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APPLICATION OF ISOTOPES*

by

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This discussion will concern itself primarily with current and potential applications of stable isotopes as tracers in a number of biomedical and environmental areas. A wide variety of problems exist in these fields whose solutions in principle are amenable to the isotopic approach. The number and diversity of these problems as well as the unique role stable isotopes can play in their solution illustrate the importance of achieving and maintaining a broad inventory of isotopic species. Experience has demonstrated unequivocally an additional overriding requirement for widespread exploration of stable isotopes by the scientific and technical community, i.e., the need for low cost availability of the materials in quantity. The role that laser-driven photochemical isotopic separations will play in meeting these goals is certain to become an important option; in specific instances this approach may be the only practical method for obtaining particular isotopes in quantity and in high purity.

Before compiling a list of possibly useful isotopic species or developing a catalog of real or imagined applications, a new, and hopefully realistic look at the overall isotope picture can be illuminating. We have over the past years, been subjected to a great deal of enthusiastic and sometimes uncritical comment regarding potential for isotopic tracers, radioactive as well as stable. At this time, the situation for radioactive tracers, certainly insofar as cost, availability and analytical detection instrumentation are concerned, is in relatively good shape when compared with that existing for stable isotopes. In no way, however, should we consider these two approaches

to be truly competetive; they are in reality complementary courses, each with definite specific advantages under particular conditions. The two major practical factors inhibiting the bioenvironmental application of radioactive tracers are (1) the difficulty and often the impossibility of obtaining detailed molecular structure information and (2) the growing limitations or prohibitions to the use of radioactive agents in both clinical medicine and environmental research. It is, furthermore, quite unlikely that society will relax the restrictions being continually imposed on the use of radiation in both human and environmental research.

Turning now the the real world of stable isotope availability, it is interesting to note that only one element, deuterium, can be currently obtained, together with a broad spectrum of its compounds, at a cost, purity and quantity which permits its uninhibited use as a tracer. At a recent visit to middle-sized university chemistry department, I was impressed to find literally tens of kilograms of deuterated compounds were on the stockroom shelves ready and available for use by the departmental staffs. No compounds of the other so called common biologically important isotopes of carbon, oxygen, or nitrogen were available, in spite of the really significant progress that has been made in the past few years in separating these elements.

This last point prompts a look back for a few minutes on the history of stable isotope separation and usage. In so doing, we should recognize also that at this time it is only in the case of deuterium that the technology for the production, i.e., separation, of an isotope has reached technical maturity. What we need now is to achieve a similar state of affairs for a

number of other isotopes. The challenge to laser technology is to make this method competitive.

Historical Background

Before enumerating and attempting to discuss a whole series of real or imagined applications, a brief history and a look at the evolution of isotopic studies seems worthwhile in order to put the subject in proper perspective. The idea of using isotopes as tracers is no new notion; its genesis in fact goes back almost to the original discovery of their existence. Their significant separation and application actually began in the early 1930's and in this country both the academic community and private industry, notably the Eastman Kodak Company, commenced an effort to obtain such key biological tracers as nitrogen, carbon and oxygen. Any of you who remember 1940 and 1941 may recollect the almost feverish activity at a number of laboratories aimed at the development and construction of mass spectrometers for use in isotopic assay. Looking back at this period of science, poised just before our involvement in the war, one sees quite clearly that stable isotopes were becoming quite de rigueur in chemistry, molecular spectroscopy and, more importantly, in the rapidly emerging and developing sciences of biochemistry and general biomedical research.

By the end of the war and primarily as "spinoff" from the Manhattan Project successes, a completely new and different situation had developed. Stable isotopes, except for deuterium, were more or less in eclipse in the biomedical areas and the newly available radioactive isotopes were

monopolizing tracer application in most al' fields. Sporadic efforts were being made to obtain ^{15}N, ^{13}C and the oxygen isotopes, but the quantities available were small and the costs exhorbitant. Other than this small effort, the conversion and dedication of a few calutrons at Oak Ridge to the electromagnetic separation of relatively small amounts of a variety of isotopes, mostly metals, the chemical exchange effort at the Mound Laboratory, and at Oak Ridge and the limited cryogenic distillation activity at LASL, the application of stable isotopes was largely dormant. With few exceptions, this condition persisted until the late 1960's.

