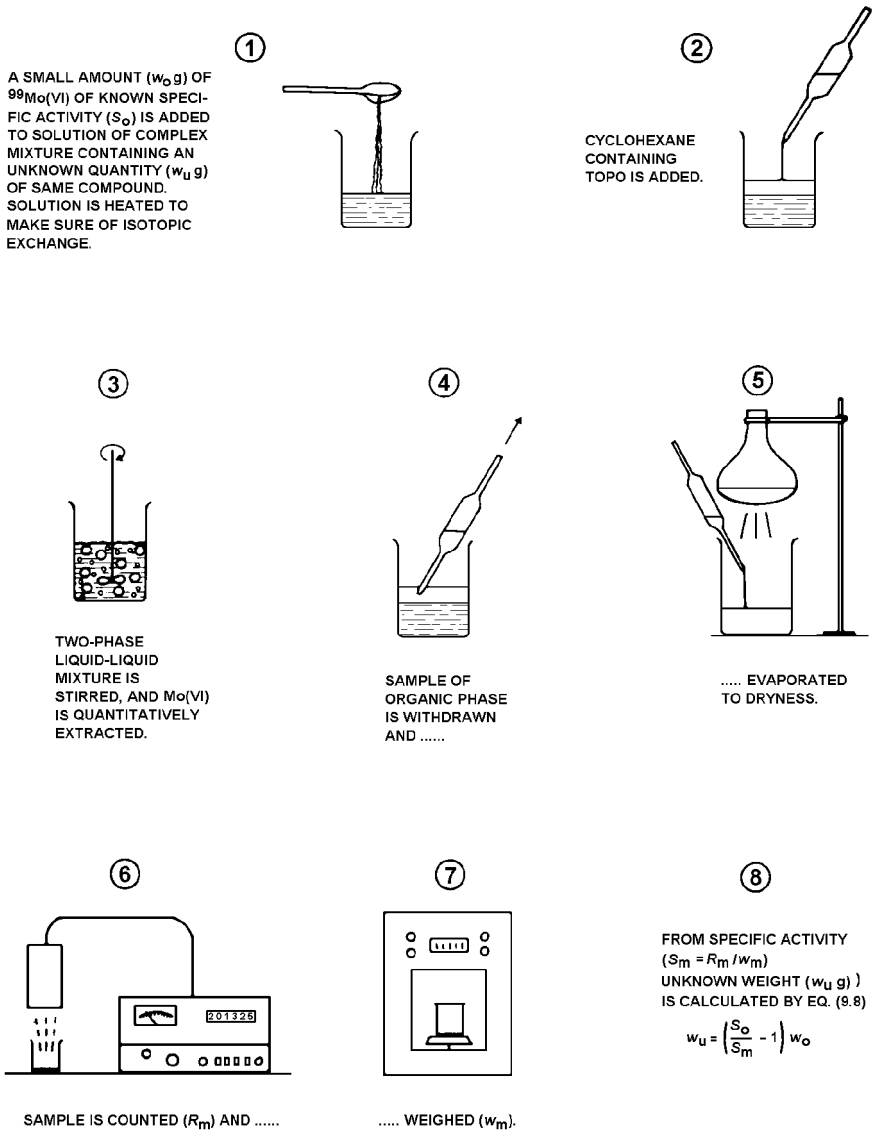

FIG. 9.5. Sequence of steps in isotope dilution for determining the amount of a Mo(VI) complex in a composite mixture.

in the original sample is calculated by

$$w_u = (S_0 / S_m - 1) w_0 \tag{9.8}$$

The specific activity is defined by (4.49): $S = A/w$ Bq g^{-1}; since only the ratio S_0 / S_m is used in (9.8), the activity A can be replaced by the measured radioactivity R when the detection efficiency ψ is the same.

This technique is of particular advantage where quantitative separation of the desired compound is not feasible, as illustrated already by de Hevesy in 1932: In determination of micro amounts of lead by anodic precipitation, quite varying results were obtained. By addition of a known amount of "radiolead" and measuring the radioactivity of lead at the anode, the yield of the precipitation could be determined, and - although the electrolytic precipitation was inefficient - an exact analysis was obtained.

In some cases the measurement of the final sample utilizes a technique other than weighing, but the principle remains the same. Isotope dilution is used, for example, in the determination of naphthalene in tar, of fatty acids in mixtures of natural fat, of amino acids in biological material, etc.

9.3.3. *Activation analysis*

Activation analysis is a highly sensitive nondestructive technique for qualitative and quantitative determination of atomic composition of a sample. It has been particularly useful for determination of elements in complex samples (minerals, environmental samples, biological and archeological objects, etc.), because it provides a simple alternative to much more difficult, tedious and destructive techniques. Its main limitation is the demand for a strong irradiation source.

In activation analysis advantage is taken of the fact that the decay properties such as the half-life and the mode and energy of radioactive decay of a particular nuclide serve to identify uniquely that nuclide. The analysis is achieved by the formation of radioactivity through irradiation of the sample either by neutrons or charged particles. Neutron irradiation is by far the more common technique, and hence this method is often referred to as *neutron activation analysis*, NAA. A major advantage in activation analysis is that it can be used for the simultaneous determination of a number of elements and complex samples. If the counting analysis of the sample is conducted with a Ge-detector and a multichannel analyzer, as many as a dozen or more elements can be measured quantitatively and simultaneously (*instrumental NAA*, or *INAA*).

A sample is irradiated to form an amount R of radioactive nuclide according to the relationship (cf. §15.2):

$$R = \psi \phi \sigma N (1 - e^{-\lambda t_{irr}}) e^{-\lambda t_{cool}} \tag{9.9}$$

We assume that irradiation is carried out by a homogeneous particle flux ϕ, in a neutron reactor. The minimum amount of an element which can be detected increases with the efficiency of the measuring apparatus ψ, the bombarding flux ϕ, the reaction cross-section σ, the irradiation time t_{irr} (up to saturation activity), the decay constant, λ, of the radioactive nuclide formed, and the time from end of bombardment to start of counting, t_{cool}. By proper selection of t_{irr} and t_{cool} the sensitivity for any element can be changed and interferences minimized. Table 9.1 shows the limits of detection in INAA.

TABLE 9.1. *Limits of detection for 71 elements in a thermal neutron flux of 10^{17} n m^{-2} s^{-1} (1 h irradiation)*

Limit of detection (μg)	Elements
$1–3\times10^{-6}$	Dy
$4–9\times10^{-6}$	Mn
$1–3\times10^{-5}$	Kr, Rh, In, Eu, Ho, Lu
$4–9\times10^{-5}$	V, Ag, Cs, Sm, Hf, Ir, Au
$1–3\times10^{-4}$	Sc, Br, Y, Ba, W, Re, Os, U
$4–9\times10^{-4}$	Na, Al, Cu, Ga, As, Sr, Pd, I, La, Er
$1–3\times10^{-3}$	Co, Ge, Nb, Ru, Cd, Sb, Te, Xe, Nd, Yb, Pt, Hg
$4–9\times10^{-3}$	Ar, Mo, Pr, Gd
$1–3\times10^{-2}$	Mg, Cl, Ti, Zn, Se, Sn, Ce, Tm, Ta, Th
$4–9\times10^{-2}$	K, Ni, Rb
$1–3\times10^{-1}$	F, Ne, Ca, Cr, Zr, Tb
10–30	Si, S, Fe

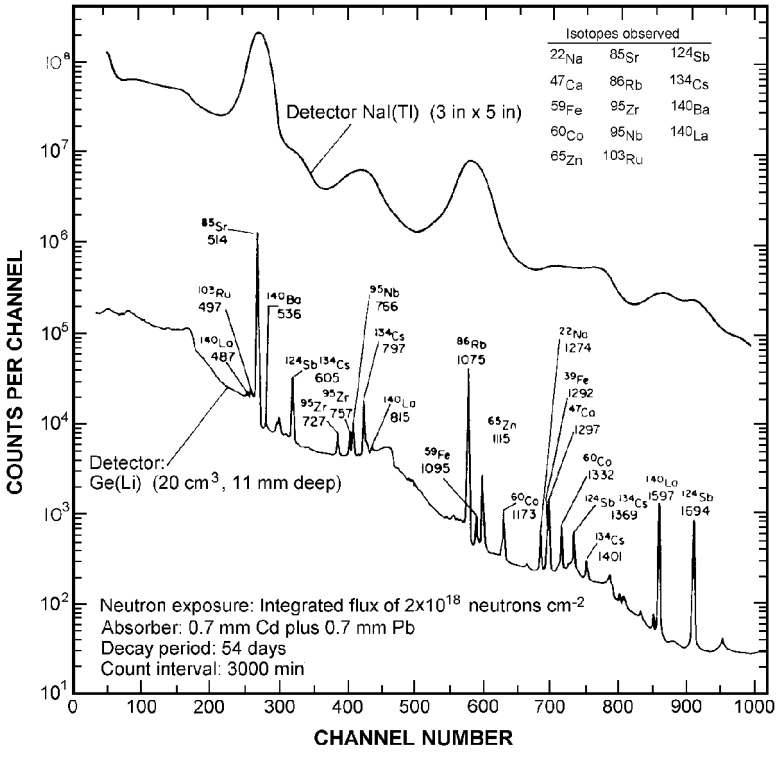

FIG. 9.6. γ-spectrum of neutron-activated sea water. (From Cooper, Wogman, Palmer and Perkins.)

Figure 9.6 shows a typical NAA spectrum obtained with a multichannel analyzer equipped with scintillation (upper curve) or semiconductor (lower curve) detectors. Each peak can be ascribed to a certain γ-energy, which in most cases identifies the nuclide. A number of nuclides can be identified simultaneously with semiconductor detectors, but with NaI(TI) scintillation detectors the poor resolution limits simultaneous multi-element analysis.

The area under the peak (shaded area in Fig. 8.5(b)) is proportional to the amount of the radioactive nuclide. If all other factors in (9.9) are known, the number of target nuclide atoms N can be calculated.

When complex mixtures are irradiated, such as geological or biological samples, there may be some difficulties in peak assignment. The energy spectrum is then scanned at repeated time intervals and from the decrease of the peak area with time the half-life of the peak may be established. This is a valuable additional aid in the assignment of the peak to a certain nuclide.

While in principle it is possible to calculate the amount of the desired element through the use of the proper values for the cross-section, flux, irradiation time, and half-life in (9.9), a simpler approach has been developed that avoids errors implicit in the uncertainties of each of these values. The unknown and a known standard of similar composition are irradiated and counted in an identical fashion. A direct comparison can be made according to the following relationship:

$$\frac{\text{Weight of element in unknown}}{\text{Weight of element in standard}} = \frac{\text{Activity of element in unknown}}{\text{Activity of element in standard}}$$

or

$$w_u / w_0 = R_u / R_0 \tag{9.10}$$

Sometimes such a large number of competing radioactivities are produced in the bombardment process that it may be necessary to conduct some chemical purification (RNAA, radiochemical NAA). This is particularly true if simple counting of β-activity or γ-ray spectrometry using NaI(TI) counting is used. However, with the development of semiconductor detectors and INAA the increased resolution in the spectrum allows simultaneous determination of as many as 15 or 20 competing radioactivities, usually without the necessity of chemical purification. Analysis of trace constituents in air and water, in soil and geological samples, in marine and in biological systems are some of the interesting applications of the NAA technique. Examples of on-line NAA include sorting ore minerals and oil well logging. In forensic science, by using NAA to measure the composition of the material adhering to a hand which has held a gun during firing, it is possible to determine the type of ammunition and even the number of shots fired. Trace metal analysis of plants can be used to determine the location in which that plant has been grown (used, for example, for identification of marijuana growers). The trace constituents of archeological and art objects play an important role in ascertaining their authenticity and the identification of place of origin; the use of nondestructive NAA has been extremely valuable in this field. Activation analysis of the mineral content of pigments has enabled scientists to determine the authenticity of paintings attributed to certain artists since, in times past, each artist prepared his own paints by distinctive and individual formulae. A

painting entitled "Christ and Magdalene" done in the Old Dutch style was proved to be a twentieth century forgery when NAA showed < 7 ppm silver and < 1.3 ppm antimony in the white lead paint. The sixteenth and seventeenth century Dutch paintings have white lead with about 10 - 1000 ppm silver and 50 - 230 ppm antimony.

