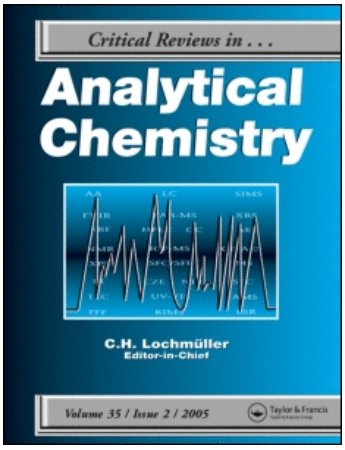

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N. K. Baishya; R. B. Heslop; James R. DeVoe

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PRINCIPLES AND APPLICATIONS OF SUBSTOICHIOMETRIC TECHNIQUES OF ANALYSIS

Authors: **N. K. Baishya**
Chemistry Department
The University of Gauhati
Gauhati-14
Assam, India

R. B. Heslop
Chemistry Department
The University of Manchester Institute of Science and Technology
Manchester, M60 1QD, England

Referee: James R. DeVoe
Analytical Chemistry Section
National Bureau of Standards
Washington, D.C.

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I. INTRODUCTION

The production of radioisotopes of most of the elements has been made possible in the last 25 years with the development of nuclear reactors, and radiochemical methods of analysis are ceasing to be thought of as specialized techniques. Radioanalytical methods are of particular importance in the determination of traces of elements in various materials, and the method of neutron-activation analysis has proved notably useful for a large number of the elements. This method is a particularly sensitive one which enables picogram quantities of some elements to be determined with acceptable precision. Radioisotope-dilution analysis is another technique which takes advantage of the high sensitivity of the measurement of the radiation emitted by radionuclides. However, this technique has not been developed as successfully as that of neutronactivation for a number of reasons which we shall discuss later.

There is little doubt that the development of radioanalysis was hindered for several years because the chemical separation of the element had to be followed by a determination of the specific activity, and therefore of the weight, of the fraction which was isolated for radioassay. This impediment affected the growth of radioisotope-dilution analysis much more than that of neutron-activation analysis, a particularly unfortunate consequence, because the former technique does not require a source of neutrons and generally requires less time than the latter.

In the past decade, however, the application of the substoichiometric principle[1] to radiochemical separations has greatly simplified the procedures for both neutron-activation analysis and radioisotope-dilution analysis. The basic principle behind both is the same, namely, that by the use of substoichiometric amounts of reagent it becomes possible to equate the ratio of the specific radioactivities of a sample and a standard to that of their respective radioactivities. Nevertheless, we shall begin this review by describing the application of the principle first to activation analysis and then to dilution analysis, because we feel that this treatment will clarify the principle.

II. THE PRINCIPLES OF SUBSTOICHIOMETRIC SEPARATION

A. Radioactivation Analysis

A method of analysis in which the amount of a particular element is determined by measuring its

radioactivity is called a radiometric method. Natural potassium, for example, contains the radioisotope potassium-40 which is always present in the same isotopic abundance. It is therefore possible to determine the weight of potassium, w, in a sample by measuring the count-rate, A, obtained from it, and comparing with the count-rate A_s obtained from a standard, a pure potassium salt containing a known weight w_s of the element, under exactly the same conditions in the same counting equipment. The relation is simply

$$w = \frac{w_s A}{A_s} \qquad (1)$$

The only condition is that the radioactivity be due solely to potassium.

The vast majority of the elements we wish to determine by analysis are not naturally radioactive, but we can produce radionuclides from most of them by irradiation in a flux of neutrons, of charged particles such as α-particles, protons or deuterons, or in some cases of γ-rays. If a sample and a standard are irradiated under conditions in which the activating flux can be assumed to be uniform, the amounts of the product nuclide obtained in the two are exactly proportional to the amounts of target nuclide originally present in them. In practice, the easiest uniform activating flux to produce is that of thermal neutrons in a nuclear reactor; furthermore, neutrons are particularly versatile for initiating nuclear reactions. Neutron activation is in fact the most common form of radioactivation which is used.

Suppose we irradiate a copper-containing alloy of known weight and a piece of pure copper of mass w_s in the same small can in a nuclear reactor. The weight of copper in the alloy, w, should be related to the radioactivity induced in the sample, represented by a count-rate A in a particular counting apparatus, by an equation of the same form as Equation 1, where A_s in this case is the count-rate given by the pure copper. The only condition is that all the radioactivity should be due to isotopes produced from the irradiation of copper, but in most cases this condition is not met. Suppose, for example, the alloy contains aluminum; then activity due to sodium-24 as well as activity due to copper-64 will be induced in the sample:

$$^{27}_{13}\mathrm{Al}(n,\alpha) \rightarrow {}^{24}_{11}\mathrm{Na}(\beta^-,\ 1.39\ \mathrm{MeV},\ 15\ \mathrm{hr})$$

$$^{63}_{29}\mathrm{Cu}(n,\gamma) \rightarrow {}^{64}_{29}\mathrm{Cu}(\beta^-,\ 0.57\ \mathrm{MeV},\ \beta^+ \text{ and } \gamma,\ 12.8\ \mathrm{hr})$$

As a consequence of the production of a radionuclide other than that formed from the copper, a direct measurement of the β-activities of sample and standard would be quite worthless in such a typical case. In about 80% of the procedures which have been reported for determining traces of elements by neutron-activation analysis, some kind of chemical separation has proved necessary. Before meaningful measurements can be made, radiochemically pure specimens have to be prepared, i.e., specimens in which all the radioactivity is due to radioisotopes of the same element in the same oxidation state. The radionuclide which is eventually assayed is usually isotopic with the element to be determined, but is not necessarily so. For example, the most precise method for determining traces of sulfur by neutron activation resolves finally into the measurement of the activity from the phosphorus-32 formed in the reaction

$$^{32}\mathrm{S}(n,p) \rightarrow {}^{32}\mathrm{P}(\beta^-,\ 1.71\ \mathrm{MeV},\ 14.3\ \mathrm{d})$$

in preference to the sulfur-35 produced in the reaction

$$^{34}\mathrm{S}(n,\gamma) \rightarrow {}^{35}\mathrm{S}(\beta^-,\ 0.17\ \mathrm{MeV},\ 87\ \mathrm{d})$$

The production of a radiochemically pure specimen for radioassay involves a chemical separation such as precipitation, solvent extraction, ion exchange, or electrolysis. A typical precipitation procedure can be exemplified by the determination of copper at the 10 ppm level in a specimen of aluminum foil weighing 50 mg. When the specimen is dissolved after irradiation, the solution contains only 0.5 μg of copper, an amount that is insufficient for satisfactory precipitation, for example as CuCNS. It is customary to add at this stage an isotopic carrier, an inactive solution of Cu^{2+} ions sufficient to raise the total copper content of the solution to about 10 mg in a typical case. A pure specimen of copper(I) thiocyanate is then made by reducing Cu(II) to Cu(I) and precipitating with an excess of CNS^- ions.

In treating the standard which was irradiated with the sample we have to recognize that a suitable 50-mg specimen of the pure metal contains 10^5 times as much copper as the sample itself. A suitable procedure would be to dissolve the standard, and by successive dilutions to make up a suitable volume containing only about 0.5 μg. It would then be necessary to add carrier before precipitation, exactly as for the sample. The

procedure ensures that the actual count-rates obtained from the radiochemically pure precipitates are of similar magnitude, which is the preferred condition for satisfactory radioassay.

If the same amount of carrier is added in each case and the efficiency of the precipitation is the same, the weight of copper in the sample, w, is related to the weight in the standard, w_s, by the equation

$$w = d w_s \frac{A}{A_s} \quad (2)$$

where d is the dilution factor, the fraction of the standard selected for preparation of the specimen for radioassay, and A and A_s are the count-rates given by the precipitates from sample and standard, respectively, in the same position in the same counting equipment.

If, however, the amounts of carrier added are the same but the weights of precipitate obtained from sample and standard are, respectively m and m_s, Equation 2 is modified to

$$w = d w_s \frac{a m_s}{a_s m} \quad (3)$$

where a and a_s are the count-rates obtained from the two precipitates. The principles are exactly the same if the specimens for radioassay are separated by solvent extraction or any other mode of separation which employs an excess of reagent.

Thus, activation analysis involving such procedures of radiochemical separation requires the measurement of the chemical yield of the separation process as well as the activity. However, if the same amount of the element from both the test sample and the standard can be isolated from an exactly equal amount of the carrier added (i.e., $m = m_s$), only a measurement of activity will be required.

Equation 3 then reduces to

$$w = d w_s \frac{a}{a_s} \quad (4)$$

and the quantity of the element to be determined can be computed directly from the count-rates obtained from the sample (a) and from the standard (a_s) provided the following two conditions are fulfilled:

1. The amount of inactive isotopic carrier added to the test sample must be exactly equal to the amount added to the standard sample in the chemical treatment following irradiation.

2. Exactly the same amount of the element which is to be determined must be isolated for radioassay from the prepared solutions.

The first condition can be fulfilled by adding to both the sample and the standard exactly equal amounts of the carrier in large excess compared with the weight of element to be determined (w). Circumstances in which the carrier cannot be added in large excess should hardly ever arise. The value of w rarely needs to exceed a microgram unless the element to be determined has a particularly low cross section for activation, the neutron flux available is particularly weak, or the product nuclide has a long half life. Moreover, if the approximate value of w is known, the amount of standard which is used for chemical separation is such that $d\ w_s$ is $(1 \pm 0.2)w$, the sum of inactive isotope and active isotope will be the same within 1% in the two prepared solutions even if there is only a 20-fold excess of carrier; in such cases the solutions will effectively satisfy the first condition.

The second condition is achieved by adding to the solutions of the sample and the standard equal amounts of the complexing or precipitating reagent which are smaller than the amount corresponding stoichiometrically to the quantity of carrier present. The reagent used must either be consumed quantitatively or at least to the same extent in the formation of the complex, and the complex formed must be easily separable from the excess of unreacted element.

Thus, the course of a substoichiometric determination by neutron-activation analysis can be summarized as follows.

1. Standard and test samples are irradiated simultaneously under the same conditions.

2. After dissolving the samples and the standard, exactly equal amounts of the carrier are added to both solutions.

3. Both solutions are treated simultaneously under the same conditions with a substoichiometric amount of a suitable organic reagent, and the resulting compound is then separated from the unreacted ions by appropriate separation procedures.

4. Finally, the activity of exactly equal amounts of the separated element is measured under the same counting conditions.

B. Radioisotope-dilution Analysis

In radioisotope-dilution analysis, a knowledge

of the specific activities before and after isotopic dilution is essential. To calculate this, it must be possible to isolate enough of the material under study to permit evaluating both m and m_s, either by weighing a suitable form of precipitate or by other physicochemical methods. This is naturally rather difficult in trace analysis. However, if it is possible to separate from the solution of original specific activity S_s ($=a_s/m_s$) and from the solution having after isotopic dilution the specific activity S ($= a/m$) exactly equal weights of the element to be determined (i.e., $m = m_s$), the weight, w, of the element in the test sample can be computed directly from the activities which are isolated, using the equation

$$\underline{w} = \underline{w}_s\left(\frac{\underline{a}_s}{\underline{a}} - 1\right) \qquad (5)$$

instead of

$$\underline{w} = \underline{w}_s\left(\frac{\underline{S}_2}{\underline{S}_1} - 1\right) \qquad (6)$$

For successful determination of the test element the following conditions must be fulfilled.

1. Isotopic equilibrium must be achieved in the sample formed by mixing of the radioactive and inactive species.

2. The weight of radioisotope (w_s) added to the test sample must be precisely known. It can be determined either by reverse isotope dilution or by the general technique used in neutron-activation analysis. These first two conditions apply to all radioisotope dilution analyses, whether stoichiometric or substoichiometric.

3. The activities a_s and a must be substoichiometrically isolated, using exactly the same amount of reagent, from both the standard solution of the radionuclide and its mixture with the test solution. The amount of reagent must be less than that which corresponds stoichiometrically to the total amount of element in the less concentrated solution.

The same principle can also be applied in reverse isotope-dilution analysis.[2] In this method two different portions of a solution of radionuclide of original specific activity S_s are mixed with equal volumes of the test solution containing an unknown weight w of the test element. The specific activities are then:

$$\underline{S}_1 = \frac{\underline{S}_s\underline{w}_1}{\underline{w}_1 + \underline{w}} \quad \text{and} \quad \underline{S}_2 = \frac{\underline{S}_s\underline{w}_2}{\underline{w}_2 + \underline{w}}$$

where w_1 and w_2 are the weights of radioisotope added to the first and second halves of the test solution, respectively. From the above equations

$$\underline{w} = \frac{\underline{w}_2(\underline{S}_2 - \underline{S}_1)}{\underline{S}_1\underline{w}_2/\underline{w}_1 - \underline{S}_2} \quad . \qquad (7)$$

If the specific activities $S_1 = a_1/m_1$ and $S_2 = a_2/m_2$ and if $m_1 = m_2$, Equation 7 becomes simply

$$\underline{w} = \frac{\underline{w}_2(\underline{a}_2 - \underline{a}_1)}{\underline{a}_1\underline{w}_2/\underline{w}_1 - \underline{a}_2} \quad , \qquad (8)$$

where a_1 and a_2 are the activities substoichiometrically isolated from the first and second halves of the test solution.

III. THE PRINCIPLES OF SOME METHODS OF SUBSTOICHIOMETRIC SEPARATION

Out of the large number of analytical separation procedures available, the choice of one for substoichiometric separation will depend largely on the nature of the element to be analyzed and also on the number and nature of the accompanying elements. A theory underlying the different substoichiometric methods of separation[13] will enable one to choose the optimum conditions to be used so as to increase the selectivity of a reagent even when it is not a specific one for the particular element to be analysed. The most commonly used methods are:

A. Precipitation,
B. Solvent extraction of metal chelates,
C. Solvent extraction of ion-association compounds,
D. Ion-exchange separation of water-soluble chelates,
E. Electrolysis, and
F. Replacement substoichiometry.

A. The Precipitation Method

In measuring the chemical yield in neutron-activation analysis or the change in specific activity in isotope-dilution analysis, a gravimetric determination by precipitation of the desired element with a suitable reagent is widely used. However, if an excess of precipitating reagent is employed,

other elements which are present may also be precipitated in large amounts. Substoichiometric precipitation increases the selectivity and also obviates the need for the absolute determination of chemical yield, though the reproducibility of the method must naturally be established in a preliminary investigation. Since the activity is measured on equal amounts of the precipitate (precipitated by the same substoichiometric amount of the reagent), the precipitates need not be dried to constant weight.

Although it is rare for one precipitating reagent to be specific for a particular metal, the threshold pH for effective precipitation depends quite critically on the solubility product of the complex which is formed, if, as in the usual case, the precipitating agent is a weak organic acid.

Let us consider the general precipitation reaction

$$M^{n+} + nHA = MA_n + nH^+ \quad .$$

If the acid dissociation constant of HA is given by

$$K_{HA} = \frac{a_{H^+} \cdot a_{A^-}}{a_{HA}}$$

and the solubility product of MA_n by

$$K_s = a_{M^{n+}} \cdot (a_{A^-})^n \quad ,$$

then the condition for precipitation is that the product $a_{M^{n+}} \cdot (a_{A^-})^n$, which is $a_{M^{n+}} \{(K_{HA} \cdot a_{HA}/a_{H^+})\}^n$, is greater than K_s.

Suppose that under the conditions of the substoichiometric precipitation at least 99.9% of HA is to react to form precipitate, then a_{HA} must be less than 0.001 c_{HA}/mole l^{-1}* where c is the original concentration of HA.