In 1967, initially as the result of informal inquiries from a few biomedical scientists to what is now the Division of Biomedical and Environmental Research of ERDA, a fresh look was taken at the potential benefits which might accrue from a new vigorous program in isotopic separations. The time was certainly propitious for such a new effort for a number of very simple reasons. These were (1) the development of a vastly improved physico-chemical technology for the separation of isotopes, particularly the light isotopes of biomedical importance, (2) the development and availability of analytical instruments of high sensitivity and applicability to chemical structure determination, i.e., mass spectrometry including G.C.A. equipment, NMR spectrometry and a much improved battery of optical spectroscopic devices, (3) the growing importance of molecular biology and metabolic studies in clinical medicine opening a whole new series of problems amenable to isotope approaches, (4) a realization that the use radioactive would soon be limited or even proscribed in many routine human studies, and finally,

(5) environmental considerations restricting the use of radio isotopes in ecological, agricultural and meteorological research. These factors all were of importance in setting up the ICON program at Los Alamos. The success of this program in making available kilogram quantities of carbon, oxygen, and nitrogen isotopes at much reduced prices followed by the present upsurge of important scientific results based on this availability should be an incentive for further efforts. The catalog of inexpensive isotopes needs to be expanded to include all elements of biomedical and environmental interest. Laser driven photochemical methods have two important roles to play here, (1) as a potentially competitive process to existing technologies, and (2) as a means to obtain isotopes not now available.

Representative Applications

Before considering some representative examples of stable isotope applications, I would like to reemphasize the fact that, leaving aside deuterium, enriched nuclear fuels, are not the only other obviously important province of separation technology and science. Insofar as society's basic needs are concerned, the large scale availability of C_{13}, ^{15}N, or some isotope of Iron or Calcium may be equally important. This view is, of course, the central point of my discussion. A few specific examples of both current and hypothetical applications are now in order. Typical of ongoing open ended research problems which will continue to require significant quantities of isotopes are (A) studies of nitorgen cycling in agriculture, (B) the broad application of ^{13}C in clinical research and diagnosis and (C) the use of the rare and unique methane species, $^{13}CD_4$, as an atmospheric tracer in environmental and meteorological research. These applications have been addressed in

some detail in recent reports from the Los Alamos Scientific Laboratory. An abbreviated rationale of these studies follows:

A. Agricultural Studies. Sharply rising costs of fertilizer, the sputtering of the green revolution, and increasing demands for food and fiber have given a new urgency to more efficient incorporation of nitrogen into plant protein. At the same time there is a growing environmental concern that overuse of fertilizer will lead to nitrogen pollution of water supplies. Devising agricultural practices of fertilizer and water management to meet these needs is dependent upon quantitative information on nitrogen uptake and incorporation into plants. The stakes here are high, environmental and economic: hundreds of millions of dollars worth of fertilizer are applied each year to U. S. forms alone. Even a few percent increase in the efficiency of nitrogen uptake into high quality plant protein would save many dollars and lives. Cooperative long-term field experiments by the T.V.A., the U. S. Department of Agriculture and the University of California (under sponsorship of the N. S. F.) are beginning to answer these questions. These and related experiments annually require the use of kilograms of ^{15}N and metric tons of ^{14}N (produced under ERDA sponsorship at the Los Alamos Scientific Laboratory) incorporated into nitrogen fertilizers. These studies have stimulated great interest in extending such investigations to the many other climate zones and soil types in the United States and Western Europe. It has also awakened interest in the use of isotopes to monitor the quality of plant, proteins and carbohydrates and how they are affected by water and fertilizer management, and by the use of plant

growth hormones, herbicides, and pesticides The untapped potential of stable isotopes in the latter area is enormous.