It has been found that hair contains trace metals (e.g., Cu, Au, Ce, Na) in ratios which are typical for a particular individual, and activation analysis can be used to identify hair from a particular person. This application achieved public notice when it was found that hair from Napoleon had a relatively large amount of arsenic, indicating that some time prior to his death he had received large doses of arsenic. Through analysis of the hair of the Swedish king Erik XIV (who died suddenly in 1577 after a meal of pea-soup) it has been found that he must have received lethal amounts of arsenic as well as large amounts of mercury. The latter is assumed to have been taken into his body through the use of a mercury compound for treatment of an old wound.

The high sensitivity of activation analysis has made it very useful in environmental pollution studies. Table 9.2 lists the limits of detection for some elements in sea water under the conditions specified in the table.

Elements with very low sensitivity for thermal neutron bombardment (e.g. the lightest elements) can often be measured through irradiation with either fast neutrons (FNNA) or charged particles (CPAA); in the latter case eqn. (9.9) must be modified, see §15.2. Thus oxygen can be analyzed by bombardment with 14 MeV neutrons (σ = 37 mb) yielding ^{16}N, which decays ($t_{½}$ 7.13 s) by emitting energetic β^- and γ (6 - 7 MeV). In FNAA and CPAA the flux may not be homogeneous, and (15.7) - (15.9) must be used. CPAA is usually employed for elements of atomic number less than 10 and is normally limited to surface analysis because of the short range of charged particles in solid materials. Surface concentrations of 0.01 - 0.02 $\mu g/cm^2$ can be detected. Irradiation by protons, deuterons,

TABLE 9.2. *Estimated minimum detectable concentrations of pollutant elements in sea water by INAA and by RNAA*

Trace element	Typical reported concentrations in open ocean ($\mu g\ l^{-1}$)	Minimum detectable concentrations ($\mu g\ l^{-1}$)	
		INAA[a]	RNAA[b]
Hg	0.02–0.2	0.05	0.001
Cd	0.06–0.7	16 000	0.001
Ag	0.002–0.05	1.0	0.003
As	2–3	Not possible	0.000 1
Cu	0.5–2	Not possible	0.002
Cr	0.02–0.6	0.3	0.003
Zn	0.5–10	0.2	0.01
Sn	0.02	Not possible	9
Se	0.08	0.2	0.02
Sb	0.2	0.02	0. 000 03

[a] 25 ml sea water; 1 d irradiation at 10^{17} n m^{-2} s^{-1}; 40 d decay; 1000 min count on 20 cm^3 Ge(Li)-detector; based on 3 × above background-Compton contribution in peak areas.

[b] 500 ml sea water; elements chemically separated; 1 d irradiation at 10^{17} n m^{-2} s^{-1}; 3 d decay; 500 min count on 20 cm^3 Ge(Li)-detector; based on 2 × above background-Compton contribution in peak areas.

and ^{4}He have all been used. This technique should not be confused with PIXE described in §6.8.2. In PIXE high energy protons are used to induce X-ray fluorescence in the sample, and the analysis with the multichannel spectrometers is done simultaneously with the bombardment. In activation analysis the sample is counted after the end of the irradiation. Generally, charged particle irradiation techniques are more expensive than neutron activation analysis.

9.3.4. *Substoichiometric analysis*

Isotope dilution analysis require the determination of either the chemical yield in the separation process or of the specific activity. This can be avoided by applying the *substoichiometric principle*, which may also increase the sensitivity of the analytical method.

The method requires three samples: (1) the test sample containing the unknown weight w_u of the element or compound X of interest; (2) a standard of the same element (preferably in a similar matrix, subscript s); and (3) a nonactive carrier (usually a solution, subscript c), of the same element or compound X.

If a test sample containing the unknown weight w_u of the element or compound X and a standard containing a known weight w_s^0 of the same are irradiated under identical conditions,

$$w_u = w_s^0 A_u / A_s \tag{9.11}$$

where A_u and A_s (or R_u and R_s, if measured under identical conditions) are the total radioactivities contained in sample and standard. If the test sample contains other radioactivities in addition to that in the standard, the preceding relation can be applied only when the measurement technique is isotope specific, for example, when high-resolution gamma spectroscopy is used, in which case interference from undesirable radioactivity is eliminated.

When simple counting equipment must be used or highly complicated test samples are involved, it may be desirable to isolate chemically the element or compound of interest. This can be done through selective chemical procedures using a *non-radioactive carrier* of element X. The carrier is added to the irradiated test sample (containing w_u), which is processed through the different purification steps. Finally a sample of almost (or sufficiently) pure X is isolated, and its activity R_{u+c} and weight w_{u+c} measured. It is also necessary to run the irradiated standard with added carrier through the same chemical separation procedures. With the exception of w_u, the final equation (9.12) has terms that are known or measured:

$$w_u = w_s^0 \{R_{u+c}(w_c^0 + w_u)/w_{u+c}\}/\{R_{s+c}(w_{s+c}^0 + w_s^0)/w_{s+c}\} \tag{9.12}$$

Usually, the amount of carrier is much greater than the unknown and the standard, that is, $w_c^0 \gg w_s^0$, and $\gg w_u^0$. Then if equal amounts (by weight) of the nonactive isotopic carrier are added to the unknown sample and the standard, the equation reduces to

$$w_u = w_s^0 (R_{u+c} w_{s+c})/(R_{s+c} w_{u+c}) \tag{9.13}$$

This equation can be simplified even further. In the chemical separation procedure a *substoichiometric amount* of reagent is added, provided the conditions are such that this reagent quantitatively reacts with X. For example, zinc is extracted quantitatively from aqueous solutions buffered at pH 8 by dithizone in chloroform. If the amount of dithizone is less than that of zinc after adding a carrier of nonradioactive $ZnSO_4$, only part of the zinc (e.g., 25%) is extracted, but the dithizone is quantitatively bound to zinc in the organic phase. Thus varying amounts of zinc in the aqueous phase do not change the amount in the organic phase, which is constant, though the specific activity varies. The two chloroform solutions, from test plus carrier, and from standard plus carrier, contain equal amounts of Zn. Liquid-liquid extraction is commonly used for this technique.

The foregoing is an example of the basic principle of substoichiometric analysis. Under these conditions $w_{s+c} = w_{u+c}$ and

$$w_u = w_s^0 R_{u+c}/R_{s+c} \tag{9.14}$$

Thus by carefully choosing proper experimental conditions, the analytical procedure is reduced to two radioactivity measurements. For precise results the value of w_u must be comparable to w_s^0, which can be ascertained by a few initial survey experiments.

This substoichiometric analysis technique can be applied to most metals with a high degree of accuracy and a sensitivity of 10^{-6} to 10^{-10} g of X.

When the substoichiometric principle is applied to isotope dilution analysis, the relationship becomes

$$w_u = w_s^0 (R_s/R_{u+s} - 1) \tag{9.15}$$

where w_s^0 is the weight of the standard added, and R_s and R_{u+s} the radioactivities measured from the substoichiometrically separated samples of the standard and of the mixture of standard and unknown. The specific activities need not be determined as in (9.8) because equal weights of standard (w_s) and sample plus standard (w_{u+s}) are isolated by using the substoichiometric principle.

The usefulness of this technique for routine determination of numerous chemical elements in various matrixes has been demonstrated by Ruzicka, Stary, and others. It is also applicable to organic compounds and known in medicine as radioimmunoassay.

9.4. Applications to general chemistry

In no other area have radioactive tracers played such an important role as in the studies of chemical and biological reaction paths. This is, of course, due to that, in principle, in each radioactive decay the atom announces its position. Thus the detection sensitivity can approach the ultimate limit. A radioactive nuclide, as for example ^{14}C (β^- $t_{½}$ 5730 y), ^{32}P (β^- $t_{½}$14.282 d), or ^{198}Au ($\beta^-\gamma$, $t_{½}$ 2.6935 d), can be followed through a number of different chemical reaction steps, revealing details of metabolic or process reactions impossible to discover by other techniques.

9.4.1. *Determination of chemical reaction paths*

The use of radioisotopes in the study of the steps in a chemical reaction system is well established. Let us consider a few examples to illustrate this technique.

If phenol is labeled with deuterium or tritium in the hydroxyl group and warmed to a temperature slightly below decomposition, the labeled hydrogen migrates to other hydrogen positions of the benzene ring either by intra-molecular rearrangement or by inter-molecular reactions. However, using C_6H_5OT and C_6H_4TOH yields C_6H_4TOT, which can be formed only through inter-molecular collisions, thus eliminating intra-molecular rearrangement as the reaction mechanism.

The study of the reaction steps in the photosynthesis of carbohydrates from atmospheric CO_2 in the presence of light and chlorophyll is an outstanding example of the value of the tracer technique. The overall process (which involves many steps) can be written as

$$6\ CO_2 + 12\ H_2O \xrightarrow[\text{chlorophyll}]{\text{light}} C_6H_{12}O_6 + 6\ O_2 + 6\ H_2O$$

Using partition chromatographic technique and tracers of ^{14}C, ^{32}P, and T, Calvin and co-workers were able to identify the intermediate steps involved. The experimental procedure is usually as follows (Fig. 9.7). Plants are placed in atmospheres containing ^{14}C-labeled CO_2 and irradiated with light. After different irradiation times the plants are removed and sections are digested to dissolve the material. A few drops of the solution containing the substance to be separated (metal ion, organic molecule, etc.) are placed a few centimeters from the end of a paper strip. The paper strip is hung vertically and dipped into a solution so that the initial point of placement of the substance is near the bottom of the strip above the solution level. Capillary forces draw the solution upwards and bring it into contact with the adsorbed substances at the starting point. As this occurs the substance moves a certain distance up the paper from the starting point with the distance traveled dependent on the kind of paper, the solution used, and the chemical properties of the substance. In such experiments, a certain R_f value for each substance can be defined as

$$R_f = \frac{\text{distance the substance of interest has traveled}}{\text{distance the liquid front has traveled}} \tag{9.16}$$

A typical solvent system for metal ions may be a mixture of acetone, dilute HCl, etc., while for organic substances it is possible to use mixtures of phenol and water, acetylacetonate and water, etc. Figure 9.8 shows a two-dimensional paper chromatogram; in this case it has been run initially with a particular solvent mixture, then (after drying) turned 90° and run with a second solvent mixture, thus increasing the selectivity of the separation. The separated substance can be quantitatively recovered by cutting out the spot and leaching the compound from it. The substance is identified either from its R_f value or further analyzed by standard methods.

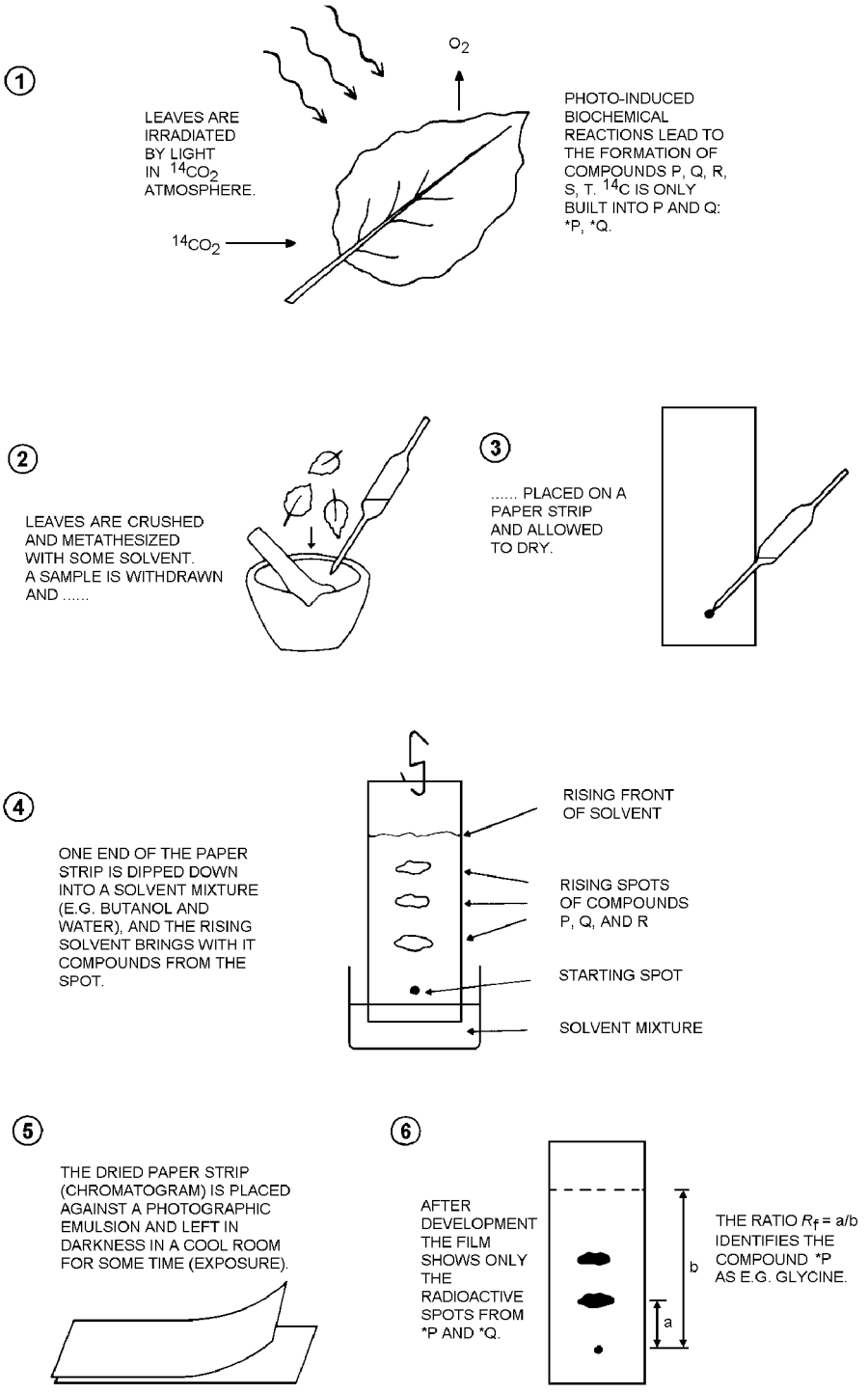

FIG. 9.7. Paper chromatographic method for determination of which of components P, Q, R, S and T in a leaf are involved in photosynthesis.