Thus

$$\frac{a_{M^{n+}} \times \left\{K_{HA} \times (0.001\ c_{HA}/\text{mole}\ l^{-1})\right\}^n}{(a_{H^+})^n} > K_s \qquad (9)$$

Rearranging and taking logarithms:

$$pH > \frac{1}{n}\left\{n(pK_{HA}) - pK_s - \log a_{M^{n+}} - n \log \frac{c_{HA}}{\text{mole}\ l^{-1}} + 3n\right\} \qquad (10)$$

As the solutions of metal ion and reagent in neutron-activation analysis separations usually have concentrations near 10^{-2} mole l^{-1}, Equation 10 becomes

$$pH > \frac{1}{n}\left\{n(pK_{HA}) - pK_s + 2 + 5n\right\} \qquad (11)$$

For iron (III) cupferrate, $pK_s = 25$, $pK_{HA} = 4.2$, and $n = 3$; hence cupferron is used up quantitatively in the substoichiometric precipitation of Fe^{3+} if the pH exceeds 1.5. For aluminum cupferrate, for which $pK_s \doteq 18.6$, the pH must exceed 3.7. Thus, the selectivity of the reagent depends on the choice of pH, and may be further increased if necessary by the use of masking agents.

A substoichiometric separation by a precipitation reaction is always to be preferred to one using an excess of reagent, because the only metal ion to be precipitated is that which forms the most insoluble complex under the conditions, whereas an excess of reagent would be more likely to precipitate other metal ions present in the solution. The major disadvantage of precipitation methods is that there is always a certain amount of adsorption and coprecipitation of traces of non-isotopic radionuclides which may be produced in irradiation.

B. Solvent Extraction of Metal Chelates

One of the most efficient methods of separation, used in various fields of chemistry, is the method of solvent extraction, in which a chelate formed between a metal and an organic complexing reagent is extracted by a suitable organic solvent. The method has been adapted with success for substoichiometric separation. In practice, the desired element is made to combine with less than the stoichiometric amount of a chelating reagent, and the resulting compound is separated by extraction into a suitable organic solvent. Since few of the reagents are specific, the primary consideration is to improve the selectivity for the desired element. The optimum conditions can be derived from the equation for the extraction process:

$$M^{n+}_{aq} + n(HA)_{org} = (MA_n)_{org} + nH^+_{aq} \qquad (12)$$

The extraction constant K_{ext}, is given by

$$K_{ext} = \frac{[MA_n]_{org}\ [H^+]^n}{[M^{n+}]\ [HA]^n_{org}} \qquad (13)$$

*The notation is intended to emphasize that the concentration c expressed in moles l^{-1} must be divided by moles l^{-1} to give a dimensionless quantity equal to the relative activity a. See Heslop, R. B., *Numerical Aspects of Inorganic Chemistry*, Elsevier, Amsterdam, 1970.

For more than 99.9% of HA to be used in forming the complex

$$[MA]_{org} > 0.999 \frac{c_{HA}}{n} ,$$

where c_{HA} is the original concentration of HA in the organic phase. In these conditions the total amount of complexed metal is given by $\frac{c_{HA}}{n} \times V_{org}$, where V_{org} is the volume of solvent, and the total amount of the metal left unreacted in the aqueous phase, $[M^{n+}]\ V_{aq}$, is given by

$$[M^{n+}]\ \underline{v}_{aq} = (\underline{c}_M \cdot \underline{v}_{aq}) - \left(\frac{\underline{c}_{HA}}{n} \cdot \underline{v}_{org}\right) \qquad (14)$$

The threshold pH for the condition $[HA]_{org} = 0.001\ c_{HA}$ can thus be derived by substituting in Equation 13 and rearranging to obtain

$$[H^+]^n = \frac{\underline{K}_{ext} \left(\underline{c}_M - \frac{\underline{c}_{HA} \cdot \underline{v}_{org}}{n\ \underline{v}_{aq}}\right) (0.001\ \underline{c}_{HA})^n}{\frac{\underline{c}_{HA}}{n}} \qquad (15)$$

Replacing equilibrium concentrations by relative activities using

$$\underline{a}_x = \frac{[x]}{\text{mole } \ell^{-1}}$$

which is acceptable since the solutions are dilute, and hence making K_{ext} dimensionless also, it is possible to express Equation 15 in the logarithmic form

$$pH = \frac{1}{n} \log \left(\frac{1}{n} \cdot \frac{\underline{c}_{HA}}{\text{mole } \ell^{-1}}\right) - \frac{1}{n} \left(\frac{\underline{c}_M}{\text{mole } \ell^{-1}}\right)$$

$$- \frac{\underline{v}_{org}}{n\ \underline{v}_{aq}} \cdot \frac{\underline{c}_{HA}}{\text{mole } \ell^{-1}} - \frac{1}{n} \log \underline{K}_{ext}$$

$$- \log \frac{0.001\ \underline{c}_{HA}}{\text{mole } \ell^{-1}} \qquad (16)$$

The first two terms on the right have little influence on the threshold value of the pH. If, as in a typical case, the amount of HA which is added is one half of the stoichiometric amount required, and $V_{org} = V_{aq}$, the sum of these first two terms is zero.

In activation analysis the weight of carrier added is commonly about 10 mg in 10 ml, and the corresponding value of c_{HA} is therefore of the order of 10^{-2} mole l^{-1}. Thus, Equation 16 can be simplified to

$$pH = 5 - \frac{1}{n} \log \underline{K}_{ext} \qquad (17)$$

Thus, the threshold value of pH for the determination of a metal can be predicted if K_{ext} is known.

Figure 1 illustrates the variation with pH of the efficiency of extraction of Bi^{3+} with a substoichiometric amount of dithizone in carbon tetrachloride, in which the concentrations are approximately as described above. For this system log $K_{ext} = 9.98$ and therefore

$$5 - \frac{1}{n} \log \underline{K}_{ext} = 5 - \frac{9.98}{3} = 1.7 .$$

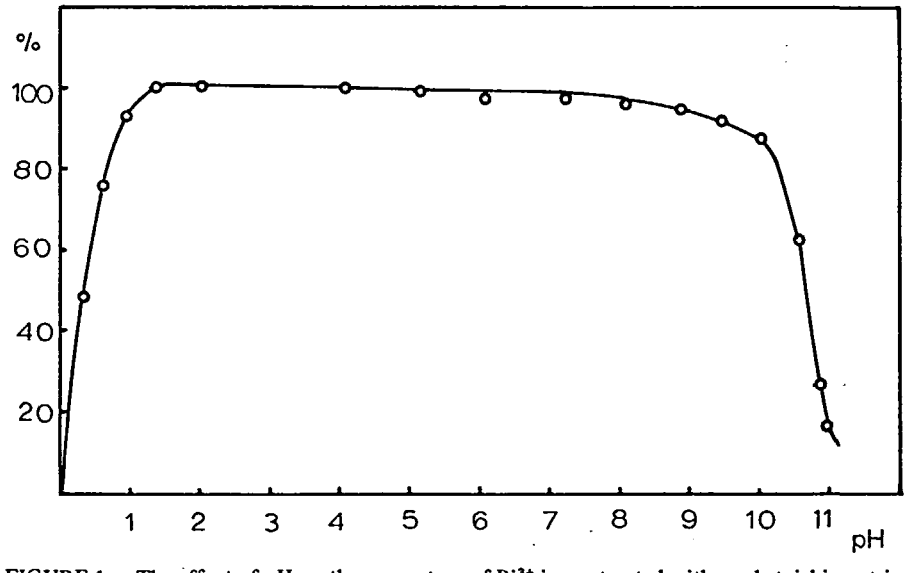

FIGURE 1. The effect of pH on the percentage of Bi^{3+} ion extracted with a substoichiometric amount of dithizone in carbon tetrachloride.

The poorer extraction at very high pH is probably due mainly to the formation of insoluble hydrated bismuth oxide.

The form of the curve for the pH dependence of the extraction of molybdenum(VI) with oxine in chloroform (Figure 2) at the high pH end is probably due mainly to changes in the character of the Mo(VI) species and to the dissociation of the oxine.

The suitability of a reagent can be assessed from the effect of pH on the extractability of the metal chelate. Data on the extraction of various metals with an excess of acetylacetone in benzene,[4] dibenzoylmethane in benzene,[5] benzoylacetone in benzene,[4] 8-hydroxyquinoline in chloroform,[5] cupferron in chloroform,[6] dithizone in carbon tetrachloride,[7] and with dimethylammonium-diethyldithiocarbamate in carbon tetrachloride or in chloroform[8] provide information on the optimum pH conditions to be used for the extraction of their metal chelates and, in many cases, for the avoidance of interference.

In the determination of trace amounts of metal by isotope-dilution analysis, the amount of metal isolated is usually between 1 ng and 1 μg, and this is usually isolated in a volume of about 10 ml. These figures correspond approximately to concentrations of 10^{-5} to 10^{-8} mole l^{-1} of the reagent in an organic phase. Usually, for convenience, the volume of the organic solvent chosen is one tenth of the volume of the aqueous phase. If more than 99% of the reagent is to react with the metal ion during formation of the extractable chelate (i.e., $[HA]_{org} < 0.01\ c_{HA}$), the pH of the extracted solution must satisfy the condition

$$pH > -\log \frac{0.01\ c_{HA}}{\text{mole } l^{-1}} - \frac{1}{n} \log K_{ext} \quad ,$$

i.e., $pH > 10 - \frac{1}{n} \log K_{ext}$ for the weakest of the solutions mentioned above.

This indicates that the determination of trace amounts of metals by radioisotope dilution must be carried out at higher pH than similar determinations by neutron-activation analysis. The choice of the reagent is, therefore, limited by two factors.

1. The reagent used must form an extractable chelate for which the value of the extraction constant, K_{ext}, is sufficiently high to permit carrying out the determination in an acidic medium, thereby reducing the possibility of interference caused by hydrolysis or adsorption of the test element on the walls of the vessels.

2. The organic reagent is a weak acid, and at higher pH it passes into the aqueous phase because of dissociation. Extraction should be carried out from a medium whose pH does not exceed the value

$$pK_{HA} + \log c_{HA} + \log \frac{V_{org}}{V_{aq}} \quad ,$$

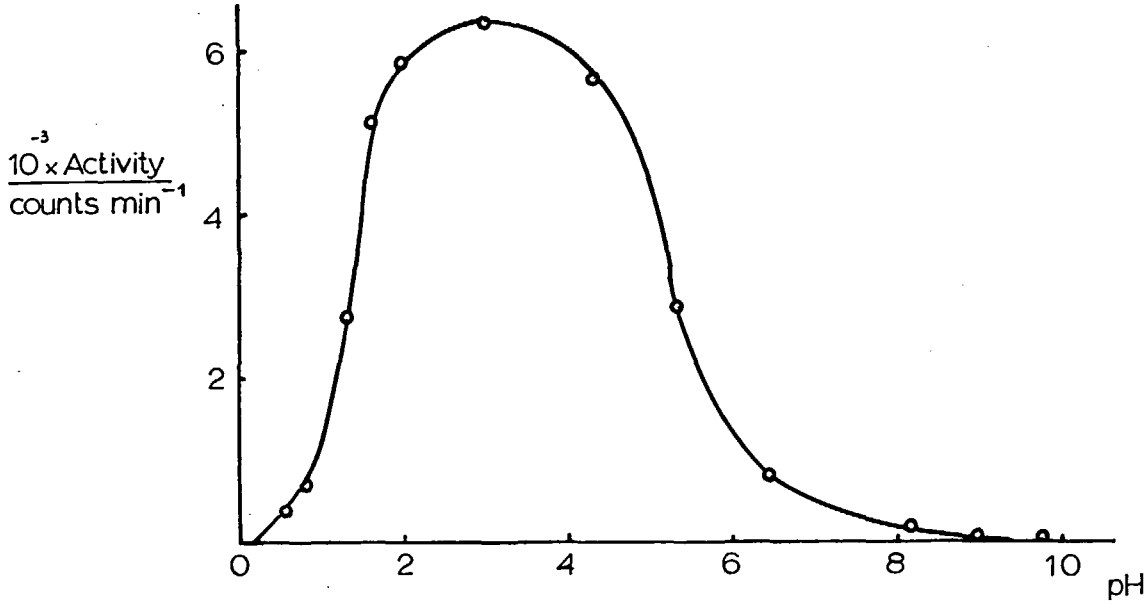

FIGURE 2. The substoichiometric extraction of molybdenum with oxine in chloroform: dependence on pH.

where q_{HA} is the distribution coefficient for HA between organic and aqueous solvents.

For this reason the number of suitable reagents for radioisotope-dilution analysis is limited in comparison with those for neutron-activation analysis.

Before we leave the subject of the solvent extraction of metal chelates we should examine the effect of using a substoichiometric amount of reagent on the selectivity of the method. Consider two metals M and M′ which, respectively, form complexes MA_n and $MA_{n'}$, with HA. If the extraction constant for the former is K and that for the latter is K' into the same solvent, it can be shown by substitution in Equation 13 that for a mixture of the two metal ions in aqueous solution extracted by HA in the organic solvent:

$$\frac{[MA_n]_{org}}{[M'A_{n'}]_{org}} = \frac{K\,[HA]_{org}^{(n-n')}\,[M]_{aq}}{K'\,[H^+]^{n-n'}\,[M']_{aq}}$$

at equilibrium. Supposing that the initial concentrations of the metal ions are the same and a stoichiometric amount of HA is used, then for $[M]_{aq}$ to be less than $10^{-2}\,[M']_{aq}$ at equilibrium when $n = n'$, the ratio K/K' must exceed 10^4 for 100 times more of M than of M′ to be extracted. But if only sufficient reagent is added to convert one half of M to the complex, the ratio $[M]_{aq}/[M']_{aq}$ at equilibrium is about 0.5 and the ratio K/K' need only exceed 200 for 100 times more of M than M′ to be extracted under otherwise similar conditions. The argument is somewhat altered if $n' \neq n$ because the selectivity is then pH-dependent, but the use of a substoichiometric amount of reagent will always increase selectivity. Similarly it can be shown that the use of a substoichiometric amount of reagent increases the selectivity of precipitation methods also. The selectivity may be further increased if necessary by the use of masking agents which form stronger complexes with M′ than with M.

C. Solvent Extraction of Ion-association Compounds

The technique of substoichiometric separation based on solvent extraction of metal chelates is applicable to elements which form chelates with very high extraction constants but not to those with low extraction constants or to non-metallic elements. However, the solvent extraction of ion-association compounds can often be used with advantage for substoichiometric separation. The possibility of solvent extraction of ion-association compounds has been considered theoretically by Alimarin and Perezhogin[9] and by Ruzicka and Zeman[10] who discuss extraction of anions with heavy cations such as tetraphenylarsonium, tetraphenylphosphonium, and tetraphenylsulfonium. The extraction can be expressed as follows:

$$nT^+ + Z^{n-} = [T_nZ]_{org} \qquad (18)$$

where T^+ is the heavy cation and Z^{n-} is the anion to be extracted. The extraction constant is given by

$$K_{ext} = \frac{[T_nZ]_{org}}{[T^+]^n\,[Z^{n-}]} = \frac{q}{[T^+]^n} \qquad (19)$$

For a substoichiometric separation to be reproducible, at least 99% of the heavy cation must be consumed in forming an extractable compound with the element to be separated. Therefore, for $n = 1$,

$$[T_nZ]_{org} \cdot V_{org} > 0.99\, c_T \cdot V_{aq} \qquad (20)$$

where V_{org} and V_{aq} are the volumes of the organic and aqueous phases and c_T is the original concentration of the cation. After the equilibrium has been reached

$$[T^+] < 0.01\, c_T \quad \text{and} \quad [Z^-] = c_Z - c_T \ ,$$

where c_Z is the original concentration of the anion in question.