B. Medical Studies. The demonstrated ability of stable isotopes in clinical research depends mainly on three considerations: (1) the isotopes are non-radioactive and afford the opportunity to apply tracer techniques to infants, young children, and pregnant women, areas of clinical research which have previously been inaccessible because of the radiation hazard inherent in the use of tritium and carbon-14; (2) the isotopes can be detected readily in urine and the breath, allowing the development of non-invasive (e.g., no vein punctures or biopsies) tests for the early detection of metabolic diseases and organ malfunctions; (3) compounds multiply labeled with stable isotopes can be detected at extremely low levels in body fluids or tissues using 'state of the art' mass spectrometers, allowing the quantitation of metabolites or drugs with a sensitivity that often exceeds that attainable with radio-isotope tracers as in radio-immuno assays.

The rationale for the development of non-invasive tests, such as breath tests, for the early detection of metabolic diseases (or organ malfunction) is that one manifestation of the disease or defect is an acceleration or diminution in the rate of oxidation of organic compounds in foods (e.g. proteins, carbohydrates, fats) to carbon dioxide which appears in the breath. By feeding the patient carbon-13 labeled food components such as lipids, the changed rate of oxidation can be followed indirectly by comparing the rate of appearance of carbon-13 in excess of the naturally occurring amount (1.1%) in the breath carbon dioxide of the patient relative to normal control subjects. The development of

These carbon-13 breath tests is still in its infancy but already promising results have been obtained for the diagnosis and management of intestinal disorders and for the detection of liver malfunction.

Strong interest has been expressed by a number of clinical investigators throughout the United States in applying the carbon-13 breath test to the study, diagnosis, and treatment of other metabolic disorders and organ malfunctions, including lactose intolerance in infants; intestinal bacterial overgrowth; genetic disorders of amino-acid metabolism in infants and children; malfunctions of the liver; thyroid disorders; early diabetes; and adrenal cortical disease.

C. Atmospheric Applications. Cooperative experiments among investigators at the LASL, the University of Chicago, the National Oceanic and Atmospheric Administration, and the Weapons Establishment at Aldermaston, England, using heavy methanes as atmospheric tracers, provides a dramatic example of the potential of stable isotopes. The experiment was undertaken because there is a growing need to understand quantitatively the details of air circulation as they relate to the transport of pollutants and their destruction. With regard to the latter, the role of the protective ozone layer is of special concern. Many theoretical models have been developed but there is a paucity of experimental data due primarily to the lack of a suitable long-range tracer gas. Ideally such a tracer should be nonradioactive, nontoxic, and nondepositing. Tracers such as SF_6 and certain of the freons, which have been used successfully in short range experiments (100 miles or less), are not suitable because the background levels are too high to allow the detection of the tracer after a reasonable amount had been released 500-2500 miles away. Mass-21 methane,

having the highly improbable composition of four deuterium atoms and one carbon-13 atom ($^{13}CD_4$), does fulfill these requirements.

Natural methane itself, composed of one carbon-12 and four hydrogen atoms (CH_4), occurs naturally only to the extent of ~ one part per million parts of air. Because carbon-13 and deuterium have a small natural abundance, the statistical probability of the natural occurrence of $^{13}CD_4$ is ca. one for every 10^{18} molecules of natural methane. Because of this very low natural background, it proved possible to detect quantitatively the release of 84 gms of $^{13}CD_4$ at distances 1500 to 2000 kilometers from the release point in air by a technique in which methane was separated and the methane-21 content was measured with a mass spectrometer. The synthetic mass-21 methane was released in Idaho Falls, Idaho and detected two-three days later at special collection stations in Minnesota, Iowa, and Michigan. This experiment shows that tracer studies with nonradioactive substances should become feasible on a continental, and perhaps global, scale, thereby providing the environmental scientist with a powerful new tool to study the atmospheric, aquatic, and terrestial movement and transformations of pollutants.