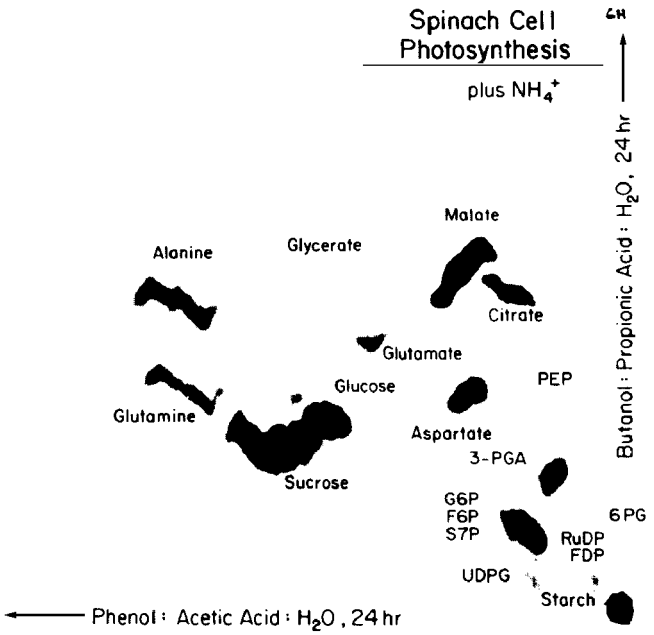

FIG. 9.8. Two-dimensional paper radiochromatogram of ^{14}C-labeled products in photo-synthesis after exposure to $^{14}CO_2$ atmosphere. (Courtesy Calvin and Lemmon.)

9.4.2. *Determination of chemical exchange rates*

If two different chemical species with some element in common are mixed in solution, exchange of this common component may occur. The chemical equation would have the form

$$AX + BX^* \rightleftharpoons AX^* + BX$$

Since the type and concentration of the chemical species remain unchanged, it is impossible to observe the exchange unless the atoms in one reactant are labeled. By using X^*, a radioactive isotope of X, the reaction may be followed, and at equilibrium the activity should be uniformly distributed between the two chemical species, i.e. the specific activity of X^* will be the same for both AX and BX. Of course, if AX and BX are both strong electrolytes, uniform distribution is essentially immediate upon mixing. If at least one of the reactants is an inorganic complex or an organic molecule, the exchange may be measurably slow if it occurs at all.

Since the chemical form of the reactants is not altered by the isotopic exchange, there is no change in heat content. However, the entropy of the total system is increased when uniformity in the distribution of the isotopes of X is achieved throughout the system. This entropy increase provides a decrease in the free energy, making isotopic exchange a spontaneous reaction. Despite this spontaneity, the exchange may be prevented or made

very slow by a large energy of activation requirement in the formation of a necessary transition state.

For the exchange reaction represented above, the rate of increase of AX^* is equal to the rate of formation minus the rate of destruction of AX^*. The rate of formation is the product of the rate of reaction k_r, the fraction of reactions which occur with an active BX^*, and the fraction of reactions which occur with an inactive AX. Using the following notation

$$a = [AX] + [AX^*] \tag{9.17a}$$

$$b = [BX] + [BX^*] \tag{9.17b}$$

$$x = [AX^*] \tag{9.17c}$$

$$y = [BX^*] \tag{9.17d}$$

the rate of formation k_f is equal to

$$k_f = k_r (y/b)(a-x)/a \tag{9.18a}$$

In a similar fashion, the rate of destruction k_d is equal to

$$k_d = k_r (x/a)(b-y)/b \tag{9.18b}$$

Therefore

$$dx/dt = k_f - k_d = k_r (ay - bx)/(ab) \tag{9.19}$$

The solution of this equation is

$$\ln(1 - F) = -k_r t (a + b)/(ab) \tag{9.20}$$

where $F = x_t / x_\infty$ (x_∞ is the value of x_t at $t = \infty$, i.e. equilibrium). The rate of exchange k_r is evaluated from the slope of a plot log $(1 - F)$ versus t. If more than one rate of exchange is present due to exchange with nonequivalent atoms in a reactant, it may be difficult to resolve this curve sufficiently to obtain values for the reaction rates. Isotopic exchange is a standard tool of the scientist studying the kinetics of chemical reactions whose half-lives are longer than a minute.

One example of isotope exchange can be used to illustrate the value of these studies. Consider the exchange between di- and trivalent chromium in $HClO_4$ solutions. If the total chromium ion concentration is 0.1 M, it takes 14 days for the exchange to reach 50% completion at room temperature. Inasmuch as the di- and trivalent cations are both positively charged, it is unlikely that they can approach each other closely enough to exchange an electron directly to allow a reversal of oxidation state, and a more likely mechanism is that an anion is involved as a bridge between the two cations such that the intrusion of the anion reduces the repulsion between the two cations. If this model of the

isotopic exchange mechanism is valid, it could be proposed that the reaction mechanism would be

$$Cr(III)^{*} + X^{-} + Cr(II) \rightarrow [Cr^{*}\text{-}X\text{-}Cr]^{4+} \rightarrow Cr(II)^{*} + X^{-} + Cr(III)$$

Such a reaction mechanism would be fostered by the presence of anions that form complexes more readily than perchlorate ion. If HCl solutions are used rather than $HClO_4$ it is found that the exchange takes place more rapidly and the half time of exchange is only 2 min, which agrees with the proposed mechanism since chloride ions are known to be more favorable to complex formation than perchlorate ions. Without the use of radioactive (or isotope separated) chromium to label one of the original oxidation states there would be no means of identifying the exchange.

9.4.3. *Determination of equilibrium constants*

Determination of cation (M^{z+}) – anion (L^{-}, for ligand) solution equilibria can advantageously be done using radioactive metal tracers because of the ease with which the metal concentration can be measured, as e.g. in the determination of *solubility products*

$$K_{s0} = [M^{z+}][L^{-}]^{z} \tag{9.21}$$

or *complex formation constants*, also named *stability constants*

$$\beta_n = [ML_n^{z-n}]/[M^{z+}][L^{-}]^{n} \tag{9.22}$$

At trace concentrations of the metal (i.e. $[M]_{tot} \ll [L^{-}]$), the complexing anion concentration is unaffected by the metal ion concentration, which allows easy calculation of the values of these two important variables in the system. The experimental techniques used for this purpose are based on two-phase equilibria: solubility (solid/liquid), paper electrophoresis (paper/aqueous solution), solvent extraction (organic solvent/water) and ion exchange (resin/water). The equilibria measured have been shown to be independent of the metal concentration in the range 10^{-3} to $< 10^{-13}$ M, as long as no polynuclear complexes (i.e. with several metal atoms per complex molecule) are formed (cf. §9.2.3).

(a) *Solubility*

The sensitivity of tracer detection makes measurement of solubilities relatively simple. This is illustrated by the first radioactive tracer experiment by de Hevesy and Paneth in 1913 in which the solubility of lead chromate was determined. Chromate ions were added to a solution of $PbCl_2$ containing a known amount of ^{210}Pb, precipitating the lead as $PbCrO_4$. The precipitate contained 2030 "radioactive units", and had a weight of 11.35 mg. The specific activity was thus 2030/11.35 = 179 "units" mg^{-1}. Shaking the precipitate with water dissolved 2.14 units per 1000 ml. The solubility was calculated to be 2.14/179 = 0.012 mg l^{-1} or 3.7×10^{-8} M Pb^{2+}. If $[Pb^{2+}] = [CrO_4^{2-}]$ the solubility product would be $K_{s0} = (3.7 \times 10^{-8})^2 = 1.4 \times 10^{-15}$. The modern value is 2×10^{-14}.

(b) *Solvent extraction*

As described in §9.2.6 the solvent extraction technique requires (i) a liquid two-phase system consisting of an organic solvent in contact with an aqueous solution, and (ii) the presence of an extractant (commonly a weak organic acid, abbreviated HA), which reacts with the metal ion to form an uncharged metal-organic complex MA_z, that preferentially dissolves in the organic phase. The distribution of the metal between the organic and aqueous phases can be shown to be fit the relation

$$D_M = K_{DC}\, \beta_z\, [A^-]^z / \Sigma \beta_n [A^-]^n \qquad (9.23a)$$

where D_M is the distribution ratio of the metal as defined by eqn. (9.6), and K_{DC} is the *distribution constant* of the uncharged complex MA_z. $[A^-]$ is referred to as the free ligand ion concentration; using trace metal concentration, $[A^-]$ is easily calculated from the amount of acid, HA, added, its dissociation constant K_a, pH and the liquid volumes. From measurements of D_M as a function of $[A^-]$, the formation constants β_n for the complexes MA_n^{z-n} are calculated.

Figure 9.9 shows the distribution of lutetium (using trace concentrations of ^{177}Lu, ($\beta^-\gamma$ $t_{½}$ 6.71 d) between an aqueous solution and benzene containing an organic complex former (HA = acetylacetone). Eqn. (9.23.a) has been fitted to the experimental points by regression analysis to yield the equilibrium constants, by which the solid curves have been calculated.

Studies of this kind are often easy to do. However, the Lu-acetylacetone system was chosen as it was not as simple, yet good results were obtained by careful use of the tracer technique: Because the Lu concentration was 10^{-8} M, 10^{-5} M Nd^{3+} was added as *hold-back carrier* to avoid sorption losses (§9.2.3). At the pH's that had to be investigated Lu^{3+} (and

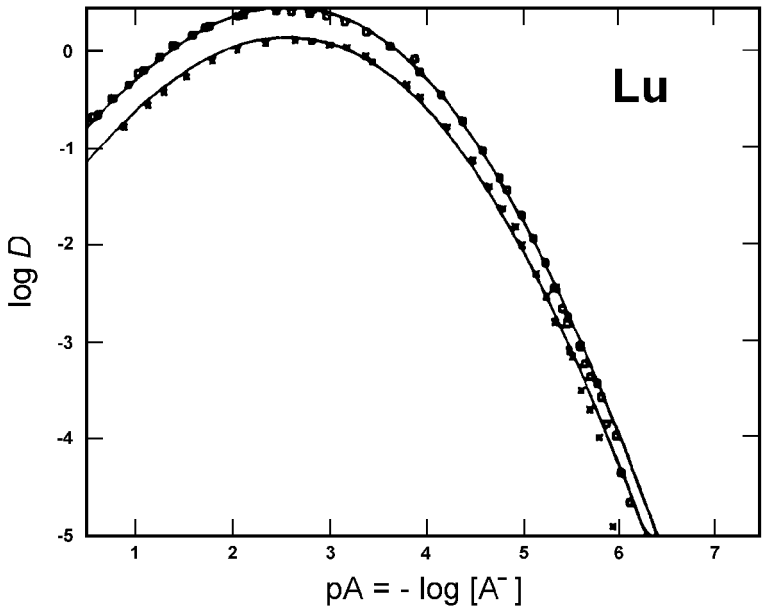

FIG. 9.9. Distribution of ^{177}Lu (β^- $t_{½}$ 6.71 d) in 1 M $NaClO_4$/benzene, acetylacetone. Upper curve $[HAa]^0_{org}$ 3.0 M, lower curve 1.0 M. (From Albinsson)