Thus, if less than 1% of the cation is to remain unreacted in the aqueous phase when extraction equilibrium is reached, the value of the extraction constant must correspond to

$$K_{ext} = \frac{c_T\,(V_{aq}/V_{org})}{(0.01\,c_T)\,(c_Z - c_T)} \qquad (21)$$

In a typical practical example $V_{aq}/V_{org} = 5$ and $c_Z = 2\,c_T$, (i.e., the amount of heavy cation is one half of the stoichiometric one). Equation 21 then becomes

$$K_{ext} > \frac{500}{c_T} \ . \qquad (22)$$

In neutron-activation analysis, where milligram amounts of carrier are usually used, c_T is about 1 to 10 mmole l^{-1} and the value of the extraction constant, K_{ext}, must be 5×10^4 to 5×10^5

In the case of isotope-dilution analysis, where reagent concentrations are much lower, the value of K_{ext} must be extremely high, as high as 5×10^{11} where the sample contains only nanograms of the element to be determined.

TABLE 1

Extractabilities of Various Anions in the Form of Ion-association Compounds with Tetraphenylarsonium (TPA), Tetraphenylsulfonium (TPS) and Tetraphenylphosphonium (TPP) Ions Using Chloroform as a Solvent

Reagent	TPA $\log_{10}\frac{K_{ext}}{\text{mole}^{-1}\ l}$	TPS $\log_{10}\frac{K_{ext}}{\text{mole}^{-1}\ l}$	TPP $\log_{10}\frac{K_{ext}}{\text{mole}^{-1}\ l}$
Chloride	1.5	1.8	1.5
Bromide	2.9	2.0	2.8
Iodide	4.7	3.3	3.7
Thiocyante	3.8	3.2	4.8
Chlorate	4.4		4.2
Bromate	2.2	1.5	1.9
Perchlorate	4.5	4.2	4.5
Permanganate	4.7	4.5	4.7
Perrhenate	4.5	4.2	5.0
Nitrate	4.0	1.9	2.9
Nitrite	1.5	1.2	1.2
Chromate (pH 2.4)	4.1	3.7	2.6
Chromate (pH 11.5)	2.9	2.9	2.2

The extractabilities of different anions with the tetraphenylsulfonium, tetraphenylarsonium, and tetraphenylphosphonium cations can be predicted from the values of extraction constants based on the experimental results of Bock et al.[11-13] (Table 1). The TPA and TPP cations appear to be suitable for substoichiometric determinations of manganese (as MnO_4^-), rhenium (as ReO_4^-), and perhaps chromium(VI), by neutron-activation analysis. Manganese has in fact been determined,[14] in the absence of gold and rhenium, by extraction with a substoichiometric amount of tetraphenylarsonium chloride into chloroform. In the presence of gold, however, a preliminary separation of manganese with diethyldithiocarbamate into chloroform was necessary. Rhenium has been determined[15,16] by substoichiometric extraction with the tetraphenylarsonium ion after a preliminary separation by solvent extraction with methyl ethyl ketone or diethyldithiocarbamate had removed other interfering elements. The substoichiometric extraction of chromium(VI) with the tetraphenylarsonium cation has been verified by the present authors. Besides, a large number of other anions such as $AuCl_4^-$, $Au(CNS)_4^-$, $TlCl_4^-$, and $SbCl_6^-$, which are known to form stable ion-association compounds with heavy cations of the types mentioned above, should be suitable for substoichiometric determination of the respective metals. Alimarin and Perezhogin[17] demonstrated this principle in the substoichiometric determination of gold by neutron-activation analysis. These authors have pointed out[9] that the extractions of these chloro-anions are heavily dependent on the concentration of HCl in the solution, simply because their formation in aqueous solution is strongly influenced by it. The $FeCl_4^-$ ion, for example, requires a very high value of [HCl] for its formation, and gold can be extracted as $Ph_4AsAuCl_4$ from solutions containing a thousandfold molar excess of Fe(III), without interference from the iron, at [HCl] values below 1.0 mole $l.^{-1}$. This strong dependence on [HCl] thus provides a very simple means of improving the selectivity of the method (Figure 3).

In addition to the chloro-anions, the fluoro-, bromo-, iodo-, cyano-, and thiocyanato-complexes of heavy metals like Ta, Bi, Mo(V), and W(V) might be suitable for extraction with Ph_4As^+. The extraction of large unipositive ions such at Tl^+, Cs^+, and Rb^+ with large anions such as the BPh_4^- ion could provide a further extension of the application of this particular principle.

One disadvantage of the method is that the partition of the reagent in the case of ion-

association extraction systems involving cations such as tetraphenylarsonium, tetraphenylsulfonium, and tetraphenylphosphonium is not dependent on pH. However, the controlled oxidation of heavy transition metals to oxoanions suitable for extraction as ion-association compounds could possibly be used to increase selectivity rather as contrasted to the use of pH in the solvent extraction of metal chelates. Alimarin and Perezhogin used the difference between the formal potentials of the Re(VII)/Re(VI) and Tc(VIII)/Tc(VI) couples to separate perrhenate from pertechnetate as Ph_4AsReO_4. Figure 4 shows the effect of Sn^{2+} ions in dilute H_2SO_4 solution on the extraction. As the concentration of Sn^{2+} is increased the fraction of technetium which is extracted falls rapidly because technetium(VII) is reduced to technetium(VI), but the extraction of rhenium is hardly affected. A preliminary oxidation or reduction can also be used to increase selectivity. The present authors[18] achieved a preliminary separation of chromium from other metals and from interfering anions by oxidizing to chromium(VI) with cerium(IV) sulfate, extracting int isobutyl methyl ketone, and then back-extracting into water.

D. Ion-exchange Separation of Water-soluble Metal Chelates

Consider a metal ion M^{n+} which reacts with a chelating anion Y^{m-}, such as the quadrinegative ethylenediaminetetraacetate ion, to form a negative ion $MY^{(n-m)}$. Supposing that a substoichiometric amount of Y^{m-} is added to a solution of M^{n+}, then the conditions for substoichiometric separation will be fulfilled if more than 99.9% of Y^{m-} is used in forming the chelate and if the negatively charged chelate can be separated from the metal cation. The separation can be achieved by removing the hydrated metal ions on a cation-exchange column.

Under conditions of pH in which the chelating agent is largely dissociated, the stability constant β_{MY} for the metal chelate can be written, omitting the ionic charges, in the form

$$\beta_{MY} = \frac{a_{MY}}{a_M \cdot a_Y}$$

At low concentration it is sufficient to take a_X as $\frac{[X]}{\text{mole } l^{-1}}$

Thus $\beta_{MY} = \frac{[MY]/\text{mole } l^{-1}}{[M][Y]}$

Supposing that the original concentration of M

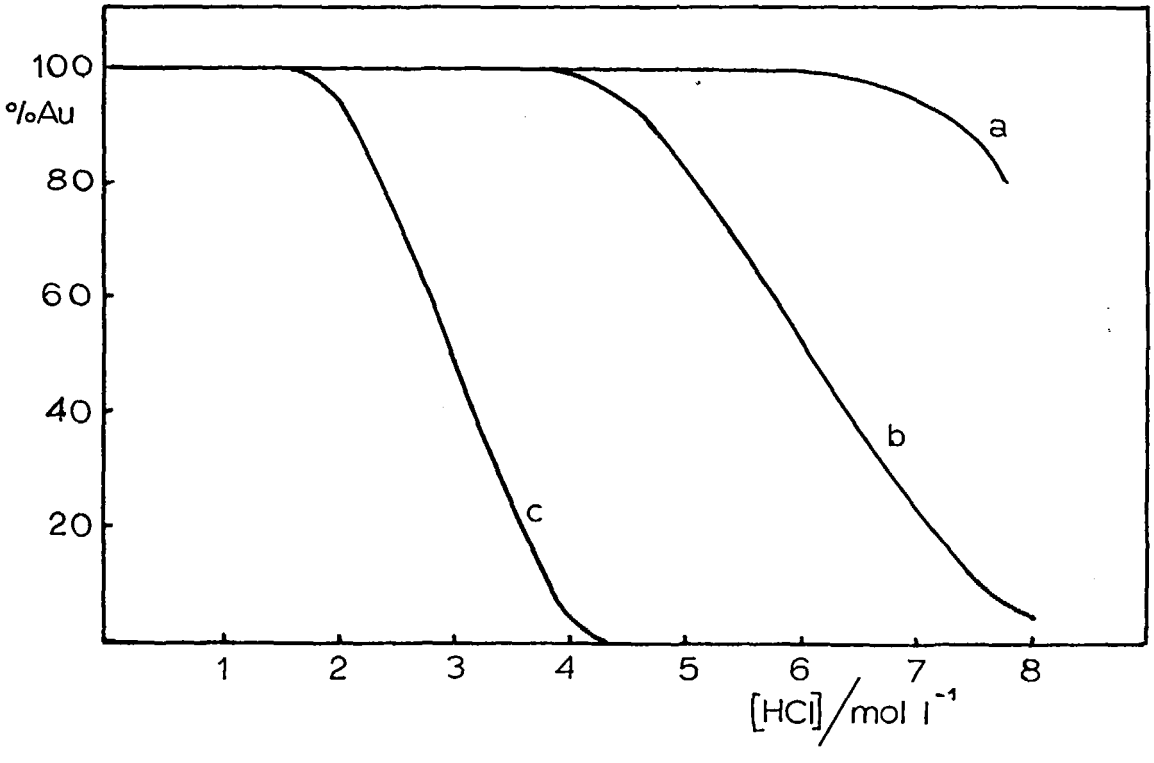

FIGURE 3. The effect of hydrochloric acid concentration on the substoichiometric extraction of $AuCl_4^-$ with Ph_4As^+ in the presence of Fe^{3+} ions. (a) Fe:Au = 1:1; (b) Fe:Au = 100:1; (c) Fe:Au = 1500:1.

was c_M, and that c_Y represents the original concentration of Y, then if 99.9% of Y is converted to MY at equilibrium

$$[MY] = 0.999\ c_Y$$

$$[Y] = 0.001\ c_Y$$

and $$[M] = c_M - c_Y$$

Thus

$$\beta_{MY} = \frac{c_Y \text{ mole } l^{-1}}{(c_M - c_Y)\ (0.001\ c_Y)} \qquad (23)$$

If the amount of Y which is added is one half of the amount of M present, the equation simplifies to

$$\beta_{MY} = \frac{1}{0.001\ c_Y/\text{mole } l^{-1}}$$

as the limiting condition for quantitative conversion of Y to MY. Thus, a substoichiometric separation is possible with solutions for which $c_Y = 10^{-3}$ mole l^{-1} if $\beta_{MY} > 10^6$ Some values of $\log_{10} \beta_{MY}$ are given in Table 2 for ethylenediaminetetraacetate chelates and 1,2-diaminocyclohexanetetraacetate chelates.

The selectivity of the method can be estimated in a similar way to that for the solvent extraction method. If two metals M and M′ compete in the reaction with Y to form MY and M′Y then

$$\frac{[MY]}{[M'Y]} = \frac{\beta_{MY}\ [M]}{\beta_{M'Y}\ [M']}$$

at equilibrium. Consequently, if the equilibrium values of [M] and [M′] are equal, it follows that the ratio $\frac{\beta_{MY}}{\beta_{M'Y}}$ must be greater than 10^3 for the interference due to M′ to be negligible; even if [M′] is 10^2 [M] it is only necessary for $\log_{10}\beta_{MY}$ -$\log_{10}\beta_{M'Y}$ to be greater than 5. Thus, it can be seen from Table 2 that typical uni- and dipositive ions should not interfere with the determination of typical terpositive ones.

The great advantage of the method outlined above arises from the high stability towards oxidative and hydrolytic decomposition of chelons like EDTA even at concentrations as low as 10^{-9} mole l^{-1}. Thus, the ion-exchange separation of soluble chelates is of particular value in the application of substoichiometric principle to radioisotope dilution.

Masking agents are of limited value in cation-exchange separations because they are effective

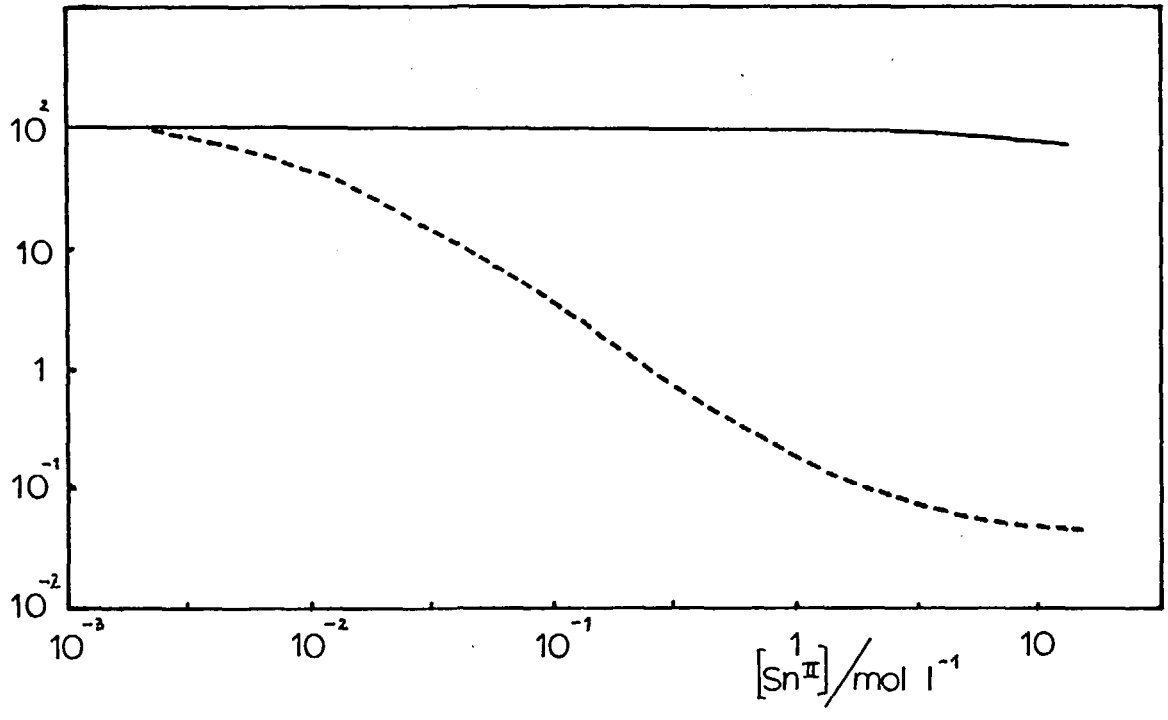

FIGURE 4. The effect of the concentration of Tin(II) ions on the substoichiometric extraction of Ph_4AsReO_4 and Ph_4AsTcO_4 in 1,2-dichloroethane (50% stoichiometry): Vertical axis shows relative activities of extracts. Rhenium: solid line; Technetium: dotted line.

TABLE 2

Stabilities of Chelates of Metal Ions with Ethylenediaminetetraacetic acid, H_4 Y, and 1,2-diaminocyclohexanetetraacetic acid, H_4 Z

Cation	H_4Y	H_4Z
	$\log_{10}\beta$	$\log_{10}\beta$
Ag^+	7.1	8.2
Ca^{2+}	10.7	12.5
Cu^{2+}	18.9	21.6
Pb^{2+}	18.3	19.5
Fe^{3+}	25.1	
In^{3+}	25.0	
Sc^{3+}	23.0	25.4

only if the complexes they form are retained by the exchanger. However, preliminary separation of the element to be determined from diverse elements can often be achieved by solvent extraction or some other method. Provided sample and standard are treated in exactly the same way, it is not even necessary for the extraction to be quantitative, because the subsequent use of a substoichiometric method ensures that equal amounts are collected for radioassay.

One possible disadvantage of the cation-exchange method is that the chelate anion may dissociate on the column as the metal ion originally in equilibrium with it is progressively withdrawn.

$$MY^{(n-m)} \longrightarrow M^{n+} + Y^{m-}$$

Usually the rate of dissociation is so slow that the loss of chelonate is trifling, but in the experience of the present authors this is by no means always the case.