Sooner or later the growing requirements for isotopic studies of the types outlined will exceed current capacity for production. In any scale up to larger outputs the photochemical route should certainly be given another and closer look.

Stable sulphur isotopes, currently being separated at ERDA's Mound Laboratory also constitute a very important stable tracer for biomedical research, particularly in metabolic studies. Its use as an environmental tracer can be expected to be of importance, subject to the usual economic considerations.

D. Biomedical Application of Metallic Isotopes. Up to this point only nonmetallic low z elements have been considered, elements readily forming volatile compounds and whose isotopes may be separated by standard physico-chemical processes, i.e., distillation, isotopic exchange, etc. The stable isotopes of a number of metals are of great interest as biomedical tracers, particularly in clinical medicine. Probably the most obviously important and applicable of these are Iron 58 and Calcium 46 or 48 respectively the least abundant naturally occurring stable isotopes of these elements. Iron 58 would be particularly useful and timely owing to the present curtailment of the general use of radioactive tracers in routine clinical, especially hematological, studies.

Another area of increasing medical importance is that of bone metabolism, specifically calcium deposition and resorption. A plentiful supply of stable calcium isotopes would be of inestimable value in attacking these problems.

Finally, there are a number of other trace elements important in human metabolism and this list is constantly being added to. The mechanisms of action as well as the optimum amounts of these elements needed in many organisms, including man, is largely unknown. Here, too, the availability of stable tracers would be of help in the elucidation of mechanisms, and the diagnosis and the treatment of a number of deficiency diseases. Among these elements are selenium, copper, chromium, molybdenum and possibly others. Recent information concerning selenium is particularly interesting; in not too large concentrations the element is a well-known poison yet it is an essential element at very low levels.

In conclusion, we see quite clearly that there are extremely important applications of high purity stable isotopes across the entire

periodic chart of the elements. We have looked very briefly at a few of these applications, and in doing so have recognized need for more than just token production.

TABLE I

SOME CHARACTERISTICS OF THE STABLE ISOTOPES
OF CARBON, OXYGEN AND NITROGEN

Isotope	"Natural" abundance (%)	Nuclear spin
^{12}C	98.9	-
^{13}C	1.1	1/2
^{14}N	99.6	1
^{15}N	0.4	1/2
^{16}O	99.8	-
^{17}O	0.04	5/2
^{18}O	0.2	-

TABLE II

CURRENT COSTS OF SOME COMMONLY USED ISOTOPES*

Isotope	Enrichment	Form	Price per gram isotope
Carbon-13	90.0%	CO_2	$61.10
Carbon-12	99.95%	CO	4.60
Nitrogen-15	95-99.0%	NH_3	95.30
Nitrogen-14	99.99%	Ammonium Sulphate	0.154
Oxygen-16	99.98%	Oxygen gas	1.80
Oxygen-17	20-40.0%	Oxygen gas	377.50
Oxygen-18	90-99.0%	Oxygen gas	141.80

*From Stable Isotopes Catalog
Mound Laboratory

TABLE III

CURRENT COSTS OF STABLE IRON ISOTOPES*

Isotope	Natural Abundance	Enrichment	Cost/mg
Fe-54	5.90	90%	$1.50
Fe-56	91.52	98-99.8%	0.05
Fe-57	2.245	90%	2.30
Fe-58	0.33	50-70%	14.75

*Oak Ridge Electromagnetically Separated

TABLE IV

CURRENT COSTS OF STABLE CALCIUM ISOTOPES*

Isotope	Natural Abundance	Enrichment	Cost/mg
Ca-40	96.92	99 - 99.9%	$ 0.25
Ca-42	0.64	65 - 90 %	6.00
Ca-43	0.13	50 - 70 %	35.00
Ca-44	2.13	98 %	2.30
Ca-46	0.0032	40 - 47 %	880.00
Ca-48	0.179	75 - 95 %	16.00

*Oak Ridge Electromagnetically Separated