

Comment prepared by Alfred P. Wolf for Panel on
Theory of Hot Atom Chemistry, IAEA, Vienna, May 13-17, 1974

Applied Hot-Atom Chemistry, Labeling of Compounds, Isotope Production.

The direct application of research in Hot-Atom Chemistry to the field of Nuclear Medicine in the development and preparation of radiopharmaceuticals has no parallel in any other area of chemistry. In attesting to this fact one need only consider the number of young scientists who did their research in hot-atom chemistry who are now employed in nuclear medicine related endeavors and who still use hot atom chemistry techniques and knowledge in the daily execution of their work. The emphasis on hot-atom chemistry in the literature of these other disciplines is another indication. Another perspective of this strong influence can be seen in the fact that groups in these other disciplines (nuclear medicine and radiopharmaceutical research and application) deliberately seek out people trained in hot atom chemistry in order to effect the use of that discipline in these new areas. Thus young scientists are being sought for their skill as hot-atom chemists rather than as chemists generally qualified for a particular job.

The title of this comment is indeed broad and would require a long monograph to do it justice. It is my purpose to focus attention on some of the more general aspects and problems that the hot-atom chemist can concern himself with.

There is now a fair amount of information in the literature that will allow the chemist to see the broad perspective of the interdisciplinary aspects of radiopharmaceutical research and production. The most recent compendium that can be used as a starting point is Volumes I and II of the Proceedings of a Symposium entitled "Radiopharmaceuticals and Labelled Compounds", held by the IAEA and WHO in Copenhagen 26-30 March 1973. It

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is IAEA publication STI/PUB/344. Many of the pertinent references can be found in the article by Wolf, Christman, Fowler and Lambrecht, p. 345, Vol. I. An additional bibliography of about 800 references is available from the author of this comment.

Hot-atom chemistry had its initial and most direct impact in developing radiopharmaceuticals labeled with carbon-11, nitrogen-13, oxygen-15, fluorine-18 and iodine-123. The research and development needed to prepare a particular radiopharmaceutical starts with production of the nuclide by means of an appropriate nuclear reaction. The most prevalent important "reagents" are protons, deuterons, helium-3 and helium-4. Photons for photonuclear reactions have also been used but only to a very limited degree. The same is true for fast neutrons. The nuclide can be prepared as starting material (using standard radiochemical techniques) in the form of some simple product precursor (usually using hot-atom techniques) or occasionally in the form of the final product (using radiochemical or hot-atom techniques). Once the nuclide has been obtained it can be used in ordinary synthetic or biosynthetic processes in order to incorporate it into suitable compounds. Analytical control of these compounds is then the last step before delivery to the user (either for biological research, preclinical evaluation or clinical evaluation). There is perhaps one notable exception here, namely the use of excitation labeling which deals with nuclide incorporation after parent nuclide production.

It would be my contention that hot-atom chemists, be they primarily radiochemists, organic chemists or physical chemists, would be best suited to carry out the realization of radiopharmaceutical preparation from target bombardment to the delivery of compound. There are, however, some peripheral aspects of the field to which hot-atom chemists can make important

contributions. I would include here the radiolytic self destruction of the product (which draws heavily on the field of radiation chemistry) and the effect of the results of the nuclear decay process on the compound in-situ (organism, animal or man; Biological Effects of Nuclear Transformations). A review of the early literature of this latter field shows a total lack of involvement by hot-atom chemists with a resulting confusion in interpreting some results. This is now changing. Aspects of nuclear medicine such as absorption edge scanning and the use of potentiators for therapy in in-situ nuclear decay therapy which could also profit from overlap with hot atom chemistry will not be considered here.

Nuclide Production

There are a number of aspects to nuclide production; choice of target nuclide, availability of excitation functions, design of target (gas, liquid or solid), special problems in dissipation of heat and controlling unwanted radiolysis in the target, health physics considerations in facilitating flexibility and cost of preparation, development of on-line methods, emphasis on nuclides of short half-life with appropriate decay schemes.