Briscoe and Dodson[19] have pointed out that the choice of pH and the nature and concentration of the buffer used to achieve the maximum conversion of metal to its chelate complex are not necessarily the best ones when the stage of ion-exchange separation is reached. For example, the commonly used acetate buffers themselves form anionic complexes with many metals and prevent them from being retained on the cation-exchanger. They propose instead of cation-exchange the use of solvent extraction with a complexing agent weaker than EDTA to separate the metal ions from the anionic chelates, which remain in the aqueous solution. In their theoretical treatment they consider the extraction of a terpositive lanthanide ion (M) with thenoyltrifluoroacetone (HA):

$$M + 3\,HA_{org} = MA_{3_{org}} + 3\,H$$

(charges are omitted for convenience of representation) from the anionic complex formed with the EDTA ion (Y):

$$M + Y = MY$$

They make use of the concepts of the α-coefficient:

$$\alpha_Y = \frac{[Y']}{[Y]}$$

where $[Y']$ is the total concentration of EDTA in all its forms, H_4EDTA, H_3EDTA^-, H_2EDTA^{2-} etc., and of the conditional stability constant K', where

$$K' = \frac{[MY]}{[M][Y']} ,$$

to obtain the following expression for K, the ratio of the extraction constant for MA_3 to the stability constant of MY:

$$K = \frac{K_{ext}\,(MA_3)}{K_{stability}\,(MY)} = \frac{[MA_3]_{org}[H]^3[Y']}{[MY][HA]^3_{org}\,\alpha_Y} \qquad (24)$$

In the case where the conversion to MY is 50% stoichiometric and HA removes the rest of the metal into an organic phase equal to the aqueous phase in volume, K becomes

$$K = \frac{[H]^3[Y']}{[HA]^3_{org}\,\alpha_Y} \qquad (25)$$

$[HA]_{org}$ itself is not a simple term because HA dissociates and, furthermore, there is some undissociated HA in the aqueous phase. If

$$\frac{[H][A]}{[HA]} = K_{diss}\,(HA)$$

and P_{HA}, the partition coefficient of HA molecules between the phases is

$$P_{HA} = \frac{[HA]_{org}}{[HA]} ,$$

it can be shown that

$$\alpha_A = \frac{[HA']}{[HA]_{org}} = 1 + \frac{[HA]}{[HA]_{org}} + \frac{[A]}{[HA]_{org}}$$

$$= 1 + \frac{1}{P_{HA}} + \frac{K_{diss}}{P_{HA}} \qquad (26)$$

The value of α_A can thus be calculated from P_{HA}

and K_{diss}, and substitution in Equation 25 then gives

$$\underline{K} = \frac{[H]^3[Y'] \underline{\alpha}_A^3}{[HA'] \underline{\alpha}_Y} \quad (27)$$

If $[Y']$ is to be only 0.001 c_{HY}, where c_{HY} represents the concentration of EDTA which would be present if no reaction had occurred, then

$$\underline{K} = \frac{[H]^3 10^{-3} c_{HY} \underline{\alpha}_A^3}{[HA']^3 \underline{\alpha}_Y} \quad (28)$$

From this it is possible to calculate the maximum amount of HA which can be added to remove free metal ions without breaking down more than 0.1% of the EDTA chelate.

Briscoe and Dodson showed that quite concentrated solutions of thenoyltrifluoroacetone could be used; for example at pH 4 a concentration greater than 0.01 mole l^{-1} was suitable to extract the excess of Tb^{3+} from a solution containing only 1 μmole l^{-1} of EDTA. Thus, their method cannot be criticized on the grounds that the solutions of complexing agents needed to remove the excess of metal ions are so dilute as to be unstable.

E. The Electrolytic Method

The electrolysis of solutions at controlled potential in identical cells in series can also be adapted to substoichiometric analysis by the use of radioisotope dilution. In one method of procedure a solution containing an unknown mass m of the element to be determined is placed in one cell, with a carrier electrolyte such as potassium nitrate to reduce the resistivity. An equal volume containing only the carrier electrolyte is added to the other cell. Then a solution of a radioisotope of the element to be determined, of total activity α_t and of mass M, is added to both the cell containing the sample and to the control cell. The specific activity of the element is thus $a_t/(M + m)$ in the sample cell and a_t/M in the control cell.

The solutions are electrolyzed, the applied potential being carefully controlled to avoid interference by other ions, and an amount Y of the element is deposited from each solution. The activity removed from the sample solution is thus $\frac{Y\alpha_t}{M+m}$ and from the control solution $\frac{Y\alpha_t}{M}$. The total activities of the sample, a, and of the control solution, a_c, are measured under exactly the same counting conditions as those used for the measurement of a_t. Then

$$\frac{\underline{Y}\underline{\alpha}_t}{\underline{M} + \underline{m}} = \underline{\alpha}_t - \underline{\alpha} \quad ,$$

$$\frac{\underline{Y}\underline{\alpha}_t}{\underline{M}} = \underline{\alpha}_t - \underline{\alpha}_c \quad ,$$

$$\therefore \frac{\underline{M} + \underline{m}}{\underline{M}} = \frac{\underline{\alpha}_t - \underline{\alpha}_c}{\underline{\alpha}_t - \underline{\alpha}} \quad ,$$

$$\text{and } \underline{m} = \underline{M} \frac{\underline{\alpha} - \underline{\alpha}_c}{\underline{\alpha}_t - \underline{\alpha}} \quad . \quad (29)$$

For highest precision the values of m and M should be similar and Y should be about $\frac{1}{2}M$. It is obviously a considerable advantage to know the approximate value of m in designing the experimental conditions.

The method has the advantage inherent in all electrolysis that separation is highly selective provided there is even a moderate difference in deposition potential between the ion to be discharged and the diverse ions which are present. The disadvantage is that the solutions require particularly careful preparation; for example, it may be necessary to remove dissolved oxygen. McClendon, De Voe, Pella, and Purdy[20] used the controlled-potential coulometric procedure to determine cadmium in zinc spelter and in high-purity zinc. The cells had anodes made from spirals of platinum wire enclosed in low-resistance glass, and the cathodes were of mercury.

F. Replacement Substoichiometry

A method which may prove to be of very great value has been described by I. Obrusnik[21] who used it in the neutron-activation analysis of indium. In an aqueous alkaline medium containing cyanide ions, the only elements which can be extracted with dithizone are indium, tin(II), bismuth, lead, and thallium(I). Bismuth and lead do not interfere in the activation method because of their nuclear properties, tin can be removed easily by washing the dithizone extract, and the radioisotopes of thallium are all pure β-emitters which cannot be counted by γ-scintillation as can indium-116 m or indium-114 m.

Unfortunately, the extraction constant for indium dithizonate in the presence of cyanide is too low to make direct substoichiometric extraction possible, but extraction in the absence of cyanide is much less selective than that described above. Obrusnik solved the problem by extracting both standard and sample as dithizonates into

carbon tetrachloride and then shaking each organic solution with a substoichiometric amount of mercury ions in tartrate buffer. The indium was thus replaced substoichiometrically from its dithizonate, and the amount in the original sample was calculated in the usual way from the activities of the metal in the two aqueous phases.

IV. PRELIMINARY EXPERIMENTS ON SUBSTOICHIOMETRIC RADIOCHEMICAL ANALYSIS

The first consideration in applying substoichiometry to radiochemical analysis is to find a reagent which will form a suitable stable compound of the radionuclide either for precipitation from aqueous solution or for extraction by an organic solvent. In most cases organic complexing reagents can be found which are suitable, but most of them are not specific for a single element. The same reagent can often form complexes with a wide variety of different elements. In neutron-activation or isotope-dilution analysis for a trace element it is necessary to determine a small amount of it in the presence of a large excess of at least one other element. Thus, the use of substoichiometry requires that the reagent should be selective, under controlled conditions, for the desired element. The selectivity of a reagent for the desired element can usually be improved by using appropriate pH conditions or a suitable masking agent. When such methods fail, a preliminary separation of the interfering elements has to be made. Once the condition of selectivity is ascertained, the reproducibility of substoichiometric separation has to be tested. But first the true stoichiometry of reagent to element in the compound must be known.

A. Stoichiometric Ratio of Metal to Reagent

There are several methods, gravimetric, titrimetric, and so on, by which the stoichiometric composition of a compound can be determined. A similar determination, however, can be made radiometrically in either of the following ways.

1. Several labeled solutions containing different concentrations of the metal ion are adjusted to a predetermined optimum pH, and equal amounts of the appropriate reagent are added to them. Each of the resulting solutions is extracted with a fixed volume of the organic reagent, and the activities of equal volumes of the organic extracts are measured. A plot of activity against the amount of metal ion in solution will show a linear increase of activity with amount of metal until the equivalence point is reached. The determination of the dithiol equivalent of tungsten is illustrated in Figure 5. The ordinate represents the count-rate obtained from a carbon tetrachloride extract made from a solution containing

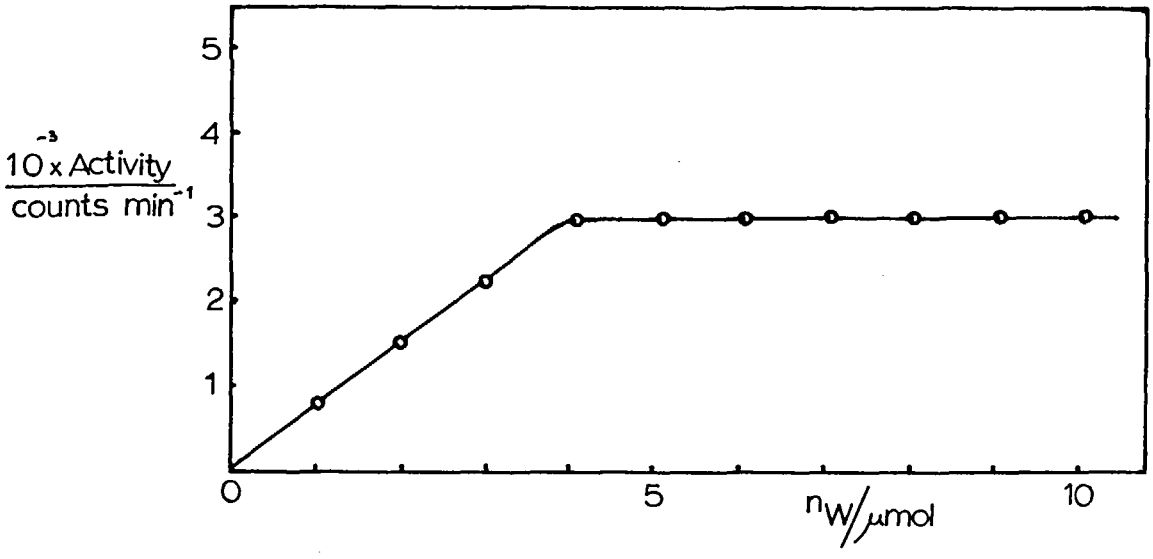

FIGURE 5. The variation of the activity of the extract as increasing amounts of tungsten are extracted with 16 μmol of toluene-3,4-dithiol.

16 μmoles of toluene-3,4-dithiol and an amount of tungstate, expressed as WO_4^{2-}, which is shown on the horizontal axis. The graph shows that 4 moles of the dithiol combine with 1 mole of tungsten, and that amounts of tungstate not exceeding 4 μmoles can be estimated substoichiometrically using 16 μmoles of the dithiol.[22]

2. To several labeled solutions, containing equal amounts of metal ion, adjusted to optimum pH, are added different increasing amounts of reagent. Each solution is then extracted with a fixed volume of suitable organic reagent, and the activities of equal volumes of these organic phases are measured. A plot of activity against the volume of reagent solution will show a linear rise in activity up to the equivalence point.

B. The Effect of pH on Substoichiometric Separation

A series of solutions is taken containing equal amounts of metal ion labeled with a suitable radioisotope. The solutions are adjusted to a specific pH, extracted with equal substoichiometric amounts of reagent, and the activities of equal volumes of extract are measured. In this way it is possible to find the range of pH over which the extent of extraction is a maximum (Figure 6).

C. Effect of Time on the Extraction Procedure

It is usual for equilibrium between the phases to be reached very quickly in the solvent extraction of metal chelates or ion-association compounds. Where the amounts of activity extracted by the same amount of complexing agent at the same controlled pH vary with time over a considerable period, it is necessary to standardize the shaking time in the analytical procedure.

D. Reproducibility of Substoichiometric Separation Under Various Conditions of Concentration

The reproducibility of substoichiometric separations can be tested by the following methods.

1. Extraction of the Element from Solutions of Different Concentration with Equal Substoichiometric Amounts of a Reagent

Solutions containing different amounts of the element are adjusted to the same predetermined, optimum pH. Each solution is then extracted with an equal amount of reagent which is substoichiometrically less than the lowest concentration of the metal ion which is used. The activities of equal volumes of the extract indicate the amounts of metal which are separated. The same type of experiment can be carried out in the extraction of ion-association compounds and when water-soluble chelates are used for substoichiometric separation. In the latter case, the chelate is usually separated with a cation exchanger. In experiments

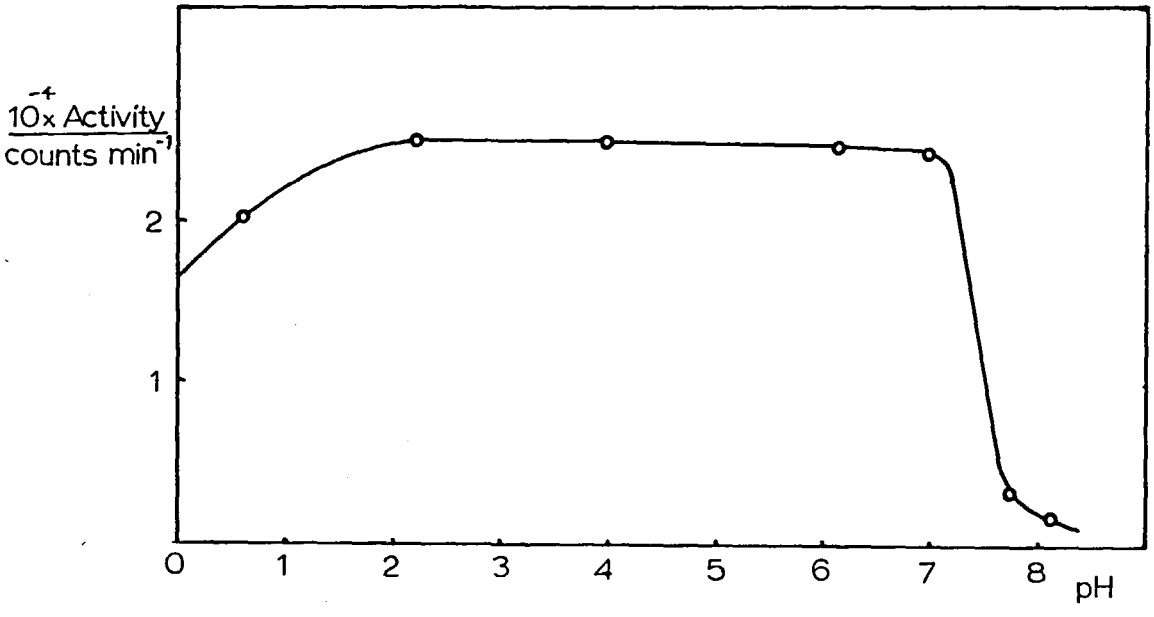

FIGURE 6. Radiometric measurement of the dependence of the extraction of antimony(III) cupferrate on pH.

on the substoichiometric separation of molybdenum with 8-hydroxyquinoline in chloroform we found[23] the reproducibility of the count-rate to be ± 0.3% from 2.0 x 10^{-3} *M* solutions in the volume range 3 to 8 ml, while in the extraction of the ion-association compound of chromium(VI) with tetraphenylarsonium chloride[18] the reproducibility was ± 1.3% from 1.0 x 10^{-2} *M* solutions in the volume range 1 to 25 ml. The standard deviation in the first case was 0.6% and in the second case 1.0%

It has been pointed out by workers active in the field of substoichiometric analysis[20,24] that a modification of the method can be applied even in cases where the amount of the element isolated by substoichiometric extraction is not strictly independent of the amount of it in solution. Figure 7 represents the variation in the amount of element extracted by equal amounts of complexing agent, expressed as activity, against the amount in solution. In the ideal case, I, the activity extracted, a, is quite independent of the concentration of the active element once the equivalence point is passed. But the experimental curve will take a shape such as that of II if the stability constant or the extraction constant of the complex is rather low, if a slightly low pH has to be used to eliminate interference from other elements, or if equilibrium is achieved so slowly that extraction becomes jointly dependent on shaking time and concentration, and the standardization of shaking time alone is therefore ineffective.