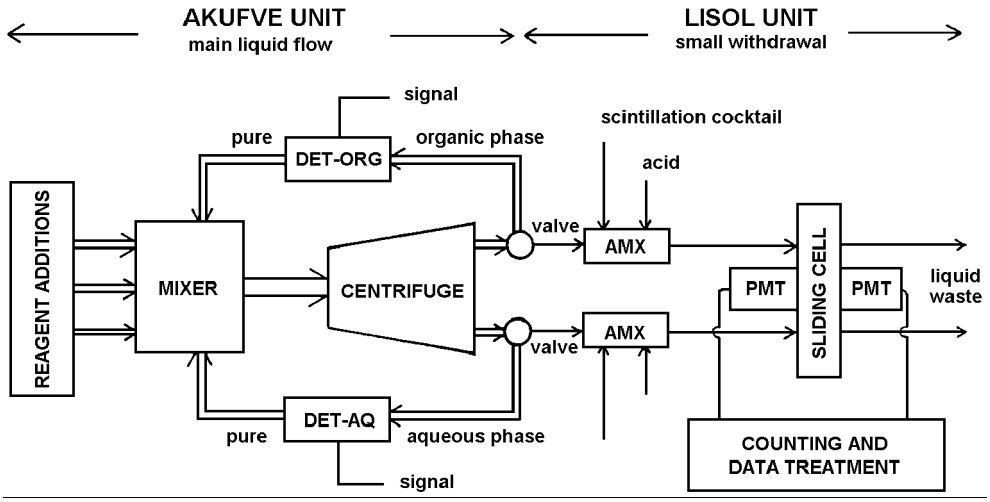

FIG. 9.10. The AKUFVE-LISOL system used in investigating the system in Fig. 9.9.

also Nd^{3+}) may hydrolyse. Also, the very low *D*-values obtained (1 to 10^{-5}) are difficult to measure exactly with conventional technique. Therefore advanced techniques were developed, see Figure 9.10: (a), AKUFVE, which is a closed flow system, where the two liquid phases are mixed continuously and separated in a special flow-through centrifuge, and, after passing detection devices, returned to the mixing chamber. (b), LISOL, an "on-line" liquid-scintillation detection technique, in which a tiny fraction of the circulating phases is withdrawn, mixed (i) with acid to suppress sorption and hydrolysis, and (ii) with a liquid scintillator, and (iii) pumped to the PMT-detector. The LISOL avoids detector memory effects occurring in conventional on-line detectors and also allows measurements of pure α- and β-emitters (cf. §8.5.2).

As a second example we choose a chemically more complicated system, which, however, in practice is simpler than the one above, and therefore of more common use. The complexation of $^{237}Np^{4+}$ by HSO_4^- in 0.1 M $NaClO_4$ was studied by SX using the system aqueous solution/$CHCl_3$ containing the organic extractant thenoyltrifluoroacetone (HTTA). In this case the relation

$$D_{Np}/D^0_{Np} = \Sigma \beta_x [HSO_4^-]^x \qquad (9.23.b)$$

can be derived, where D_{Np} is the distribution ratio of Np in the presence, and D^0_{Np} in the absence, of HSO_4^-; in this case pH and [HTTA] must be constant during the experiment, any change requiring correction. From the data in Figure 9.11 the formation constants β_x for Np(IV) sulphate complexes were determined.

The solvent extraction technique has been used extensively for studying complexation of metals for which it may not be possible or desirable to use macroscopic amounts, as e.g. for the heavy actinides or transactinides (Ch. 16)

. (c) *Ion exchange*

The technique depends on the distribution of metal cations between a solid cation exchange resin and an aqueous solution. The exchange process for the M^{z+} ion takes place according to the equation

$$M^{z+}(aq) + zRH(resin) \rightleftharpoons MR_z(resin) + zH^{+}(aq)$$

$$K_{iex} = ([MR_z]\,[H]^z)/([M]\,[RH]^z) \qquad (9.24.a)$$

omitting ionic charges and phase indices. Introducing D_{iex}, from (9.7), in (9.24.a) gives

$$D_{iex} = K_{iex}\,[RH]^z\,[H]^{-z} \qquad (9.24.b)$$

showing that D_{iex} is a constant at constant solution/resin conditions (as in column ion exchange separations). However, when used for determining equilibrium constants in a system with several metal species in solution, each ionic species must be represented by an equation of type (9.24.a), leading to rather complicated expressions.

9.4.4. *Studies of surfaces and reactions in solids*

Surface properties of solids have been studied by dipping specimens into a solution containing a suitable radioactive tracer, and, after some "exposure time", removing them, washing their surface carefully and measuring the radiation emitted from them. It has been

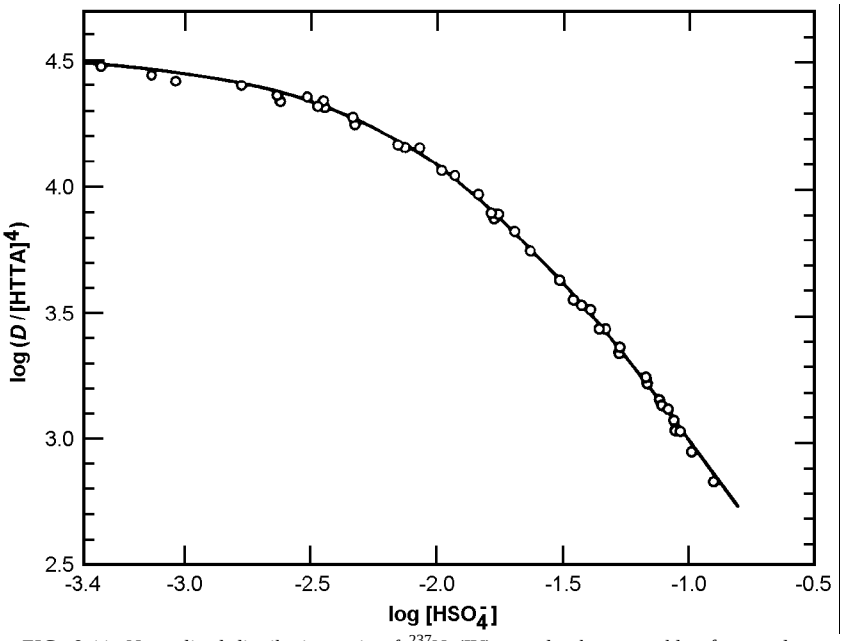

FIG. 9.11. Normalized distribution ratio of $^{237}Np(IV)$ complex between chloroform and an aqueous HSO_4^- solution. (From Sullivan and Hindman.)

shown that a very rapid exchange takes place between atoms on a metal surface and the metal ions in solution. While the exchange is a function of the nature of the surface, within minutes it may involve atoms several hundred layers deep. The depth of penetration of sorbed radioactive isotopes can be obtained from a measurement of the absorption of the radiation or by measuring the radioactivity removed by cutting, or grinding, away thin layers. With the same technique the diffusion of atoms in their own solid matrix can be studied. For example, using single crystals of silver suspended in a solution containing silver nitrate labeled with ^{110m}Ag ($\beta^-\gamma$ $t_{½}$ 249.76 d) it has been possible to demonstrate different rates of diffusion into different faces of the crystal. The surface area of solids can also be determined by measurement of the sorption of radiotracers which do not penetrate into the specimen.

If a radioactive gas is incorporated in a crystalline compound the amount of gas released (the *emanation ability*) can be measured as a function of the temperature. It is found that the emanation increases considerably at certain temperatures, indicating structural changes in the solid at those temperatures. Studies of diffusion and emanation play a valuable role in understanding the mechanism of sintering and in the formation of new solid compounds. This has been of practical importance in the cement and glass industries, in the production of semiconductors, in the paint industry, etc. Studies of surface reactions are of practical importance for flotation, corrosion, metal plating and finishing, and detergent action to name only a few applications.

The distribution of a radioactive element or compound in a composite matrix can made visible either to the naked eye or under a microscope by means of *autoradiography*. The technique is based on the blackening of photographic films when exposed to nuclear radiation (cf. §§7.2 and 7.10). The technique is best illustrated by an example.

Lead is an unwanted impurity in stainless steel even in very small amounts. In order to investigate the mechanism of its incorporation, ^{212}Pb was added to a steel melt. After cooling, the ingot was cut by a saw and the flat surface machine-polished and etched in an electrolytic bath (electro-polishing). This provided a very flat and "virgin" surface. A photographic film was placed firmly with even pressure against the metal surface, and the film was exposed in darkness in a cool room for about a week. After development of the film, darkened spots caused by the radiation from ^{212}Pb showed where on the metal surface lead was present. By taking the results into account in the production process, the negative effect of lead in the raw material could be reduced.

In another technique, a polished surface of the specimen (metal, mineral, etc.) was dipped into a solution containing a radioactive reagent, which selectively reacts with one of the constituents of the surface. A mineral was dipped into potassium ethyl xanthate labeled with ^{35}S (β^- 87.5 d); the xanthate reacted selectively with sphalerite (zinc blende), ZnS, in the sample. The distribution of the xanthate, as shown by the autoradiograph, indicated the ZnS distribution in the mineral. The low β-energy of ^{35}S, E_{max} 0.2 MeV, was an advantage to the technique because the resolution of the autoradiograph increases with decreasing particle range.

9.5. Applications to life sciences

The largest field of application of radionuclides is in the life sciences. A survey is presented in Table 9.3.

In the reactions leading to the desired product (column A) many factors must be considered. They are of such importance that we devote several separate chapters to this: Ch. 12 on nuclear reactions, Ch. 13 on particle accelerators and Ch. 15 on production of radionuclides. The incorporation of the radionuclide in a chemical compound (labelling, §15.5.3) provides it with unique properties, such as specific biological affinity (§9.5.1). When such labelled compounds are taken up by organisms (A4b → B1) they move to specific sites in the organs, signalling normal or abnormal behavior. When used in medicine (primarily C1 and C3) these compounds are referred to as *radiopharmaceuticals* (A4b).

The use of labelled compounds in life sciences is extensive, in fact, the largest single user of radionuclides is medical science. It has been said that radioactive tracers have been of equal importance to medicine as the discovery of the microscope. Presently one out of ten hospitalized patients in the United States is admitted to some nuclear medical procedure. If the intended use of the radionuclide is as an external radiation source (A4a → B2 → C2.1 or C3) its chemical matrix is of minor importance. Such sources are used for radiation treatment of cancer (C3b), radiation sterilization of food (C3c), etc. The *radiation effects* on biological systems are discussed separately in Ch. 18. In this chapter we focus our interest on radionuclides with specific chemical properties, in the order of column C, Table 9.3.

TABLE 9.3. *Survey of radionuclide use in life sciences*

A Radionuclide production
1 Target chemistry,
2 irradiation,
3 isolation
4 and processing, yields
  (a) pure radionuclide, or
  (b) labelled compound (radiopharmaceuticals)

B Source, position/administration
1 Internally (α, β or γ)
  (a) injection,
  (b) inhalation, or
  (c) oral intake.
2 Externally as γ-source

C Technique/application [detection]
1 Biochemical analysis
  (a) autoradiography [photographic]
  (b) immunoassay [counting]
  (c) DNA-analysis [photographic]
  (d) direct tracing [counting]
2 Medical imaging
2.1 Transmission Tomography (TCT) [photographic, or by counting→computer→display]
2.2 Emission Computed Tomography (ECT) [counting→computer→display]
  (a) Single Photon Emission Computed Tomography (SPECT)
  (b) Positron Emission Tomography (PET)
3 Irradiation uses
  (a) by internal sources (therapeutically)
  (b) by external sources (therapeutically)
  (c) by external sources (sterilization etc)

9.5.1. *Biological affinity*

To study how living species interact with the environment, *ecology*, one can use radioactive tracers to follow the uptake of a trace metal (e.g. cobalt) from the soil by plants, and by animals after having eaten the plant. In agriculture, this is useful in studying the uptake of trace elements necessary for plant growth. For example, it has been found that sheep need plants containing selenium in order to combat white muscle disease. The

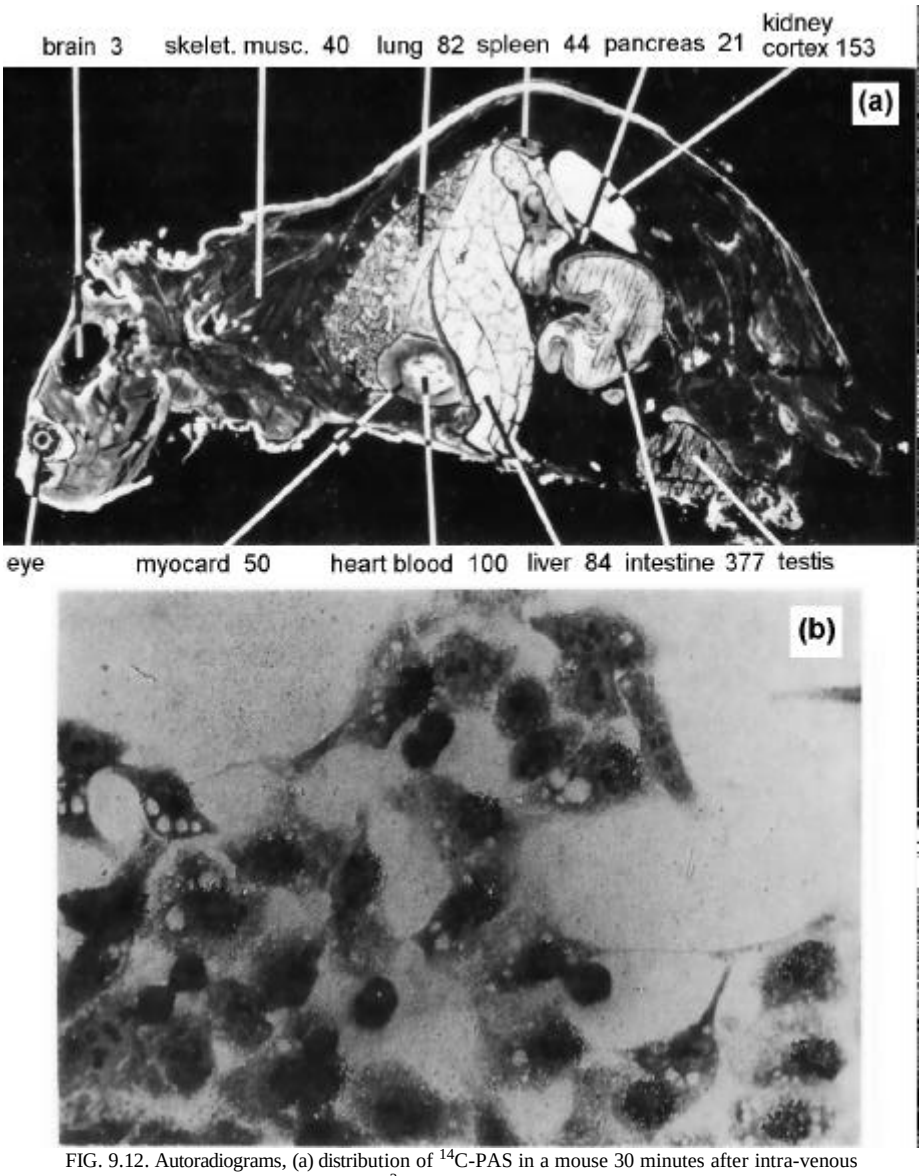

FIG. 9.12. Autoradiograms, (a) distribution of ^{14}C-PAS in a mouse 30 minutes after intra-venous injection, (b) of HeLa-cells labeled by ^{3}H-thymidine. (From Hanngren and Nias.)

turnover in nutrients fed to animals can be determined; it was found that 20% of the phosphorus in cow's milk comes directly from the feed, while 80% is taken from the cow's bone.

If a radioactively labeled compound such as an amino acid, a vitamin, or a drug is administered to an animal, the substance is incorporated to varying degrees in different organs (*biological affinity*). The substance undergoes chemical exchange with other substances in the body, is broken down, and, finally, discharged from the body (i.e. *metabolizes*). The radionuclide distribution in samples (cells, tissues, body fluids, etc) removed from living species gives significant information about the (normal or abnormal) physiology of that species. "C1. Biochemical analysis" in Table 9.3 lists these techniques, which are discussed below.

(a) *Autoradiography*

Figure 9.12(a) shows the distribution of ^{14}C-labeled p-aminosalicylic acid, PAS, the first tuberculostatic agent developed, in a 20 µm thick section of a mouse. The autoradiograph was obtained after 10 MBq ^{14}C-PAS had been injected, and the mouse (weight 20 g) had been killed by immersion into a CO_2-acetone (−80°C) mixture and sectioned. It is seen that the PAS is concentrated mainly in the lung, where it is effective against tuberculosis, and the kidney and intestine as it is excreted through these organs.

Figure 9.12(b) shows an autoradiograph of radioactively labeled cells. In the "pulse labelling" (i.e. 10 - 30 min exposure) to ^{3}H-thymidine only cells in the S-phase of the cell cycle reacts with the thymidine and thus become labeled (the very dark spots). Both the cell cycle times and number of cells in the cycle can be measured with this technique, which is important in cancer cell research.

As an alternative to using the blackening of a photographic film for radiation detection "instant imagers" based on semiconductor array detectors are commercially available.

(b) *Radioimmunoassay (RIA)*

Immunoassay is an application of the substoichiometric principle (§9.3.4) developed by Yalow (Nobel laureate in 1977) for protein analysis. In the United States tens of millions radioimmunoassays are made annually in hospitals to measure hormones, enzymes, viruses, serum proteins, drugs, and so forth. Only a drop of the patient's blood is needed, reflecting the versatility and sensitivity of this technique, which can be performed automatically. Commercial RAST-kits (Radio Allergy Sorbent Tests) are used for rapid diagnosis of allergic reactions.

In immunoassay, a known mass, w_s^0, of a labeled protein P* is allowed to react with a much smaller (substoichiometric) mass of an antibody A, so that a complex P*A is formed. The P*A is isolated and its radioactivity, R_s, measured. Under the same conditions, an identical mass, w_s^0, of labeled protein is mixed with an unknown mass, w_u, of the identical protein to be determined. This sample is also allowed to react with the same amount of antibody A as before; the complex P*A is again isolated (weight w_{u+s}) and its radioactivity, R_{u+s}, measured. The unknown weight, w_u, is then calculated from (9.15).

(c) *DNA-analysis*

The chemical composition (the base sequence) of the DNA molecules, which make up the chromosomes of the cell nucleus, is unique for each species and individual. The detailed analysis of the DNA molecule provides important information about its host. This is used in studies of the evolution of species, in forensic science to identify criminals (e.g. from

blood, sperm, etc), in transplantation of organs (kidney, tissue grafting, etc), in detection of genetic diseases, etc. The importance of DNA-analysis is constantly growing.

The sequence of the DNA analysis is as follows. (i) The cell walls are broken up by osmosis etc. and the doublestranded DNA is denatured to pieces of singlestranded DNA. The molecules may be concentrated by centrifugation. (ii) By exposing this DNA to *restriction enzymes* the DNA nucleotide chain is sectioned further into smaller fragments; different restriction enzymes cut the DNA molecule at different positions. The fragments are exposed to radioactively labelled compounds (e.g. containing ^{14}C or ^{32}P) which selectively attach to the different fragments. Alternatively to (i) and (ii), the DNA is directly labeled e.g. by ^{32}P in a cloning process; the clones will then contain ^{32}P at its P- sites also after it has been split by restriction enzymes. (iii) When the DNA samples are exposed to electrophoresis in a suitable gel (agarose, polyacrylamide, etc), the fragments distribute themselves along the potential direction according to their migration velocities. Usually 10 - 40 samples (each treated by a different restriction enzyme) are run simultaneously. (iv) After the electrophoresis, a photographic plate is placed on the gel and exposed to the radioactive fragments, producing, after development, a pattern of spots or bands on the plate. (v) The band pattern is analyzed to reveal its information about the individual. The technique has many similarities with those demonstrated in Figures 9.7 and 9.8.

9.5.2. *Transmission computer tomography (TCT)*

Conventional "x-ray pictures" show the morphological structure of the internal organs. The technique is used with x-ray or γ-ray sources; e.g. Ra was extensively used during World War I in operations at the front where electricity was lacking. To improve the contrast in the photographic pictures, dense media like barium sulfate or iodine compounds are administered to the patient; this method is said to be *invasive* and can be painful to the patient.

Though this technique is still widely in use, the 1970'ies saw a large step forward in medical imaging referred to as *computerized tomography* (CT), developed by Cormack and Hounsfield (Nobel laureates in 1979) and others. Though the radiation source is the same, the photographic plate is replaced by one or several radiation sensitive detectors, a digital computer and a display ("TV monitor"). The radiation source and detector array are moved (*scanned*) in relation to the patient, see Figure 9.13 A. This technique requires computer software to handle the reconstruction arithmetic needed to provide an image on the screen from the observed changes in count rates by the detectors (due to different absorbancies of the organs) at different geometries. Tomography means "slice"; the technique shows slices through the body on the screen. The resolution of a TCT-scan is usually ~ 1 mm, allowing quite exact pictures, e.g. of a tumor. Since nowadays only X-ray tubes are used as radiation source, the technique is handled by *radiologists* at the hospital "X-ray department".

Transmission tomography can be compared to a silent movie: one can see what happens physically with the organs. Emission tomography (next section) uses internally administered radioactive isotopes, which provides explanation to why the organs function as they do. Thus, to extend the comparison, computerized emission tomography becomes more like a medical sound movie of the patient.

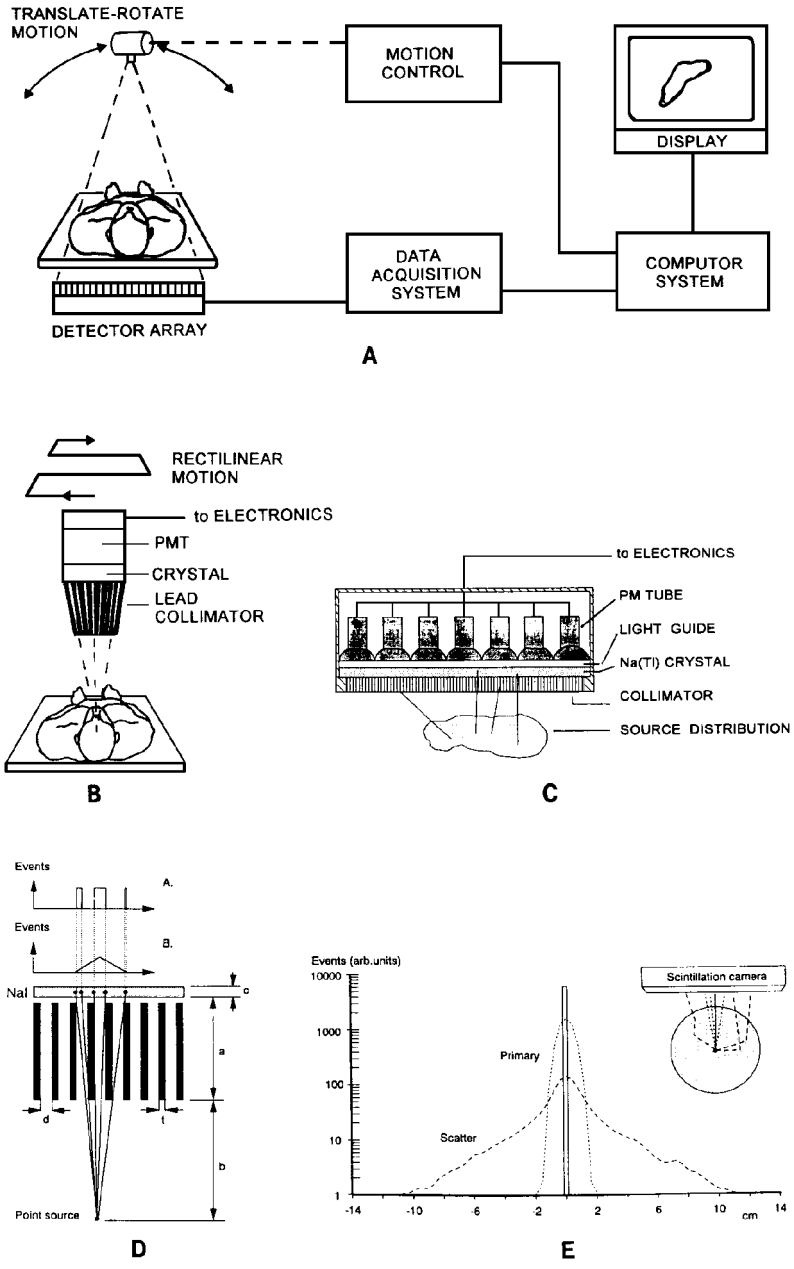

FIG. 9.13. Principles of gamma scintigraphy.