Let us take a section of the curve II which can be considered almost straight (Figure 8).

Suppose a solution contains an amount w_s of active isotope and an amount w of inactive isotope to be determined. The "corrected" value of the activity of the standard, that is the value which would be obtained if the amount of active isotope were $w_s + w$, is given by

$$a''_s = a'_s + \frac{w}{w_s} \Delta a_s \qquad (30)$$

where Δa_s is the difference between the activities extracted from solutions containing the amounts w_s and $2w_s$ of the active isotope.

The value of w is then obtained from

$$w = w_s \frac{a''_s}{a} - 1 \qquad (31)$$

where a is the activity substoichiometrically isolated from w_s of radioisotope plus w of inactive isotope. By combining equations 30 and 31 to eliminate a''_s:

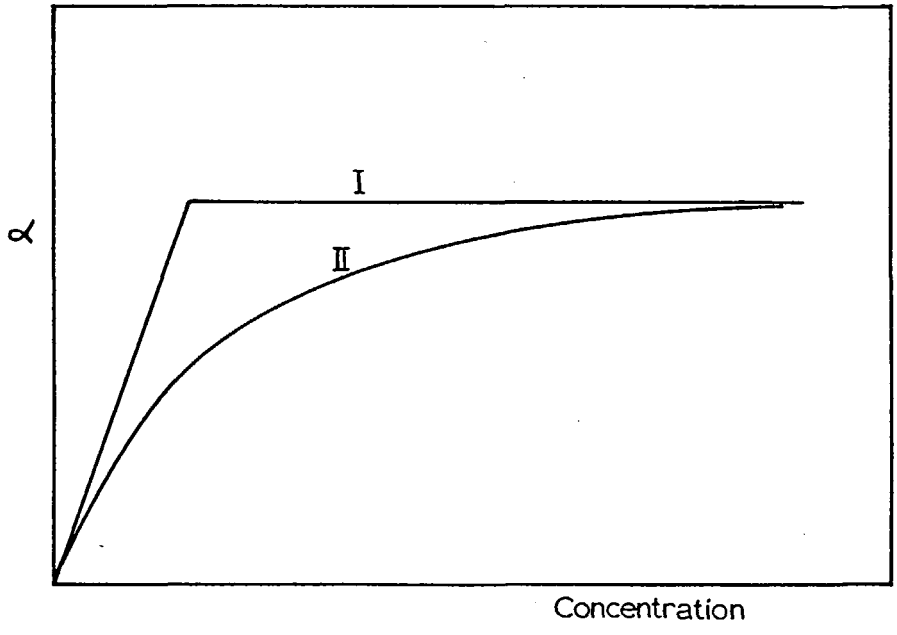

FIGURE 7. Variation of the amount of element extracted expresses as an activity, a, with the amount in solution. I. True stoichiometric extraction; II. Concentration-dependent extraction.

$$v = w_s \frac{\left(\alpha'_s + \frac{w}{w_s}\Delta\alpha_s\right)}{\alpha} - \frac{\alpha}{\alpha}$$

$$\therefore\ w\alpha = w_s\alpha'_s + w\,\Delta\alpha_s - w_s\alpha$$

$$\therefore\ v\,(\alpha - \Delta\alpha_s) = w_s\,(\alpha'_s - \alpha)$$

$$\text{and}\quad v = \frac{w_s\,(\alpha'_s - \alpha)}{\alpha - \Delta\alpha_s} \qquad (32)$$

Thus, a modified form of substoichiometric determination can be carried out by this so-called concentration-dependent method, but it is never as satisfactory as the truly substoichiometric extraction.

2. Extraction of the Element from a Solution of Fixed Concentration with Different Substoichiometric Amounts of Reagent

Solutions containing equal amounts of the element are adjusted to the predetermined optimum pH. Each solution is then extracted with different substoichiometric amounts of a reagent which forms either a chelate or an ion-association compound, or in the case of water-soluble complexonates separation is usually achieved with a cation exchanger. The activities of equal volumes of extract or eluate will increase in proportion to the increase in concentration of the reagent. However, the activity corresponding to equal concentration of the reagent, calculated from the experimental results, should be the same. In experiments on the substoichiometric extraction of tungsten with toluene-3,4-dithiol from 1.0 ml of 1.0 x 10^{-2} *M* solution we found[22] the reproducibility to be ± 1.5%, while in the extraction of chromium(VI) from 1.0 to 2.5 ml of 1.0 x 10^{-2} *M* solution with tetraphenylarsonium chloride it was ± 0.5%. The standard deviation in each case was 1.0%.

E. The Effect of Other Ions on Substoichiometric Separation

The selectivity of a substoichiometric determination can be assessed radiometrically by comparing the activities isolated from samples in the presence, and in the absence, of interfering ions. The experiments can be done in two ways, using a radioisotope of either the test element or of the interfering element. For studying the selectivity of a substoichiometric separation in isotope dilution, the radioisotope of the test element is generally

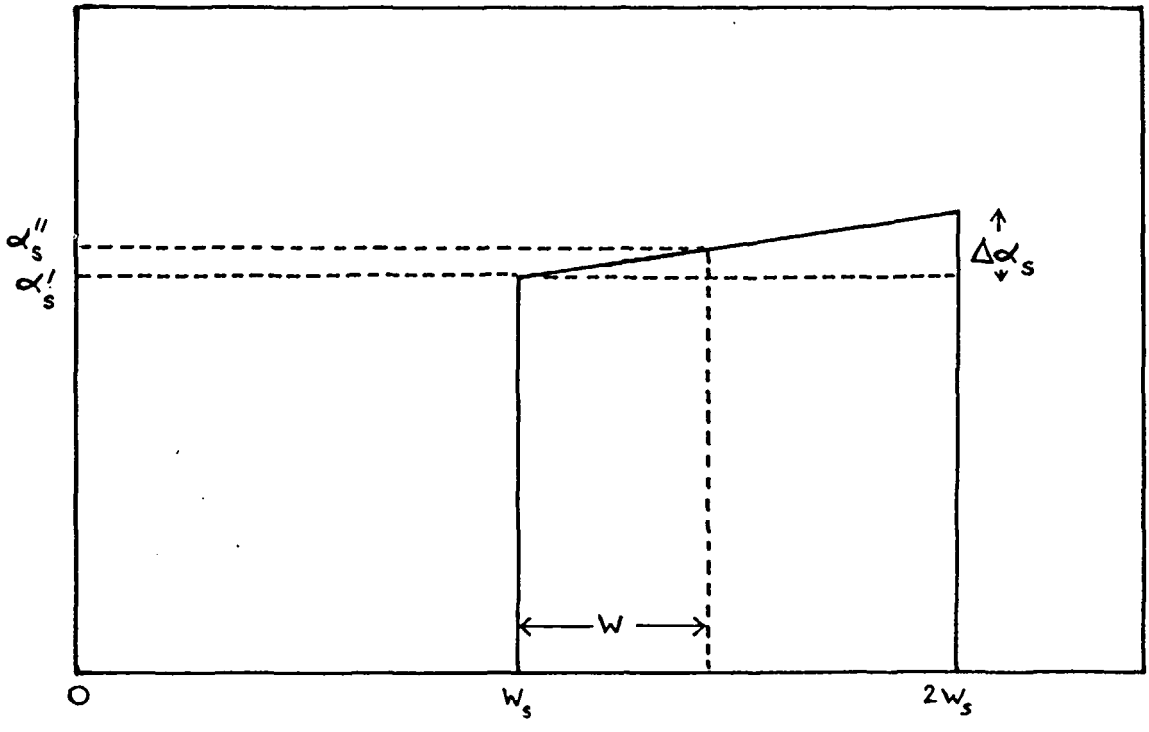

FIGURE 8. Illustration of the mathematical treatment of concentration-dependent extraction.

TABLE 3

Interference with the Extraction of Silver Caused by the Addition of Inactive Nuclides of Other Elements (1 mg in each case)

Element added	Activity isolated /counts min^{-1}	Element added	Activity isolated /counts min^{-1}
None	15,366	Sn(II)	15,168
Mn	15,229	Pb	14,912
Fe	15,292	Cu	15,520
Co	15,069	Bi	15,350
Ni	15,143	Au	64
Zn	15,175	Hg	1
Cd	15,280	Pd	407
In	15,119		

TABLE 4

Intereference with the Extraction of Gold by Copper Diethyldithiocarbamate in Chloroform Caused by the Addition of Inactive Nuclides of Other Elements

Element or other reagent[a]	Activity of extract/ count min^{-1}
None[b]	23,118
Pt(IV) (2 mg)	23,184
Sn (II) (2 mg)[b]	300
Sn (IV) (1 mg)	24,424
In (III) (2 mg)	23,345
Sb (III) (2 mg)[b]	22,475
Sb (V) (1 mg)	24,904
As (III) (2 mg)[b]	24,108
As (V) (1 mg)	24,424
Mo (VI) (4 mg)	24,108
Pd (II) (1 mg)	19,720
Pd (II) (2 mg)	12,390
Pb (II) (3 g in 1.0 *M* HNO_3)	23,830
0.1 cm^3 of 5%(v/v) H_2O_2	13,178
HNO_3 (1.5 *M*) (no HCl present)	22,835
1 cm^3 of 40% HF	22,950
0.5 cm^3 of 70% $HClO_4$	22,410
1 cm^3 of 70% $HClO_4$	22,740

[a]All extractions made from HCl of concentration 0.5-2.5 M unless otherwise stated, in the presence of 1 cm^3 of 5%(v/v) H_2O_2.

[b]No H_2O_2 present

used, and its activity is compared with that isolated in the presence of diverse elements.

Thus, to each of a series of solutions containing equal amounts of the test element is added a solution of foreign element in the desired molar ratio. The solution is then adjusted to the predetermined value of pH. An equal amount of the test sample is taken without any of the interfering elements, and all the solutions are extracted with substoichiometric amounts of reagent into a suitable solvent. The activities of equal volumes of the extracts are measured, and the interference due to foreign elements can be computed directly from the lowering of activity. The interference of inactive isotopes of diverse elements in the substoichiometric extraction of silver was studied by Pierce and Peck,[25] (Table 3), and in the substoichiometric extraction of gold by Bode and Neumann[8] (Table 4).

The same type of experiment may be carried out to evaluate the selectivity of substoichiometric extraction in neutron-activation analysis. However, in this case, there may be some disadvantage in studying the interferences by using inactive solutions of the diverse elements. From Table 4 it is seen that platinum(IV) does not interfere in the extraction of gold with copper diethyldithiocarbamate in chloroform. However, when the same interference is studied using inactive gold and radioactive platinum(IV), the latter is found to be extracted in considerable quantities (Table 5). Control experiments with the complexing agent absent showed that the platinum(IV) was extracted in the same proportion from solution in hydrochloric acid by chloroform alone. Thus, a sample of gold containing some platinum which gave both gold-198 and platinum-197 on neutron-irradiation could not be analyzed satisfactorily for gold by the use of copper diethyldithiocarbamate in chloroform, not because the platinum would compete for the complexing agent but because it would dissolve in the solvent, a fact not detectable

TABLE 5

Extraction of Labeled Diverse Elements, in the Presence of Inactive Gold, by Copper Diethyldithiocarbamate in Chloroform

Radioisotope added	Percentage of radioisotope extracted
^{110}Ag	0.03
^{76}As	0.02
^{122}Sb + ^{124}Sb	0.14
^{64}Cu	0.01
^{197}Pt	23.3
^{99}Mo	0.02
^{203}Hg	0.06
^{109}Pd	8.4

by the indirect method of investigating interferences.

In evaluating possible interferences in neutron-activation analysis, therefore, it is advisable to study the selectivity of substoichiometric separation by the direct method, using radioisotopes of the interfering elements. The results of experiments on the extraction, from solutions of inactive gold, of radioisotopes of possible interfering elements with copper diethyldithiocarbamate in chloroform are shown in Table 5.

V. APPLICATIONS OF SUBSTOICHIOMETRIC METHODS IN RADIOANALYSIS

Although the development of substoichiometry is recent, the principle has been applied successfully to the determination of a considerable number of elements. Ruzicka and Stary[26] described methods based on this principle for the determination of many metals and suggested the possibility of determining a number of others. Thus, antimony in semiconductor-grade silicon was determined[27] by activation analysis using substoichiometric extraction with cupferron. Interfering elements were removed by preliminary extraction, as cupferrates into chloroform, from antimony in its +5 state. The antimony(V) in the aqueous phase was then reduced to the +3 state and extracted with a substoichiometric amount of cupferron.

Chamaev[28] described methods of calculating the optimum conditions for such separations, and compared the experimentally observed conditions for determining antimony, iron, and bismuth by isotope dilution with those predicted from theory. Antimony in lead has been determined by isotope dilution, the chloro-complex of antimony being extracted with a substoichiometric amount of methyl violet in toluene.[2] However, other metals forming anionic chloro-complexes are likely to interfere.

Zeman, Ruzicka, and Stary[29] determined arsenic in silicon by neutron activation using substoichiometric amounts of diethyldithiocarbamate. Interfering elements like copper, silver, gold, and palladium were removed by preliminary extraction with diethylammonium diethyldithiocarbamate, and antimony(III) and tin(IV) were separated as cupferrates from the arsenic(V).

Neutron-activation analysis of bismuth has been carried out[30] by substoichiometric extraction of bismuth as the dithizonate from an aqueous solution containing cyanide ions. To avoid interference from other elements, bismuth was initially extracted with dithizone in carbon tetrachloride and then stripped with dilute nitric acid for substoichiometric extraction with dithizone.

Cadmium was determined by isotope-dilution analysis;[31] the metal was extracted by a substoichiometric amount of dithizone in chloroform from a slightly ammoniacal solution. Interferences due to mercury, silver, and copper were removed by preliminary extraction with dithizone in chloroform from a medium at pH2 whereas those due to zinc, cobalt, nickel, etc. were removed by dithizone extraction from sodium hydroxide solution in the presence of dimethylglyoxime. Pure cadmium, stripped into 0.01 M hydrochloric acid, was then substoichiometrically extracted with dithizone in chloroform.

McClendon, De Voe, Pella, and Purdy[20] determined trace amounts of cadmium by isotope dilution using solvent extraction with dithizone and also controlled-potential electrolysis. The possibility of accurate analysis using calibration curves when the separation was concentration-dependent was verified by them.