9.5.3. *Emission computer tomography (ECT) and diagnosis*

The rate of incorporation and discharge of radioactively labeled substances in the body provides a measure of the metabolism of healthy and of sick tissues. On medical patients this information is obtained by external measurements referred to as *radioisotope scanning* (RIS). Such scanning can yield information about a medical disorder much before it is observed by other means. Since the amount of radioactive tracer is very small, this technique is referred to as *non-invasive*. In hospitals the department of *nuclear medicine* is normally responsible for these investigations.

(a) *Simple scanners*

Simple scanners are designed either with one or several direction sensitive (focusing) detectors, which are moved around or above the patient in a pattern; Figure 9.13.B and C. Figure 9.14 shows the result of a kidney scan, *renography*, of a 38 year old woman who has been administered $^{197}HgCl_2$ (ECγ $t_{½}$ 2.672 d); in this case a single NaI(Tl)-PMT with collimator was moved in a recti-linear pattern over the kidneys (Fig. 9.13.B). The left picture shows that 38.9% of the compound has been fixed to the left kidney, and very little to the right kidney. This was caused by a vaginal fibrous sarcoma blocking the urethra from the right kidney. After radiation therapy some improvement is seen (right Figure). Renography is now done with ^{131}I labeled hippuric acid, or a ^{99m}Tc complex.

(b) *Gamma Camera and Single Photon Emission Computer Tomography (SPECT)*

Recent advances in nuclear medical imaging are the gamma camera, SPECT and positron emission tomography (PET, described under (c)).

Figure 9.13.C shows the gamma scintillation camera, *gamma camera*, originally developed by Anger. It consists of a two-dimensional array of 40 - 100 PMTs (often hexagonally formed for tight stacking) viewing a large flat NaI(Tl) crystal of ~ 400 mm diameter and 5 - 10 mm thick, which is located behind a lead collimator containing numerous holes. Typical hole size is 2 - 3 mm diameter and 40 mm length. Collimator dimensions (Fig. 9.13.D) depend on the E_γ; for ^{99m}Tc (E_γ 0.14 MeV) the wall thickness is 0.2 - 0.3 mm.

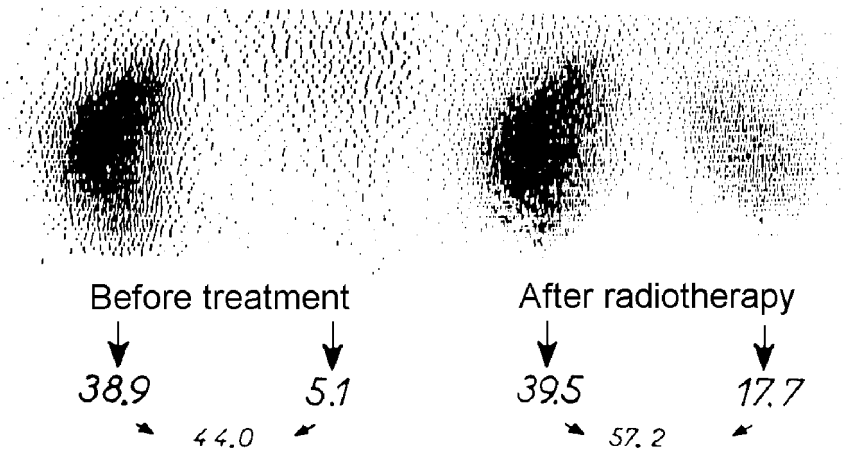

FIG. 9.14. Kidney function test by $^{197}HgCl_2$ using scintigraphy. (From Kellershohn et al.)

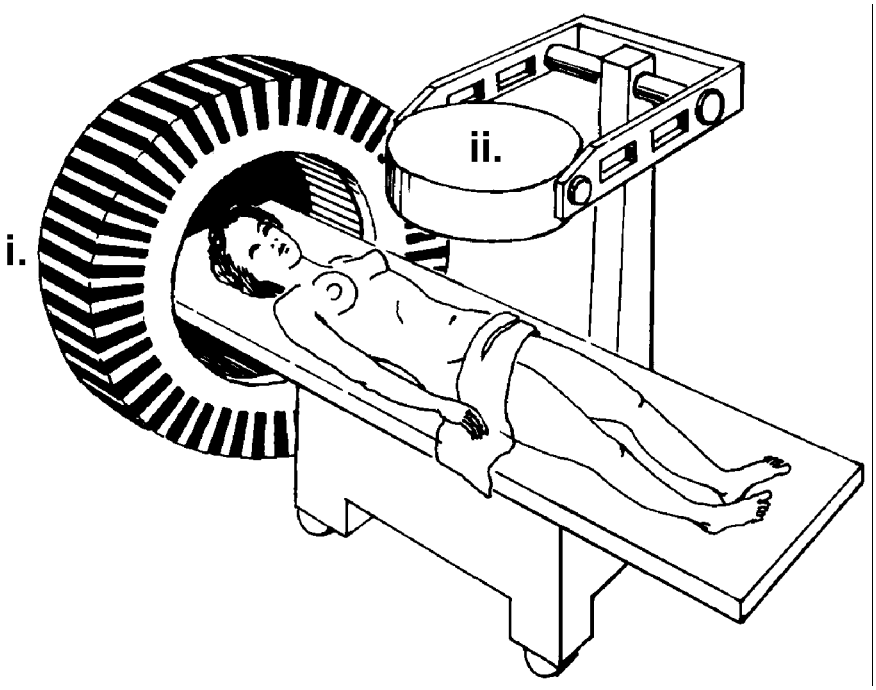

FIG. 9.15. Geometry in (i) positron emission tomography (PET) and (ii) gamma-camera.

The radionuclide injected into the patient should preferably decay by the emission of a single γ, and the lower the E_γ the better becomes the resolution of the image. Since the detectors are energy sensitive, the camera can be tuned to the primary unperturbed (Ch. 6) γ's, i.e. the signals from the PMTs are accepted only if they are near the photo-peak energy. The energy window of the detector has some width allowing some scattered photons to contribute to the number of events registered from a single point radionuclide source; this is suppressed by narrowing the energy window (Fig. 9.13 E). Figure 9.13 D indicates, in the upper diagram (A), the actual events detected through the pin holes, and how these can be sharpened into a peak if the collimator moves during the exposure time (Fig. 9.13 B); this is of particular importance in SPECT-investigations. The gamma camera is supported by hardware (Fig. 9.13.A) and extensive computer software.

One distinguishes between "scintigraphic" and "SPECT" investigations. Gamma cameras are used in both investigations, but the camera is stationary in the former case, while it usually moves in SPECT. About 95% of all nuclear imaging investigations carried out by the nuclear medicine department of a modern hospital is scintigraphy with stationary gamma camera, usually referred to as "gamma camera (investigation)". In about 2/3 of these investigations a single picture is taken of the patient's organ: heart, kidney, liver, etc. This yields an image of the organ's content of the radionuclide, i.e. of its function with respect to the pharmaceutical administered. About 1/3 of the investigations are studies of the dynamic behavior of an organ. Taking thousands of "pictures" (commonly 10 per second), storing and treating them allows a direct study of the function, e.g. heart beat. Though the resolution in such investigations is rarely better than 10 mm, they nevertheless provide information not available by TCT.

Each picture by the camera is two-dimensional; however, by positioning the camera at different angles around the patient, 3-dimensional pictures of the organs can be constructed. This is commonly done by letting the camera rotate around the patient, usually 360° in increments of a few degrees. Several large cameras at fixed positions or rotating around the patient can be used for the same purpose. The cameras can also be moved in a direction parallel to the patient. By using software similar to that used in TCT-scanning, "radiographic slices" of the patient's organs can be obtained. Such investigations are referred to as SPECT. The resolution of present commercial SPECT equipment is only 12-15 mm.

With the increasing number of radiopharmaceuticals with specific biological affinities, gamma camera and SPECT have become important diagnostic tools with numerous clinical applications, and virtually every organ in the body has been studied. Table 9.4 shows the most frequently performed imaging investigations; Table 9.5 lists data for radionuclides applied in medicine, including the amount of radionuclide needed. The radiation doses received by the patient in diagnostic investigations is usually < 10 mGy per investigation.

The SPECT technique is primarily used for cardiovascular and brain imaging. Cardiac stress tests, using $^{201}Tl^{+}$ or ^{99m}Tc labelled radiopharmaceuticals, amount in the U.S. to about 2 million a year. Brain tumors can be located by SPECT after intravenous injection of $Na^{99m}TcO_4$, as brain tumors have a very high affinity for and slow release of Tc. In comparison, the uptake of Tc in brain infarcts is low and the release fast, and from healthy parts of the brain even faster; thus various constrictions to the cerebral blood flow are easily located. A head scan can be made in 10 minutes and virtually instantaneously produces an image of the brain.

Mental disorders are diagnosed by SPECT, gamma-camera or PET using various radiopharmaceuticals, e.g. after the injection of ^{99m}Tc-HMPAO (Hexa Methyl Propylene Amine Oxide) or inhalation of ^{133}Xe. Injecting ~ 1000 MBq Tc-complex into the blood stream, about 5% of this compound moves to the brain, passes the membrane of the blood vessels and enters into the brain tissue, where it decomposes and decays with its 6.0 h half-

TABLE 9.4. *Ten of the most frequently performed imaging investigations (From Sharp et al.)*

Examination	Radionuclide	Static/dynamic	Principal application
Bone	^{99m}Tc	S	Secondary spread of malignancy
Liver	^{99m}Tc	S	Secondary spread of malignancy; cirrhotic changes
Brain	^{99m}Tc	S/D	Occult metastases; brain damage; vascular problems
Lung (perfusion)	^{99m}Tc	S	Pulmonary embolism
Lung (ventilation)	$^{133}Xe/^{99m}Tc$	D	Pulmonary emphysema
Kidneys	$^{123}I/^{99m}Tc$	D	Renal function
Hepato-biliary system	^{99m}Tc	D	Patency of the biliary tree; liver function
Thyroid	$^{123}I/^{99m}Tc$	S	Thyroid function
Heart (perfusion)	^{201}Tl	S	Cardiac infarction and ischaemia
Heart (blood pool)	^{99m}Tc	D	Cardiac wall motion

TABLE 9.5. *Radionuclides applied in nuclear medicine*

Nuclide	half-life	Decay mode	Particle energy (keV)*	Applications**
^{3}H	12.33 y	β^-	18.6 β	AN. BA all chem. comp.
^{11}C	20.39 m	ECβ^+	960 β, 511 γ	As CO_2, HCN, HCHO, CH_3I. DG PET: brain, glucose
^{14}C	5730 y	β^-	156 β	AN
^{13}N	9.965 m	β^+	1190 β, 511 γ	As NH_3. DG PET
^{15}O	2.037 m	β^+	1723 β, 511 γ	As H_2O. DG PET
^{18}F	1.830 h	β^+EC	635 β, 511 γ	BA skeleton. As ion or F_2. DG PET
^{24}Na	14.659 h	$\beta^-\gamma$	1389 β, 1369, 2754 γ	AN. BA circulatory system.
^{32}P	14.282 d	β^-	1710 β	AN. BA skeleton, bone marrow. TP: leukemia 200 MBq phosphate.
^{35}S	87.5 d	β^-	1674 β	AN
^{42}K	12.360 h	$\beta^-\gamma$	3523, 1970 β, 1525 γ	AN liquid volume. BA muscles.
^{47}Ca	4.536 d	$\beta^-\gamma$	1981, 684 β, 1297 γ	BA skeleton. DG: bone
^{51}Cr	27.704 d	ECγ	320 γ	BA spleen. DG: kidney funct.(clearance) 4 MBq EDTA.
^{55}Fe	2.73 y	EC		BA: red blood cells
^{59}Fe	44.50 d	$\beta^-\gamma$	475, 273 β, 1099, 1292 γ	DG: ion
^{57}Co	271.77 d	EC	122, 137 γ	BA liver.
^{58}Co	70.92 d	β^+	811, 511 γ	DG: vitamin B12
^{60}Co	5.271 y	β^-	315 β, 1333, 1173 γ	TP: cancer. Source $> 10^7$ MBq.
^{68}Ga	1.135 h	β^+EC	1830 β, 511, 1077 γ	BA intestine. DG: ion, EDTA or citrate.
^{75}Se	119.77 d	EC	(864) 136, 265, 280 γ	BA kidney, liver. DG: methionine
^{85}Sr	64.84 d	EC	514 γ	BA skeleton. DG: skeleton 2 MBq ion.
^{99m}Tc	6.006 h	IT	140 γ	DG: Thyroid 100 MBq TcO_4; heart 400 MBq TcO_4; lung (perfusion, emboli) 80 MBq albumin particles; liver (tumor, size, funct.) 100 MBq colloid, or 150 MBq HIDA; kidney 200 MBq DTPA (clearance), DMSA (renography), and other compounds; skeleton (metastasis) 400 MBq phosphate; brain (tumor, cerebral hemorrhage) TcO_4 or DTPA. Etc.
^{111}In	2.807 d	EC	(864) 171, 245 γ	DG: spinal cord ion, oxime or DTPA.
^{113m}In	1.658 h	IT	(392) 392 γ	DG: ion, oxime or DTPA.
^{123}I	13.2 h	EC	(1232) 159 γ	BA thyroid. DG: Kidney funct. 40 MBq hippuran; thyroid.
^{125}I	60.1 d	EC	(178) 35 γ	BA thyroid. DG: Thrombosis 4 MBq fibrinogen. Kidney function hippuran
^{131}I	8.040 d	β^-	606 β, 365 γ	DG thyroid funct. 2 MBq ion. Kidney 1-10 MBq hippuran. TP: 300 MBq ion hyperthyroidism and thyroid cancer.
^{133}Xe	5.24 d	β^-	346 β, 81 γ	DG Lung emboli, 1000 MBq gas (radiospirometry), brain.
^{137}Cs	30.0 y	β^-	514 β, 662 γ	TP: cancer. Source $> 10^6$ MBq.
^{186}Re	3.777 d	β^-	309, 362 β, 137 γ	bone cancer
^{188}Re	16.98 h	β^-	728, 795 β, 155 γ	pain
^{198}Au	2.6935 d	β^-	961 β, 412 γ	TP: 150 MBq spread of ovarian cancer.
^{201}Tl	3.05 d	EC	(480) 167 γ	BA: para-thyroid, kidney. DG Heart (infarct) 50 MBq ion