Cobalt was determined both by neutron activation[32] and isotope dilution[33] using substoichiometric extraction with 1-nitroso-2-naphthol in carbon tetrachloride in the presence of ammonium fluoride as masking agent. Interferences due to other elements were removed by preliminary extraction with cupferron into chloroform. In the case of isotope dilution, higher selectivity was

achieved by extracting copper initially as its thiocyanatocomplex into an isoamyl alcohol-ether mixture from an aqueous phase containing fluoride as masking agent. In another method,[34] based on the use of ethylenediaminetetraacetic acid in substoichiometric amounts, the negatively charged cobalt(III) chelonate was separated on a Dowex-50 cation exchanger. As many other metals form EDTA complexes, the selectivity was poor, but in a more recent method,[35] the cobalt complex formed with a substoichiometric amount of 2-nitroso-1-naphthol was separated by ascending paper chromatography using acetone-isoamyl alcohol (4:1) as the developer. The effects of iron(III), copper, and nickel were relatively small, and determination of cobalt down to 0.01 ppm was possible.

Zeman, Ruzicka, and Stary[36] determined copper in germanium dioxide by activation analysis. Their method is based on the substoichiometric extraction of copper with dithizone in carbon tetrachloride from a medium at pH 1.0 ± 0.4 and in the presence of potassium iodide. In another method,[37] radiochemical separation of copper was achieved by extraction with diethyldithiocarbamate into chloroform from a medium at pH 12 containing EDTA and citrate as masking agents. To avoid interferences due to mercury, palladium, silver, osmium, and gold, the γ-activity from ^{64}Cu was measured by means of a 200-channel analyzer. The area under the γ-annihilation peak for ^{64}Cu in the test solution was compared with the area under that produced by a standard solution. Traces of copper in aluminum, silicon, iron, zinc, gallium, and tin can also be determined similarly. In the substoichiometric isotope-dilution method,[39] copper was extracted with a substoichiometric amount of dithizone from a solution buffered at pH 4.8 ± 0.2 in the presence of 100-fold excesses of zinc, cadmium, lead, indium, thallium, mercury, bismuth, silver, manganese, tin, and iron. Only palladium, platinum, and gold interfere.

Activation analysis using quantitative isotope dilution[2] was applied to the determination of copper in tin, zinc, and silver using substoichiometric extraction with dithizone.

This method, which is due to Suzuki and Kudo,[39] involves the use of both the isotope dilution and the activation principles and is worthy of a rather more detailed treatment. If the activity of the radioisotope induced by irradiation is A and the specific activity due to the particular radioisotope is S_1, then

$$S_1 = \frac{A}{w} \tag{33}$$

where w is the weight of the element to be determined. If a suitable amount of inactive carrier, x, is added to a portion of this sample, the specific activity changes to S_2 and is given by

$$S_2 = \frac{A}{w + x} \tag{34}$$

If equal amounts are isolated substoichiometrically from the two portions, and the measured activities are a_1 and a_2, respectively, the amount, w, can be calculated from the following equation:

$$w = x \cdot \frac{S_2}{S_1 - S_2} \tag{35}$$

and, since the amounts of the element extracted are the same,

$$w = x \cdot \frac{a_2}{a_1 - a_2} \tag{36}$$

Hence w can be determined without regard to the yield by the following procedure: the solution of the irradiated sample is divided into two equal parts, to one of which a known weight of carrier (x) is added; then exactly the same amount of the radiochemically pure isotope is isolated from each part, and a_1 and a_2 are measured. The weight, w, can then be calculated from Equation 36.

The advantage of this method is that irradiation of a comparison standard is not necessary. Thus, errors that may arise from self-shielding and variations in the neutron flux are eliminated. Besides, any secondary nuclear reactions which increase the specific activity of the test element do not produce an error as in conventional activation analysis, but actually increase the sensitivity of the determination. For example, in the analysis of copper in a material which also contains zinc, some copper-64 will be produced by the reaction

$$^{64}Zn(n,p) \rightarrow {}^{64}Cu$$

$$^{63}Cu(n,\gamma) \rightarrow {}^{64}Cu$$

This will add to the activity of the copper which can then be isolated without adding measurably to its weight.

The disadvantage of Suzuki and Kudo's sugges-

tion is that it can be applied with success only if the ratio x/w is kept below about 10. Otherwise small errors in the measurement of either a_1 or a_2 make proportionately large errors in the difference $a_1 - a_2$. Thus, the amount of carrier which can be used in a trace analysis becomes limited to a few micrograms and the stability of the reagents becomes an important consideration in the very dilute solutions which are then needed for the substoichiometric separation. Furthermore the presence of impurities in the reagent can cause proportionally greater errors at such dilutions, and reagent blanks become necessary.

Ruzicka and Stary[24] have suggested that the method proposed by Suzuki and Kudo would be of particular value for activation analysis with charged particles instead of neutrons, since when particle accelerations are used it is much more difficult to ensure the same conditions of irradiation for both sample and standard than in a flux of neutrons.

But in charged-particle irradiation it is less common for the active nuclide which is produced to be isotopic with the target nuclide, and unless it is isotopic, the method cannot be applied. Therefore, it seems that the proposal will have somewhat limited application in practice.

Chromium in aluminum and aluminum-based alloys was determined substoichiometrically by both neutron-activation and radioisotope-dilution analysis.[18] The method was based on the substoichiometric extraction with 1,2-dichloroethane of the ion-association compound of chromium(VI) and tetraphenylarsonium chloride. Most of the common metal ions did not interfere. Anions like bromide, iodide, perchlorate, phosphate, nitrate, molybdate, and tungstate did, but these interferences could be removed by preliminary extraction of chromium(VI) into isobutyl methyl ketone from 1.0 M HCl, followed by stripping into water.

Activation analysis using the substoichiometric principle has also been applied to the determination of gallium in silicon aluminum, and kaolin.[40] After separation of the interfering elements by preliminary extraction of their cupferrates and diethyldithiocarbamates, gallium was substoichiometrically extracted with 8-hydroxyquinoline from a medium of pH 5.5 containing tartrate as masking agent.

Determinations of gold by activation analysis were carried out by Beardsley, Briscoe, Ruzicka, and Williams[41] using substoichiometric extraction with copper diethyldithiocarbamate in chloroform. Platinum and palladium are extracted simultaneously under the same conditions, but because they are activated only slightly by neutron irradiation they do not interfere when present in trace amounts. Highly selective separations have been reported in the determination of trace amounts of gold in high-purity materials by this method. The same authors used a similar method for the determination of gold by radioisotope dilution in auriferous ores and gold-doped semiconductor-grade silicon.[42] Gold, reduced to the +1 state with ascorbic acid, was extracted with a substoichiometric amount of zinc diethyldithiocarbamate in chloroform. Antimony(III), selenium(IV), tellurium(IV), Hg(II), and platinum(IV) interfere if present in more than 100-fold excess. Palladium can be removed by precipitation with dimethylglyoxime in the presence of EDTA.

Suzuki and Kudo,[43] using their method of radioactivation analysis accompanied by isotope dilution for the determination of traces of gold, employed rhodamine B in substoichiometric amount as extracting agent. Kukula[44] used both copper and zinc diethyldithiocarbamates for substoichiometric activation analysis of gold in iron down to 0.04 μg per g of sample. Irradiation was effected in a neutron flux of 10^{13} n cm^{-2} s^{-1} and a Ge(Li) detector and 1024-channel pulse-height analyzer were used to measure the gold-198 activity. Another method, introduced by Alimarin and Perezhogin for the substoichiometric determination of gold, is based on the extraction into chloroform of the ion-association compound formed between the anionic chloro-complex of gold(III), $AuCl_4^-$, and the tetraphenylarsonium cation. They determined gold in high-purity metals[17] and also in rocks and meteorites[45] by the above method. Under the same conditions, thallium, technetium(VII), mercury, rhenium, and osmium are also extracted. However, selectivity can be improved by using a γ-spectrometer to measure the activity of gold-198 at 410 keV. The same principle was later applied to the determination of gold in rocks by neutron-activation analysis.

The substoichiometric principle has also been applied to the determination of indium in germanium dioxide by neutron-activation analysis.[46] The negatively charged complexonate of

indium with EDTA was separated from other cations and also from excess of unreacted indium on a Dowex-50 cation-exchange resin. Preliminary extraction of indium with dithizone improved the selectivity. The principle was also applied to the determination of indium by isotope dilution.[47] Indium, along with many other elements, was first extracted with cupferron and then stripped into an aqueous phase by shaking with dilute hydrochloric acid. Bismuth forms a negatively charged complex with EDTA and thus interferes in the determination, but it was removed by preliminary extraction with dithizone in chloroform. Other metals such as the alkali metals, alkaline earths, copper, mercury(II), zinc, silver, cadmium, lead, nickel, cobalt(II), thallium(I), vanadium, molybdenum(VI), tungsten(VI), uranium(VI), chromium(III), iron(III), lanthanum, germanium, arsenic(III), and tin(IV), even in 100- to 1000-fold excess, did not interfere. Titanium, zirconium, thorium and gallium did not interfere unless they were in tenfold excess.

The substoichiometric determination of iron by neutron activation is based on the extraction of iron(III) into chloroform with substoichiometric amounts of cupferron. The procedure has been applied to the determination of iron in various materials.[48] A preliminary extraction with diethyldithiocarbamate removes interfering foreign ions, and the last traces of interfering metals remaining in the aqueous phase are isolated as their cupferrates from iron present in the bipositive state. The method has also been applied to the determination of iron by isotope dilution,[49] but since cupferron is not stable in very dilute solution the method is not suitable for determination of submicrogram amounts of iron. Earlier, Starý and Ruzicka[50] used EDTA to form the negatively charged iron(III) complexonate which was subsequently separated from the aquated cations with a Dowex-50 cation-exchange resin. This method has been claimed to give better results than determinations by flame photometry, graphite dc arc, copper spark, colorimetry, or activation analysis. Even in one hundred-fold excess, thallium(I), silver(I), cobalt, nickel, zinc, manganese, cadmium, lead, mercury, and aluminum do not interfere because their complexes with EDTA are thermodynamically so much less stable than that of iron. The stability constant of the chromium(III)-EDTA complex is approximately the same as that of iron, but since the chromium complex is formed only in boiling solutions it does not interfere in the determination. Only indium(III), gallium(III), bismuth(III), and thorium(IV), which all form very strong complexes with EDTA, interfere with the separation. Recently, determinations of iron by isotope-dilution analysis were performed by substoichiometric precipitation of filter paper.[51] Iron(III) solution, applied in the form of a spot, is precipitated with a substoichiometric amount of potassium ferrocyanide on a filter paper, and the excess of iron is washed from the spot with 0.05 M HCl.

Lead in granite was determined by isotope dilution[52] using a substoichiometric extraction with dithizone in the presence of cyanide as masking agent. Thallium and bismuth interfere in the extraction but can be removed by extracting with diethyldithiocarbamate and then stripping the lead alone from the organic extract with dilute nitric acid.

Traces of manganese in various materials were determined by substoichiometric neutron-activation analysis.[14] Manganese-56 was isolated in its radiochemically pure form by extraction into chloroform as tetraphenylarsonium permanganate with a substoichiometric amount of the reagent. Gold and rhenium interfere. In the presence of these elements a preliminary extraction of manganese with diethyldithiocarbamate into chloroform was used, followed by stripping of the manganese with dilute sulfuric acid. Perezhogin[53] applied the same method to the determination of manganese in high-purity lead by neutron activation.

The principle has also been applied to the determination of mercury both by neutron-activation analysis and isotope dilution.[54] The auto-analyzer technique developed by Ruzicka and Williams,[55] which is described briefly in the later section VI. B, has also been applied to the determination of traces of mercury.[56] Substoichiometric separation was effected by solvent extraction with a solution of zinc dithizonate in carbon tetrachloride. A modification of the method using the same reagent and solvent has been developed and also applied to the determination of mercury.[57] A selective determination of trace amounts of mercury by isotope dilution was done using substoichiometric extraction with dithizone in carbon tetrachloride.[58] Recently, a substoichiometric determination of mercury was

carried out by extraction of its bromo-complex with ether or ethyl acetate.[59] Chloride, cyanide, and thiocyanate interfere, although iron(III) does not.

Molybdenum in semiconductor grade germanium dioxide was determined[60] by the separation of radiochemically pure molybdenum-99 using a substoichiometric extraction with 8-hydroxyquinoline into chloroform. Palladium, which is reported to interfere, can be removed by preliminary extraction as its dithizonate. Nadkarni and Haldar[61] determined molybdenum in steel by substoichiometric extraction with α-benzoinoxime. Tungsten, being co-extracted with molybdenum, interferes; the interference is initially removed by scavenging with tungstic acid, and molybdenum is then extracted successively into ethyl ether and then into water to separate it from nickel, chromium, and other elements. The present authors[23] investigated the use of cupferron in substoichiometric amounts and compared the results for the determination of molybdenum in germanium dioxide with those obtained using oxine. The counting technique was modified and the interference of various ions was evaluated.

Isotope-dilution methods can be applied to the determination of heavy rare earths[62] by forming their complexonates with substoichiometric amounts of EDTA and separating them on a cation-exchange resin. Interference due to other elements must be removed by preliminary extraction with cupferron and diethyldithiocarbamate. The determination of holmium and thulium in aqueous solution has been described.

Rhenium was determined by substoichiometric extraction of the ion-association compound tetraphenylarsonium perrhenate with chloroform or dichloroethane. To increase the selectivity in the determination of rhenium in molybdenite and in meteorites,[15] scavenging with precipitated hydroxides and a preliminary extraction of perrhenate with methyl ethyl ketone was used, whereas in the determination of rhenium in granite[63] a preliminary diethyldithiocarbamate extraction in chloroform was used to remove interference due to gold.

Scandium has been determined[64] by activation analysis using substoichiometric extraction with thenoyltrifluoroacetone and chloroform. Interfering metals can be masked by cyanide, and traces of zirconium and hafnium can be removed by a preliminary extraction with thenoyltrifluoroacetone. The scandium content can be determined precisely from the area of the γ-peak of scandium at 1.119 Mev. Scandium in meteorites was determined[65] by complexation with a substoichiometric amount of EDTA followed by separation on a Dowex-50 cation-exchange resin.

A substoichiometric determination of silver in germanium dioxide and metallic lead[66] is based on the dithizone extraction of silver with carbon tetrachloride. Interference due to gold, palladium, and mercury is avoided by successive separations with two substoichiometric amounts of the reagent; most of the other metals do not interfere. The same method has been applied to the determination of silver in silver-doped iron.[25] Suzuki[67] determined silver in plant materials by isotope dilution using substoichiometric extraction with dithizone. In another method, silver was determined by an electrolytic deposition method[68,69] in which the test and standard samples in cells in series were electrolyzed using a mercury-coated silver cathode at a controlled potential of +250 mV relative to the standard calomel electrode from a nitric acid-potassium nitrate solution. A new technique,[51] based on the precipitation of silver sulfide on filter paper with substoichiometric amounts of sodium sulfide and subsequent washing with dilute aqueous ammonia (1:1) to remove the unreacted silver ions, has been developed for the determination of submicrogram amounts of the element.

Thallium in milk powder and platinum in fish and tea were determined by activation analysis using the substoichiometric principle.[70] For thallium the method is based on the replacement of the metal from thallium(I) dithizonate in chloroform, formed by extraction with an excess of dithizone, with substoichiometric amounts of an aqueous solution of mercury(II). In the case of platinum, interfering elements were first removed from platinum in its +4 state by preliminary extraction with diethylammonium-diethyldithiocarbamate. Platinum(IV) was then reduced to the +2 state and extracted with a substoichiometric amount of copper diethyldithiocarbamate.

Tungsten in molybdenum-containing materials was determined by isotope dilution using substoichiometric extraction with toluene-3, 4-dithiol.[71] Molybdenum was removed by preliminary extraction with dithiol and carbon tetrachloride; subsequent extraction of the tung-

sten from strongly acidic solution in the presence of the strongly reducing Ti^{3+} ion ensured minimum interference from the molybdenum which remained. Determinations of tungsten in aluminum by activation analysis used the same reagent.[24]

Yttrium was determined by substoichiometric isotope-dilution analysis.[72] The negatively charged yttrium chelonate with EDTA was separated from the unreacted yttrium ion by electrophoresis. However, a preliminary separation of yttrium by extraction chromatography with di(2-ethylhexyl)-phosphoric acid was necessary.