* Particle energy (decay energy), ** Common radiochemical species; ion = ionic as chloride, sulfate, etc.
AN = biochemical analysis, BA = biological affinity, DG = diagnostically (imaging), TP = therapeutically

life, allowing detailed imaging of the brain. The average absorbed whole body dose in such a SPECT scan is about 0.01 Sv. Figure 9.16 (right) shows three ^{133}Xe gamma-camera pictures of patients with Alzheimers disease (ALZ), frontal lobe dements (FLD) and multi-infarct dements (MID). ^{133}Xe decays by emitting an 80 keV γ, thus the pictures show

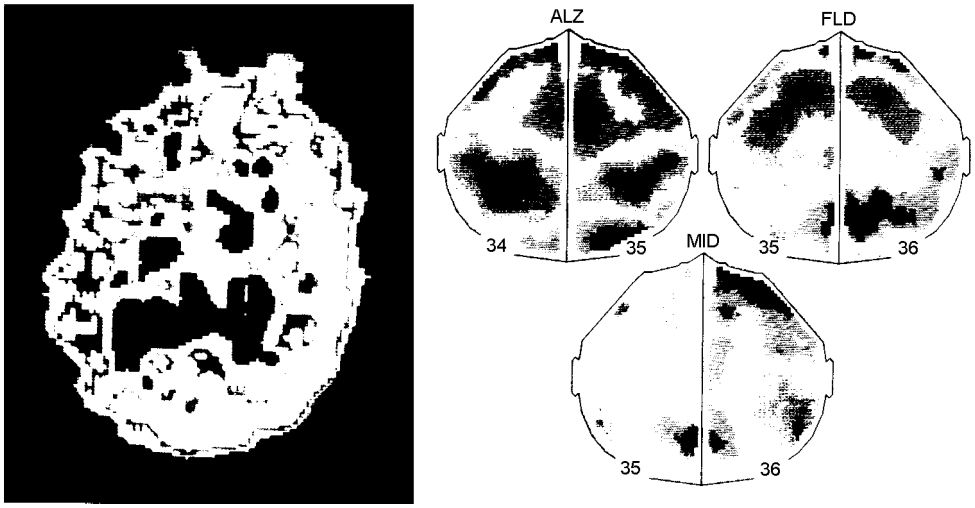

FIG. 9.16. (a) A PET scan to identify a blood occlusion, (b) gamma-camera scans of subjects with ALZ, FLD and MID (Courtesy Kernforschungsanlage Jülich and Lund Psycho Geriatrics Dept.)

primarily the ^{133}Xe in the brain cortex (regional-Cerebral Bloods Flow test, r-CBF); in this investigation 256 small scintillation detectors were positioned like a helmet around the patient's head. The pictures in black-and-white shown here do not make justice to the original, more detailed, color pictures, the colors representing the radiation intensity, i.e. blood flow at the point.

^{99m}Tc is a preferred radionuclide due to its convenience of production (from milking ^{99}Mo, §4.16, the ^{99}Mo produced by fission of ^{235}U), and short half-life which reduces radiation risks. There are > 20 differently labelled Tc-compounds commercially available for diagnostic purposes. ^{99m}Tc (together with ^{123,125,131}I) is the most frequently used radionuclide for diagnostics; about 7 million such investigations are made per year in U.S. The dominating organs investigated are in order skeleton, kidney, liver and thyroid.

(c) *Positron emission tomography (PET)*

The decay of a positron emitting radionuclide yields two 0.51 MeV γ-rays travelling in opposite directions. If photons with this energy are registered simultaneously by γ-ray detectors 180° apart, positron decay must have taken place somewhere along the line between the two detectors. This is used for *positron emission tomography*. A positron emitter is administered to the patient positioned inside a ring or hexagon of 50 - 100 scintillation-PMT detectors (there is no need for collimators); Figure 9.15. The ring is moved in a translate-rotate pattern. The location of the radioisotope in the body is mapped in a way similar to that described for SPECT. The resolution of this technique is presently of the order of a few mm.

Positron emitters cannot be produced by n-irradiation: from Figure 4.8 it is seen that only charged particle irradiation (using ^{1}H, ^{2}H, ^{4}He, etc) can result in product nuclei on the proton rich side of the stability valley, for which positron emission is the main decay mode

(competing with electron capture). Typical positron emitting nuclides used in PET are included in Table 9.5. They can be tagged to a variety of compounds.

For studying brain metabolism, ^{11}C-labeled glucose has been extensively used. The procedure is as follows:

1) $H_3{}^{11}BO_3$ is irradiated by protons in an accelerator, yielding $^{11}CO_2$.

2) Rapid automatic synthesis produces $^{11}C_6H_{12}O_6$ (glucose) or the methyl glucose derivative.

3) The glucose solution is injected into a patient. Since it is easily metabolized, the glucose goes to the parts of the brain with the highest metabolism, rather than to places with no metabolism.

4) The ^{11}C nuclide decays according to $^{11}C \rightarrow {}^{11}B + e^+$ followed by $e^+ + e^- \rightarrow 2\gamma$. The 0.51 MeV γ coincidences are registered by the PET cameras at various positions.

PET is used especially for studies of brain, heart and lungs. Figure 9.16, left, shows a brain investigation. Because glucose is the only source of energy the brain uses, the rate of glucose metabolism can be assessed throughout the brain, which is an indicator of the brain viability. In this case, the patient has been injected with ^{11}C-methyl glucose and the dark spot indicates an occlusion of the left carotid artery. The technique is quite fast: within a few hours the effect of administered drugs can be revealed.

Although TCT has now superseded other techniques in locating brain tumors, SPECT, gamma-camera and PET have provided dramatically new information of various forms of mental illness, such as epilepsy, manic depression, and dementias such as Alzheimer's disease. The development of new, selective radiopharmaceuticals will not only continue to increase the importance of this diagnostic technique but also contribute to our understanding of the functioning of the normal brain.

The use of positron emitters usually requires fast chemical separation and synthesis techniques. Fast chemical separation techniques for producing pure radioisotopes are described in Chapter 15, but for rapid chemical synthesis techniques, specialized texts should be consulted.

9.5.4. *Radiation therapy with internal radionuclides*

Radiotracers are also used for therapy though to less extent than in diagnosis (C3b in Table 9.3). The main application is the use of ^{131}I for treatment of thyreotoxicos (Graves disease with enlargement of the thyroid gland), thereby reducing the function of the thyroid. Some data for ^{131}I use: amount administered ca. 200 - 1000 MBq, organ dose to the thyroid $\sim$ 340 nGy/Bq (total dose to the glands $>$ 500 Sv); whole body dose $\sim$ 0.04 nGy/Bq. ^{32}P compounds are used in the bloodstream to destroy excess red blood cells in polycythemia. Diphosphonate compounds localize in normal bone tissue, but concentrate in cancerous bone at relatively higher levels (5 - 15 times higher). Patients receiving this type of radiopharmaceutical experience swift lowering of pain levels.

One of the most fascinating aspects of using radionuclide labelled compounds in medical therapy is to develop monoclonal antibodies, which will seek out particular types of cancer cells and bind to them. If a β-, or α-emitting radionuclide is attached to these antibodies, they will deliver a large absorbed dose to the cancer cells without needlessly irradiating the surrounding tissues. Much research is directed towards this goal of cancer therapy.

9.6. Industrial uses of radiotracers

Industry has applied radiotracers in a very large variety of ways. More than half of the 500 largest manufacturing concerns in the United States use radioisotopes in the production of metals, chemicals, plastics, pharmaceuticals, paper, rubber, clay and glass products, food, tobacco, textiles, and many other products. Radioisotopes are used to study mixing efficiency, effect of chamber geometry, residence time in reactors, flow rates and patterns in columns and towers for fractionation, absorption, racemization, etc. Some of the many uses are listed in Table 9.6 and a few are described below to reflect the scope and value of the industrial applications of radioisotopes. Quite often the radionuclide used is not isotopic with the system studied.

9.6.1. *Mixing*

Mixing is an important mechanical operation in many industries. Poor mixing may give an unsatisfactory product and low yield of the operation; unnecessary mixing is a waste of time and energy. By adding a radionuclide to the mixing vessel, or by labeling one of the components, the approach to mixing equilibrium can be followed either by external measurement or taking samples at different time intervals. Among examples of this technique are fluxing of cement, gravel, sand, and water to concrete measured by using irradiated pebbles. The homogeneity of glass melts can be determined by adding $^{24}NaHCO_3$ to the melt; organic compounds of ^{95}Zr ($\beta^-\gamma$ $t_{½}$ 64.02 d) have been used to follow

TABLE 9.6. *Radioisotope technique studies at ICI† undertaken in a typical year*

Technique	Number of applications
Level and interface measurements:	
Gamma-ray absorption	210
Neutron backscatter	480
Gamma-ray backscatter	71
Blockage detection and deposition:	
Gamma-ray absorption	132
Neutron backscatter	129
Entrainment and voidage:	
Gamma-ray absorption	86
Thickness and corrosion measurements	15
Distillation-column scans	108
Flow measurements:	
Pulse velocity	483
Dilution techniques	84
Leak detection	90
Residence-time studies	21
Carryover studies (tracer)	6

The list is not fully comprehensive as less commonly used techniques have not been included. † Imperial Chemical Industries (UK).

homogenization of oil products. Other uses have been the addition of vitamins to flour, coal powder to rubber, water and gas to oil fields, etc.

9.6.2. *Liquid volumes and flows*

The liquid volume of a closed system may be difficult to calculate from external container dimensions, particularly if there is a mixing action, either by external circulation or by internal stirring. For example, sulfuric acid volume is desired in an alkylation plant where extensive intermixing between acid and hydrocarbon prevents a well-defined level from forming. ^{137}Cs is added to the sulfuric acid and from the dilution of the added tracer the total volume of acid is calculated.

Another method is applicable to determining volumes of tanks through which there is a known constant flow. A tracer batch is put into the incoming line. Mathematical treatment, assuming complete immediate mixing of the incoming stream with the vessel contents, predicts that the tracer concentration in the tank falls off exponentially with a rate determined by throughput F and volume V according to the equation

$$R = R_0 \, e^{-Ft/V} \tag{9.24}$$

where R_0 is the counting rate at zero time (break through of radioactivity at tank exit) and t is the time when the count rate R is obtained at the same point.