Zinc as a trace element in germanium dioxide was determined by neutron-activation analysis[36] using selective extraction with a substoichiometric amount of dithizone in carbon tetrachloride in the presence of diethanolaminedithiocarbamate as a masking agent. The same principle has been applied in the determination of zinc in pure water[73] and other materials[74,75] by isotope dilution. Kudo[76] determined zinc in gallium arsenide by the method of quantitative isotope dilution.

The principle of substoichiometric precipitation has been applied to the determination of traces of zirconium and hafnium in aluminum.[77] After the chemical separation and purification procedures, zirconium was precipitated substoichiometrically as Ba_2ZrF_8 and hafnium as Ba_2HfF_8.

Among the non-metallic elements, substoichiometric isotope-dilution methods for determinations of chlorine, fluorine, and iodine are known. Chlorine as chloride was precipitated with a substoichiometric amount of silver.[78] However, iodide, bromide, and cyanide, which also form precipitates or complexes with silver, interfere with the determination.

An altogether different method has been applied for the determination of fluorine. It is based on the adsorption of fluoride from acid solution onto a definite area of glass surface;[79] the total quantity of fluoride adsorbed from solutions of different concentration varies only slightly, a fact which nearly fulfills the conditions of substoichiometry. A calibration curve constructed from studies of a series of standard solutions of known concentrations of fluoride is necessary.

A substoichiometric determination of iodine is based on the electrodeposition of iodine on a silver anode.[80] The test sample mixed with radioisotope, and the standard radioisotope solution, are electrolyzed in cells connected in series using a number of coulombs smaller than needed to release all the iodine present in the standard solution. Recently, iodine was determined substoichiometrically by radiometric precipitation with silver,[81] unreacted iodide ion being removed by electrophoresis.

It is naturally of interest to compare the precisions of substoichiometric methods with those of other procedures. Attempts to assess systematic errors have been reported in very few cases. In our own laboratory neutron-activation analyses using substoichiometric methods have been in excellent agreement with determinations made by various other procedures. However, these tests have usually been carried out on materials containing the element to be determined at the 0.1 to 2.0% level in the matrix, rather than at the 0.1 to 10 ppm level.

Information on random errors is given in only a minority of published papers. In Tables 6 and 7 we have assembled data on the ranges of precision reported in a number of the papers reviewed above. It must be remembered that in neutron-activation analysis the precision can usually be improved by increasing the strength of the neutron flux and often by increasing the length of the irradiation. In radioisotope dilution analysis, deviations can be expected to depend upon the specific activity of the standard; it is always advisable to use sufficient activity to enable between 10^4 and 10^5 counts to be made conveniently in each radioassay.

VI. INSTRUMENTATION

A. Counting Equipment

In the preface to their monograph[24] on substoichiometry, Ruzicka and Stary expressed the hope of demonstrating that more can often be achieved by applying simple chemistry than by using complicated instruments. It is certainly true that the papers so far published show workers in this field to have almost always used simple counting equipment, Geiger-Muller tubes for β-activity and thallium-activated sodium iodide crystals for γ-activity. The use of lithium-doped germanium detectors, and even the application of γ-spectrometry, have rarely been necessary.

In measuring the activities of solutions, no difficulty is encountered with γ-emitting nuclides

TABLE 6

Random Errors in Some Substoichiometric Determinations by Neutron Activation

Element	Separation	Experimental deviation	Concentration in the matrix	Ref.
Molybdenum	Extraction with cupferron	± 1.7%	0.16 ppm in GeO_2	23
Tungsten	Extraction as tungstate with toluene-3,4-dithiol	± 9%	1.1 ppm in aluminum	22
Chromium	Extraction as dichromate with tetraphenylarsonium chloride	± 2.5%	14 ppm in aluminum	18
Gallium	Extraction with oxine	± 1.8%	17 ppm in aluminum	40
Gold	Extraction with copper diethyl-dithiocarbamate	± 12%	0.1 ppm in silicon	41

TABLE 7

Random Errors in Some Substoichiometric Determinations by Radioisotope Dilution

Element	Separation	Experimental deviation	Mass of element determined	Ref.
Iron	Extraction with cupferron	± 4.3%	1.0 ng	49
Indium	EDTA and cation exchange	± 1.6%	1.1 μg	47
Copper	Extraction with dithizone	± 1.6%	10 μg	39
Zinc	Extraction with dithizone	± 3.8%	100μg	75*
Chromium	Extraction as dichromate with tetraphenylarsonium chloride	±2.5%	0.3μg	18

*The authors comment that the standard was of unnecessarily low specific activity.

or with pure β-emitters which give particles of energy greater than 700 KeV. But for β-emitters of low maximum β-energy, which produce particles incapable of penetrating the glass walls of the vessels, it is preferable to use precipitation methods and to count the solid sources with Geiger tubes having especially thin end windows. Another alternative in such cases would be to evaporate a measured quantity of a liquid extract on to a planchette for end-window counting, but this technique is tedious, and obviously less satisfactory.

B. Automatic Analyzers

Considerable efforts have been made to develop methods of continuous substoichiometric analysis. A team of workers at the University of Aston, England,[55,56] applied the Technicon "Auto-Analyzer" to the determination of mercury by solvent extraction with zinc dithizonate in carbon

tetrachloride. They claim the following advantages for an automated, continuous process:

1. The automation of sampling reduces the risk of radiochemical contamination of the workers' hands and clothes.
2. Every sample is treated in an identical way so that reproducibility of the blanks is guaranteed.
3. The time-consuming preparation of samples for radioassay is no longer necessary.

These advantages appear somewhat marginal. The activities which are required in radiochemical analysis need rarely exceed a few hundred nanocuries, and health hazards should be low for all but a very few nuclides if normal care is used in manipulation. The preparation of liquid samples for radioassay should require no more time than that required to measure accurately a volume of liquid into a tube; it is true that the preparation of precipitates for counting can take time, but automation has not yet been applied successfully to precipitation separations in any case, and the difficulties in doing so may prove insuperable.

The arrangement for continuous substoichiometric isotope-dilution analysis using an automatic analyzer is shown schematically[5,6] in Figure 9. The pumping tubes for the test, standard, and reagent solutions ensure constant delivery speeds for each. After mixing the sample and the test solution in the first coil, A, the liquid is joined by a stream of reagent and then mixed in the second coil, B, from which the mixture of aqueous and organic solutions flows into a separation unit, S. The activity of the organic solution is measured continuously at C, using a scintillation counter for γ-activities or a Geiger-Muller counter for β-activities, and recorded automatically. At first pure water is passed through Line 1, and the concentration of the active standard is adjusted to be suitable for 50 to 60% stoichiometric extraction by the reagent. After the activity, α_s, has been recorded for the standard alone, the solution to be analyzed is pumped through Line 1 and the new activity, α, is measured. The amount of the element in the test solution can then be calculated from Equation 5. Alternatively, the instrument can be calibrated by passing a number of inactive solutions of known concentration through Line 1 so that direct readings become possible. When this is done the method is suitable for concentration-dependent extraction as well as for truly substoichiometric separations.

The procedure described above is for the separation of metal chelates or ion-association compounds by solvent extraction, but the instrument could be applied equally well to complexation followed by ion exchange. In the latter case the cation-exchange columns between S and the counting unit would need to be replenished when the cation sites approached saturation with radioactive metals.

The application of precipitation methods to continuous substoichiometric analysis is likely to present very great difficulties.

The continuous process described above has a number of disadvantages which seem at the moment to outweigh the advantages enumerated earlier.

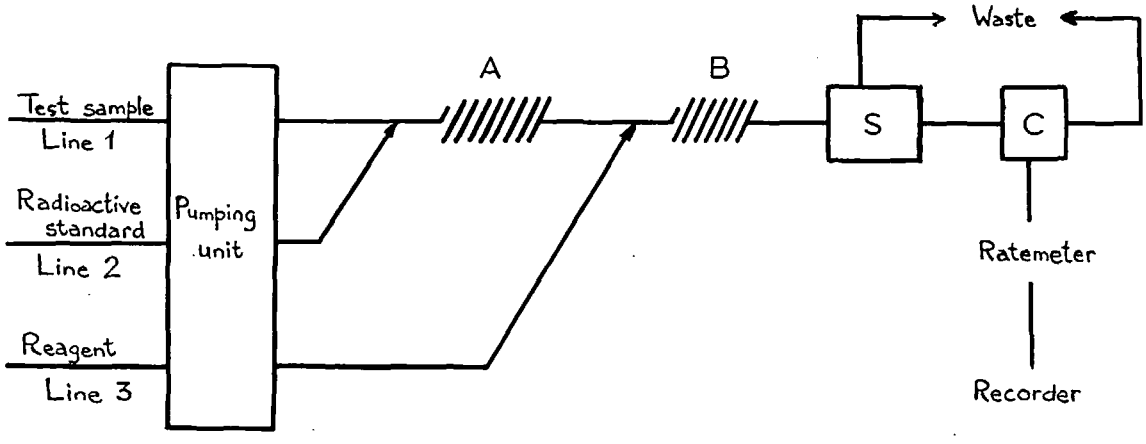

FIGURE 9. Scheme for continuous substoichiometric analysis.

1. Mixing in coils is far less efficient than manual shaking. The sensitivity of the method is found to be inferior to that of the manual method by a factor of ten.

2. The standard and the samples are not processed simultaneously, and the stability of the reagent to oxidation becomes of particular importance.

3. The tubing and coils become contaminated with adsorbed radionuclides which are liable to be replaced in later analyses by other ions which are adsorbed more strongly. Thus, spurious results can arise from the carrying forward of radioactivity which does not arise from the standard which is employed.

Ruzicka and Lamm[57] have described a modification of the above procedure which they call a semi-automated method. In it they added equal small amounts of high-activity radioisotope manually to the sample and to equal specimens of the sample mixed with known amounts of inactive standard. This is to be preferred, because the analytical result will not then be affected by any losses of the element which may occur during subsequent chemical treatment, for example, in removing interferences, before pumping through the analyzer, because such chemical processes will not affect the specific activity of the element. Another slight advantage is that the semi-automated method uses much less radioactivity than the fully automated one. Furthermore, calibration of the equipment using different amounts of inactive standard enables concentration-dependent determinations to be carried out as conveniently as in the fully-automated procedure.

VII. SOME ALTERNATIVE RADIOANALYTICAL METHODS, TREATED COMPARATIVELY

In this section we shall discuss some of the radioanalytical methods which have been used for the determination of elements in microgram and submicrogram quantities, and assess their merits and demerits in relation to substoichiometric isotope-dilution analysis.

A. Radioreagent Methods

In a radioreagent method an excess of a radioactive reagent, of exactly known specific activity, is used to form a compound with the element to be determined. The compound is then separated completely from the excess of reagent by precipitation, ion exchange, solvent extraction, or some other method before it is submitted to radioassay.

Goode[82] determined sulfur at the 1-10 ppm level in light petroleum; he used the Schöberl surface-combustion technique to oxidize the hydrocarbon, and absorbed in hydrogen peroxide solution the sulfur dioxide which was produced. The sulfate thus formed was precipitated with barium chloride labeled with barium-133, and the precipitate was thoroughly washed with methanol and radioassayed by γ-scintillation counting. The barium-133 solution was calibrated against standard sulfuric acid.

The precipitation of barium sulfate with standardized radioactive barium solutions has been used successfully in our laboratory to determine by oxygen-flask combustion the trace of sulfur introduced into fluorocarbon polymers by the sulfite used in the initiation of polymerization.

Landgrebe, Gills, and De Voe[83] converted microgram amounts of metal ions, separated by paper chromatography, into spots of insoluble, radioactive compounds for the determination of traces of manganese, cobalt, copper and iron in nickel oxide. The Mn^{2+}, Cu^{2+} and Fe^{3+} were converted to their phosphates with standardized radiophosphate; the Co^{2+} was converted to its insoluble ferrocyanide and then equilibrated with iron-59. The spots of insoluble phosphates or ferrocyanide were washed free from unreacted reagent and assayed. Iron could be detected at the 0.1 μg level and cobalt at the 10 ng level. A similar technique, used by Welford and his co-workers,[84] enabled the elements calcium, strontium, barium, and lead to be determined by precipitation with sulfur-35-labeled sulfate, and the elements beryllium and zirconium to be determined with phosphorus-32-labeled phosphate in a variety of mixtures; sensitivities of the order 10^{-10} g could be attained. The same workers[85] later determined barium, strontium, and several lanthanide elements by electrochromatographic precipitation of microgram amounts of the elements with radioactively labeled precipitants.

The great advantage of the radioreagent method is that elements can be determined which do not themselves have radioisotopes suitable for radioassay. Furthermore, as shown in the case of the

insoluble phosphates above, it can be adapted to the simultaneous determination of several elements with one standardized reagent. One disadvantage is that the substance to be determined must react quantitatively with the excess of radioreagent and form an easily separable compound. Another is that the radioreagent must be resistant to decomposition in dilute solution. Furthermore, if the element has to be removed by some preliminary separation from the test material, that separation must be quantitative.

B. Radiorelease Methods

In radiorelease analysis, as in radioreagent analysis, elements without radioisotopes suitable for direct radioassay can be determined. The element to be determined, in a suitable chemical form, is used to release from a radioactive reagent, by a quantitative reaction, an easily separable active species. Gillespie and Richter[86] estimated vanadate ions in water by pouring the liquid, at pH < 3, through a column containing metallic silver labeled with silver-110 m. The VO_2^+ is reduced, and releases Ag^+ ions:

$$VO_2^+ + 2\,H^+ + Ag = VO^{2+} + H_2O + Ag^+$$

The silver ions can then be assayed by γ-scintillation counting. As in radioreagent analysis, it is of paramount importance that the reaction which releases the radioactivity should be quantitative.

C. Phase-distribution Methods

As early as 1947 Kurbatov and Kurbatov[87] analyzed water for barium at the 10-ng level by measuring the distribution of barium-133 between the aqueous phase and a precipitate of hydrated iron(III) oxide. An adsorption isotherm was constructed by adding known amounts of barium(II) solution, tracer barium-133 ions, and iron(III) chloride, titrating with ammonia to the correct pH, allowing the hydrous iron(III) oxide to settle, and counting the supernatant liquid. Using the same technique with barium solutions of unknown strength, it was possible to determine the barium using the adsorption isotherm as a calibration curve. The method is technically rather difficult and requires very strict control of pH.

Isotopic exchange in a two-phase liquid system was used by Handley[88] to determine mercury in water at the 0.1-μg level. An acidified aqueous phase containing the mercury(II) ions was shaken with a standard solution of mercury di-n-butyl phosphorothioate, $Hg\,[(C_4H_9O)_2POS]_2$, labeled with mercury-203, in carbon tetrachloride, and the distribution ratio for the mercury between the two phases was determined from count-rates on equal volumes of aqueous and organic layers after equilibration. The value of $[Hg]_{aq}$ was then obtained from the equation:

$$\frac{[Hg]_{aq}}{[Hg]_{org}} = \frac{\text{specific activity of aqueous layer}}{\text{specific activity of organic layer}}$$

Naturally the most satisfactory results were obtained when $[Hg]_{org}$ was approximately equal to $[Hg]_{aq}$, so it was an advantage to know the approximate strength of the unknown solution.

This particular method is simple to use, but it depends heavily upon finding an organic compound which equilibrates quickly with the metal ions yet has a very low tendency to dissolve in the aqueous layer.

D. The Method of Schumacher and Friedli

These workers[89] proposed a method based on the following principle. "Carrier-free" radioisotope is added to the test metal, a suitable complexing agent is added in substoichiometric quantity, the complex which is formed is separated from uncomplexed ions, and the activities of both are measured. For example Co^{2+} (aq) and $[Co^{III}(EDTA)]^-$ were separated by paper chromatography. Counts were made on the two spots and the total weight w of cobalt was calculated from

$$w = m\,\frac{\alpha_c + \alpha_m}{\alpha_c}$$

where m is the amount of complexed metal, calculating from the amount of reagent added, α_c is the activity of the complexed cobalt, and α_m that of the unreacted metal ions. The method is simple and sensitive but the stability of the reagent against decomposition in solution is particularly important and there must be no losses in the course of the analysis. Furthermore, the complex must have a high formation constant and must resist dissociation during chromatographic separation.

E. Radiometric Titrations

The principles can be illustrated by describing the determination of zinc and cobalt by Duncan and Thomas,[90] who introduced solvent extraction into the method; earlier workers had used

precipitation reactions. They showed that zinc and cobalt could be determined in the same solution by the use of cobalt-60 tracer. Dithizone (4 x 10^{-5} M) in carbon tetrachloride was added to the aqueous solution of zinc and cobalt ions labeled with cobalt-60. The activity of the aqueous layer was measured after each addition of organic reagent, and a graph of the form shown in Figure 10 was obtained. Zinc ions have a much higher extraction constant than cobalt ions, and the activity of the aqueous layer remains unchanged while the inactive zinc is extracted. When the cobalt begins to be extracted the activity of the aqueous solution falls until all the cobalt is extracted into the organic layer. Then the volume *a* of dithizone represents the amount needed to complex the zinc and the volume *b* that needed to complex the cobalt. The precision was 0.2 μg for cobalt and 0.4 μg for zinc. The technique has the usual disadvantage of direct radiometric methods that it depends upon an exact knowledge of the concentration of the organic reagent, which must not undergo oxidation or decomposition even in very dilute solution.

Methods for automatic radiometric titration have been suggested by many authors, and the subject has been reviewed by Braun and Tolgyessy.[91]

A type of radiometric titration which incorporates substoichiometry has been described by Stary, Ruzicka, and Zeman.[92] They titrated a standard indium solution, labeled with indium-114m, against EDTA, removed uncomplexed metal ions with a cation-exchange resin, and counted the activity of the soluble chelate. Line *a* in Figure 11 represents the titration of the standard, while lines *b* and *c* represent titrations of solutions containing the standard plus unknown amounts of inactive indium. Then a horizontal line through the three titration graphs is divided in proportion to the total amounts of indium in the three solutions. The advantage of the method is that comparison is made with a standard solution of the metal, and exact knowledge of the concentration of the EDTA solution is unnecessary.

The authors also described titrations in which a solution containing indium-114m was used as a radioactive indicator for the determination of cobalt. Figure 12 represents the activities of (a)

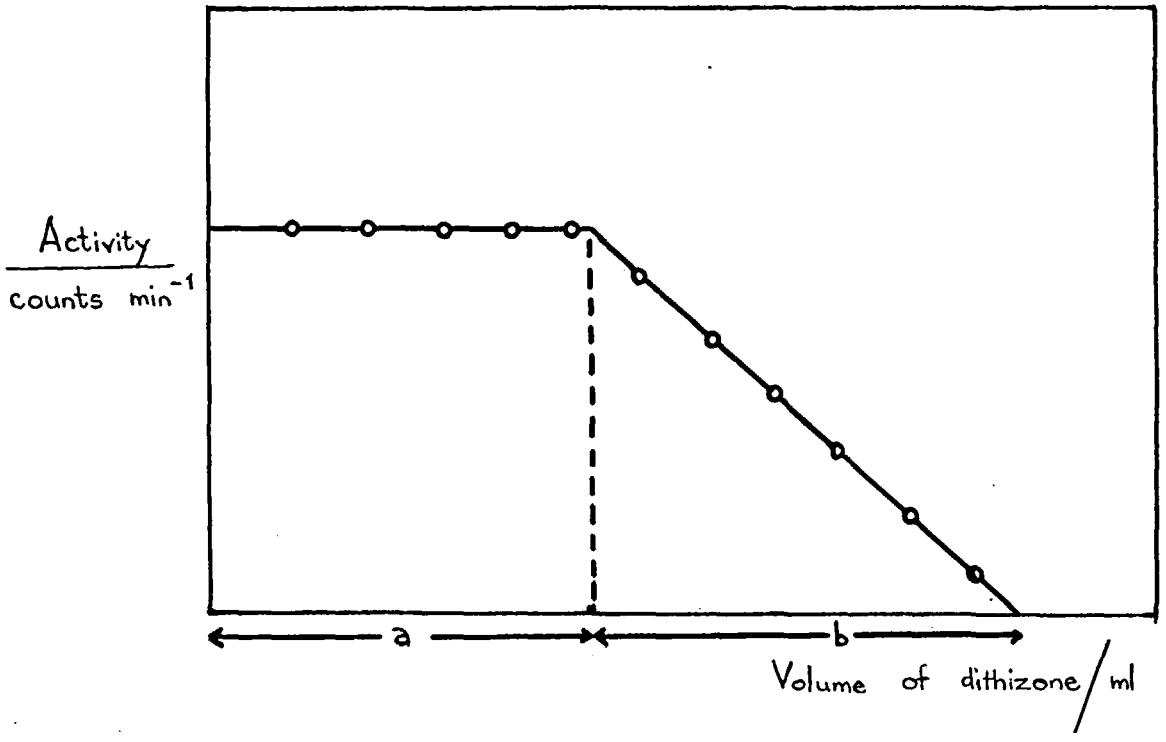

FIGURE 10. The radiometric titration of Zn^{2+} and Co^{2+} against dithizone in carbon tetrachloride. a. Dithizone needed to complex the inactive zinc; b. dithizone needed to complex the radioactive cobalt.

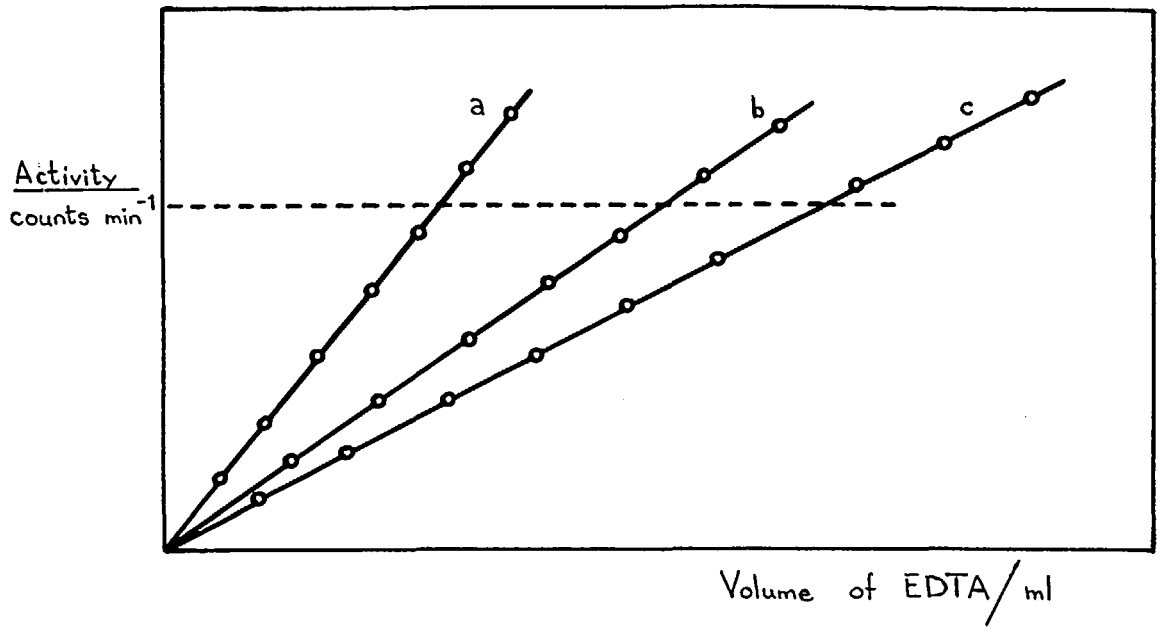

FIGURE 11. Titration of indium(III) solutions against EDTA. Activities of EDTA complexes separated from In^{3+} by ion-exchange.

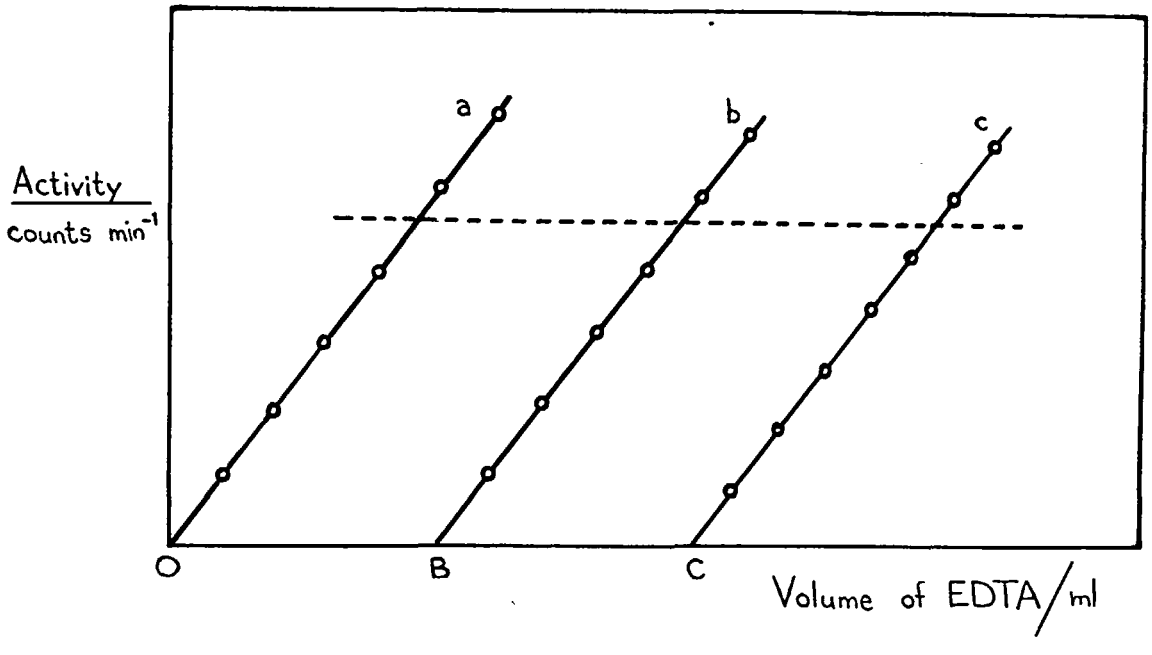

FIGURE 12. Titrations of cobalt(II) solutions with EDTA using indium-114m as tracer.

the indium-EDTA chelate alone and (b) the chelates separated from the same amount of indium mixed with a known amount of cobalt, w_s. In the second case the soluble indium-EDTA chelate does not begin to be formed until all the Co^{2+} ions are removed. The distance OB represents the amount of EDTA needed to chelate the cobalt. If line c represents the results of another determination carried out with the same amount of the original indium solution and an unknown solution of cobalt, the amount of cobalt, w, in the solution is given by

$$w = w_s \times \frac{OC}{OB}$$

In the title of their paper the authors refer to this method as that of chelating radiometric titration but it quite obviously incorporates most of the features of a substoichiometric determination.

VIII. PRACTICAL CONCLUSIONS

Although neutron-activation analysis is well established as one of the best techniques for the determination of a large number of elements at trace level, the application of substoichiometry offers the opportunity to simplify the chemistry of separation and thus to extend the basic technique to other elements. For example, a scheme of separation which takes minutes instead of hours opens up the possibility of extending activation methods to elements which produce only short-lived radionuclides on neutron irradiation.

The application of substoichiometry to isotope-dilution analysis offers even greater advantages, because radioactive tracers can be employed in the many laboratories which do not have the use of a neutron source. Isotope-dilution methods have the great advantage over other tracer methods of radiochemical analysis that losses of the test element in the course of analysis do not influence the result. The additional advantage gained by imposing the condition that exactly equal quantities of radio-carrier and of carrier plus sample should be isolated is that it is not necessary to know the precise amount of reagent that is used; the basis of the determination is the measurement of isotopic composition, rather than the measurement of distribution of activity as in other radioanalytical methods. Thus, substoichiometric methods offer an opportunity to widen the scope of isotope-dilution analysis to trace elements by completely obviating the need for the measurement of chemical yield, and it may well be that the most rapid developments in substoichiometry will be in this field. The factor which very largely determines whether the method is feasible is the stability of the reagent in very dilute solutions. Furthermore, as milligram amounts of carrier cannot be used as in activation analysis, the results are much more easily vitiated by small quantities of contaminants, and special care may be necessary in the purification of the water and other solvents which are used.

IX. POSSIBLE DEVELOPMENTS

It seems probable that methods which use solvent extraction will continue to be of major importance. Complexing agents such as dialkylphosphoric acids and dialkyldithiophosphoric acids may be found valuable; N-benzoylphenylhydroxylamine may prove a useful alternative to cupferron for some transition metals. Obrusnik's method of substoichiometric replacement seems to be capable of extensive application.

The use of chelons, which form water-soluble chelates of high thermodynamic stability, coupled with separation on ion-exchange resins, will probably continue to be the most successful method of isotope-dilution analysis for metals, though the separation of unreacted metal ions by solvent extraction may compete with ion-exchange separation in specific cases.

So far, the development of substoichiometric isotope-dilution methods for the analysis of traces of non-metals has lagged behind that for metals. However, the solvent extraction of ion-association compounds offers the greatest scope for further developments in this field. The solvent extraction of heteropolyanion complexes may also prove useful.

An entirely different approach, that of controlled-potential coulometry, is one that should be applicable in principle to many of the more easily reducible metal ions, and developments of such methods are to be expected.

A general trend will probably develop to make greater use of isotope-dilution relative to activation methods. It is generally cheaper and more convenient to use tracer nuclides than to irradiate samples in a flux of neutrons. The disadvantages incurred in the use of the very dilute solutions of

reagents which are required will be reduced as very pure reagents become increasingly available. Furthermore, substoichiometry applied to the isotope-dilution technique seems likely to lend itself to automation more easily than substoichiometry applied to neutron activation.

SUMMARY

One of the major difficulties associated with the chemical separation usually required in activation analysis for trace elements has been the need to determine the chemical yield of the separation process. In a separation using the substoichiometric principle, equal amounts of a reagent capable of converting the irradiated element and its isotopic carrier to an easily-separable form are added to the prepared sample and to the standard, but the reagent is sufficient to react with only a part of the element and carrier which is present. By this means the specific activities of the extracts or precipitates are made proportional to the total activities, and the determination of the absolute chemical yield of the separation is rendered unnecessary. Furthermore, the use of a substoichiometric amount of reagent usually increases the selectivity of the separation process.

The principle can be applied with equal, or even greater, advantage to radioisotope dilution analysis, and its use has greatly extended the application of tracer methods to the analysis of elements at microgram and submicrogram levels.

Of the methods which have been adapted for substoichiometric separations of elements, the most common are the solvent extraction of metal chelates and of ion-association compounds, and the ion-exchange separation of soluble complexonates. Precipitation methods have also been used, and both electrolysis and replacement substoichiometry are likely to increase in importance.

Substoichiometric methods have been applied with success to the analysis of many metals at trace level in a variety of materials; methods for the analysis of non-metals are also beginning to be developed. Perhaps substoichiometry will make its greatest impact in the development of isotope dilution analysis, a technique which has been neglected for trace analysis in the past because of the need to determine chemical yields. This development is particularly to be welcomed because it extends radioanalytical methods to laboratories which do not have easy access to nuclear reactors for neutron-irradiation.

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