The flow rate F of rivers and streams can be measured by injection of a radionuclide and measurement of the time for its arrival at detectors placed downstream. Because of turbulence the radioactive "cloud" becomes quite diffuse. Therefore a more efficient technique called "total count" is used. A known amount (A_0) of the radionuclide is injected into the river and a downstream detector registers a total count (R_{tot}) as the radioactivity passes; the faster it passes, the lower is the measured radioactivity. Thus

$$F = \psi \, A_0 / R_{tot} \tag{9.25}$$

ψ is the counting efficiency which has to be determined under known conditions. The technique takes into consideration both longitudinal and transversal mixing.

9.6.3. *Wear and corrosion*

Wear and materials transfer are easily followed if the material undergoing wear is made radioactive. This has been used for studying wear of parts in automobile engines, cutting tools, ball-bearings, furnace linings, paint abrasions, etc. In this case it is important that the surface undergoing wear has a high specific radioactivity. If the material cannot be tagged by adding (e.g. plating) a radionuclide, the material has to be activated by irradiation (e.g. by accelerator) to produce the radioactive species.

Corrosion in gas and oil pipe-lines on the sea floor is monitored by welding patches containing a series of long-lived radionuclides at different material depth into the pipe wall during construction of the pipe-line. Wall corrosion will remove one isotope after the other

as it proceeds. The presence of these isotopes can be monitored from time to time by sending a capsule with a suitable detector and recorder through the pipe.

9.6.4. *Chemical processing*

We have described some areas of application of radiotracers which are useful to the chemical industry. To be more general, radioactive tracers are used to seek information of flow and mixing patterns for

- parameter evaluations (mass balance, flow rates, kinetics)
- fluid dynamics (trouble shooting, residence time distributions, modelling flow phenomena)
- chemical reaction engineering (effect of flow and mixing on conversions, modelling of reaction systems, process control algorithms).

Each application is rather case specific and described in the chemical engineering literature.

9.7. Environmental applications

Nuclear weapons tests have released large amounts of radionuclides into the atmosphere, which through their own weight or by rain have been carried to the earth's surface. Geophysics has made use of this weapon "fallout". By measurements on T (as HTO water), ^{90}Sr, ^{137}Cs, and other fission products it has been possible to follow the movements of water from land via lakes and rivers into the sea, as well as to study the water streams of the oceans and the exchange between surface and deep water. As a result the circulation of water on earth has been mapped in quite detail. It has also been possible to analyze how tropical hurricanes are formed by measuring the water taken into the central part (the "eye")

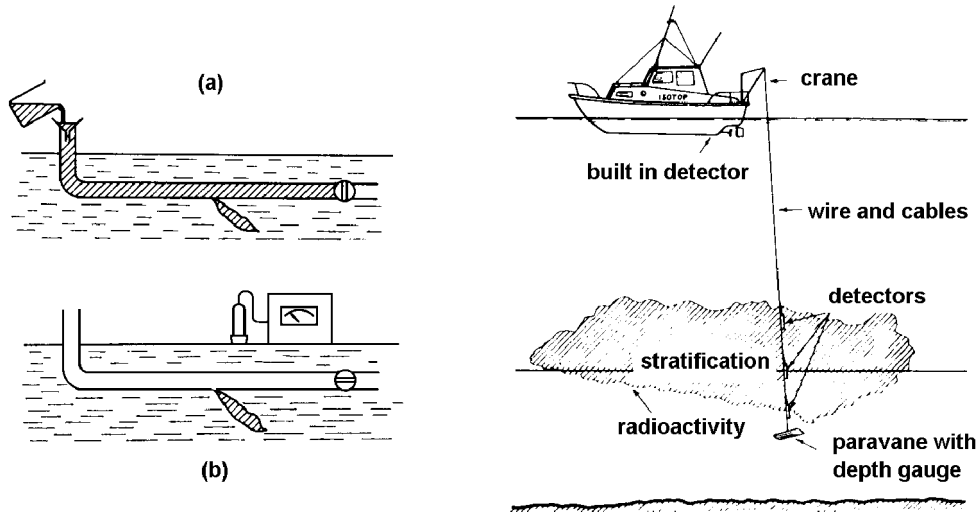

FIG. 9.17. Left, technique for finding leaks in pipes. Right, technique for measuring stream lines in the strait of Öresund. (Courtesy Danish Isotope Center.)

of the cyclone, since the HTO concentration in the normal atmosphere is different from that of surface ocean water due to isotopic effects.

Radioactive tracers like T_2O, $^{24}Na^+$, $^{82}Br^-$ ($\beta^-\gamma$ $t_{½}$ 1.471 d) and ^{51}Cr-EDTA (ECγ $t_{½}$ 27.704 d), are used in hydrology to determine the volume of natural water reserves (even underground) and to map the movement of ground and surface water as well as effluent pathways, Figure 9.17. Also the consumption of water and water flow in industries are readily determined, and leaking dams and pipes checked by radiotracers.

In order to avoid hazardous pollution it is important to discharge communal and industrial waste (silts, liquids, gases) so that the wastes are properly dispersed. The mapping of different dispersal sites is conveniently and commonly carried out by injecting a radioactive tracer at a testing spot, and then following its distribution at various depths, heights, and directions. In such a test it was found that sludge emptied into the River Thames at one point traveled upstream, which led to a repositioning of the sludge pipe exit. The simple technique of identifying hidden pipe leaks is illustrated in Figure 9.17 left. This technique is used not only for liquids, but also for checking the seal of underground electric cable hoses in which case gas tracers like ^{85}Kr ($\beta^-\gamma$ $t_{½}$ 10.72 y) or ^{133}Xe ($\beta^-\gamma$ $t_{½}$ 5.24 d) are used.

Westermark and co-workers have developed a unique method of revealing environmental history of natural rivers during the last 100 - 200 years. It is based on the freshwater pearl mussel *Margaritana margaritifera* living in these river. The mussel adds a new outer layer to its shell each year, incorporating into it trace metals (and also to some extent organics) dissolved in the water. The shell is cut and sectioned into small pieces, which are analyzed by α-track autoradiography, INAA and μ-PIXE. The latter is a "microprobe"-PIXE, i.e. the proton beam is focused by lenses to a resolution of a few microns. To get sufficient information the shell sample usually covers 3 - 15 years. With these techniques concentrations of some 30 elements have been determined retrospectively for > 100 years in a number of Swedish rivers. Several unexplained trends have been observed, e.g. decreases in Ag, Au, Fe and Co. This is believed to be related to increasing air concentrations of SO_2. The observation of an increase in Br beginning in the 1940's is believed to be due to Br-additions to gasoline fuel. The technique has great potentials for increasing our knowledge on environmental changes of trace elements in nature. It could also be used as a long term biochemical control system at environmentally strategic places.

9.8. Exercises

9.1. The blood volume of a patient is to be determined by means of ^{32}P. For this purpose 15.0 ml of blood is withdrawn from the patient and mixed with a very small volume of $Na_2H^{32}PO_4$ of high specific activity. In 1 h the erythrocytes (red blood cells) take up all the ^{32}P; 1 ml is found to have an activity of 216 000 cpm in the detector system used. Exactly 5.00 ml of this tagged sample is reinjected into the patient, and 30 min later a new sample is withdrawn; 10 ml of this gives 2300 cpm. Calculate the blood volume.

9.2. A mixture of amino acids is to be assayed for cysteine. A 1.0 ml sample (density 1 g ml^{-1}) is withdrawn, and 2.61 mg of ^{35}S labeled cysteine of specific activity 0.862 μCi mg^{-1} is added. From this mixture pure cysteine is isolated by liquid-partition chromatography; 30.6 mg is isolated and measured to give 169 000 cpm in 27% detection efficiency. What is the percentage of cysteine in the original mixture?

9.3. In order to determine the lead content of a color pigment, 8.9871 g was dissolved in conc. HNO_3, and 5.00 ml ^{210}Pb solution added. After excess acid had been removed through evaporation, excess 1 M NaCl was added, the solution heated and filtered. After cooling and crystallization, the $PbCl_2$ was washed and recrystallized, 0.3276

g of the crystals was measured in a scintillation counter, giving 185 160 counts in 5 min. 1.000 ml of the original ^{210}Pb solution gave 57 000 cpm. The background was 362 cpm. Calculate the lead content (%) of the pigment.

9.4. What is the smallest amount of indium which can be determined in a 100 mg aluminum sample using NAA with a neutron flux of 10^{16} n m^{-2} s^{-1}? Consider the neutron capture in both ^{27}Al and ^{115}In: ^{27}Al(n,γ σ 0.230 b)^{28}Al $t_{½}$ 2.25 min; ^{115}In(n,γ σ 45 b)^{116}In $t_{½}$ 14 s. The lowest detectable activity for ^{116}In is assumed to be 10 Bq, and the interference from ^{28}Al not more than 20%.

9.5. In order to determine the amount of gallium in meteorite iron, 373.5 mg meteorite iron (A) and 10.32 mg gallium oxinate (B) were irradiated in a reactor under similar conditions in 30 min. After a short cooling, A was dissolved in concentrated HCl and 4.53 mg inactive Ga^{3+} was added. After a number of chemical separation steps, which were not quantitative, a precipitate of 25.13 mg pure gallium oxinate was isolated (C). Sample B was also dissolved and diluted to 50 ml; 0.50 ml was removed, 4 mg inactive Ga^{3+} added, and gallium oxinate precipitated (D). The radioactive decay curves gave two straight lines: $\log R_C = 3.401 - 0.0213\,t$, and $\log R_D = 3.445 - 0.0213\,t$. What was the gallium content in sample A?

9.6. A 10.0 g sample of iodobenzene is shaken with 100 ml of 1 M KI solution containing 2500 cpm ^{131}I. The activity of the iodobenzene at the end of 2 h is 250 cpm. What percent of the iodine atoms in the iodobenzene have exchanged with the iodide solution?

9.7. A sodium iodide solution contains some radioactive ^{131}I. An ethanol solution was prepared containing 0.135 M of this sodium iodide and 0.910 M inactive C_2H_5I. In the exchange reaction

$$C_2H_5I + {}^{129}I^- \underset{kr}{\overset{kf}{\rightleftarrows}} 6\ C_2H_5{}^{129}I + I^-$$

the reaction rate constant is assumed to be the same in both directions: kf = kr. One part (A) of the solution was removed and heated to high temperature so that equilibrium was rapidly reached. Another part (B) was kept in a thermostated bath at 30°C. After 50 min ethyl iodide was separated from both solutions. The concentration of radioactive iodine in C_2H_5I in B was found to be only 64.7% of that in A. Calculate k ($k_r = k\,a\,b$ in §9.4.2).

9.8. With Figure 9.9 one can estimate the stability constants (β_1 - β_3) for the lutetium acetylacetonate complexes. Make this estimation using Figure 9.9. A simplified approach to estimate β_n is the use of the approximate relations $k_n = \beta_n/\beta_{n-1} = 1/[\mathrm{Aa}]_{\bar{n}=n-0.5}$ and $\bar{n} = z - \mathrm{d}(\log D)/\mathrm{d}(\log[\mathrm{Aa}])$; for Lu^{3+} $n \leq 4$, but $z = 3$.

9.9. Calculate β_4 and the distribution constant using (9.23a) and Figure 9.9.

9.10. One wants to determine the residual liquid volume of a closed sedimentation tank (nominal volume 80 m^3), which has been in use for many years, and in which $CaSO_4$ precipitates. 0.50 ml $^{24}Na_2SO_4$ (specific activity 3.2×10^8 cpm ml^{-1}) is added to the tank, and 10 ml withdrawn after 2 h of settling; measurements yield a net value (background subtracted) of 500 counts in 10 min. Calculate the free liquid volume in the tank.

9.11. Calculate the critical deposition potential ($E - E^0$) for 10^{-12} M ^{210}Bi on a gold cathode (no over-voltage) from the Nernst equation (9.4), where the chemical activity of the reduced state (Bi^0) is set to unity.

9.12. A mineral ore contains cobalt and small amounts of nickel. In order to determine the nickel concentration it must be separated from cobalt. Solvent extraction using 0.01 M 8-hydroxyquinoline in $CHCl_3$ is chosen. Which metal should be extracted from the other, and at what pH? Consider Figure 9.3 and connected text.

9.13. In a solvent extraction system consisting of uranium and lanthanum in 1 M HNO_3 and 100% TBP, $D_U = 20$ and $D_{La} = 0.07$. If a phase ratio $\theta = V_{org}/V_{aq} = 0.5$ is chosen, how much uranium is removed from the aqueous phase in three repeated extractions? How much of the lanthanum is co-extracted? The fraction extracted with n fresh organic volumes (V_{org}) from one aqueous volume (V_{aq}) is:

$$E_n = 1 - (1 + D\,\theta)^{-n} \qquad (9.26)$$

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