One of the most notable features in starting work in this area is the lack of accurate, published, excitation functions. The lack of data in this field is perhaps understandable since radiochemists and nuclear chemists in the past had no real need to consider their efforts from the point of view that someone, in fact, might need these data for production work.

Target design presents many problems. Since yield is of great practical importance there has been a shift toward using gas targets wherever possible. This shift has been a direct outgrowth of research in hot-atom chemistry. To cite just one example, the use of gas targets has replaced the use of

boron oxide as a source of carbon-11. Each topic noted in the first paragraph can be similarly documented.

Precursor Preparation

It is here that hot-atom chemistry is perhaps most directly applicable. The important problems include: the development of on-line methods for precursor preparation utilizing hot-atom chemistry and radiation chemistry to realize product formation; production of the nuclide in the "carrier free" state; choice of target if the element is to be its own carrier for the nuclide produced, e.g. suitability of the target for direct use in further reaction; choice of target for direct use of the nuclide.

Here is a rich field for research and application of hot-atom chemistry. One might focus on the production of a "carrier free" nuclide and indeed ask how one determines that it is truly "carrier free". The preparation of a "carrier free" nuclide is facilitated if the target and subsequent processing does not put it into contact with other nuclides of the same element. The boundaries of "zero" contamination become critical when one considers the nuclides currently being most actively studied: carbon, nitrogen, oxygen, the halogens. The importance of producing the highest specific activity possible is inherent in the nature of the use of a radiopharmaceutical. Loading dose effects are amply documented in the literature. The product should be a true tracer and not have concomitant drug action.

An aspect of precursor preparation (or final product preparation) which is again particularly germane to problems in hot-atom chemistry is involved in the chemistry of nitrogen-13 and oxygen-15 labeled radiopharmaceuticals. In contrast to tritium and carbon-11, the information on the hot reactions of nitrogen-13 and oxygen-15 is sparse indeed. Much of

what is available is concerned only with phenomenological approaches to studying the isotope. Basic information is clearly needed.

A further aspect has to do with the choice of nuclide such that a parent useful for excitation labeling can be prepared. This will be considered further under labeling methods.

Labeling Methods

Conventional labeling methods have been amply documented and hardly need comment here. Exploitation of non-synthetic methods such as recoil methods, radiolytic methods, labeling by exposure to atomic species, accelerated ion methods and excitation labeling methods are again the province of the hot-atom chemist. Much needs to be done here and the problems are best exemplified by considering excitation labeling methods.

Perhaps one of the most useful methods of labeling radiopharmaceuticals, in a non-specific way, is excitation labeling. That this method is important stems from two facts. The most obvious is that it frequently is successful. Less obvious is the fact that many potentially useful compounds cannot be conveniently labeled by conventional means and thus the necessity to prepare such a compound for testing must rely on less conventional methods. In excitation labeling the labeling nuclide is either positively or negatively charged or it is neutral. It may be electronically excited and it may have some small residual kinetic energy but it is not its kinetic energy which is responsible for its efficacy. The charge state and excitation are responsible for its "labeling powers". The requirements for this nuclide are simple. It should label the substrate in a single product determining bimolecular reaction. It is usually generated by bombarding a nuclide, X, to produce a parent, Y, which decays with a convenient half life to give the labeling daughter, Z. It is important that Y be produced in a radionuclidically

pure form and the relevant nuclear reaction should have a large cross section for particles which can be obtained in high beam currents. The major processes which result in charged species from the parent Y as we know, are, negatron decay, positron decay, electron capture, and internal conversion. The half life of Y should be minutes to at most a few hours. The properties of the labeling nuclide Z should include $t_{1/2} Z = 10$ seconds - a few days, $Y \rightarrow Z$ should result in a high proportion of the charged state, the $Y \rightarrow Z$ decay should result in negligible recoil energy for Z and finally Z should have a simple decay scheme. An example of what can be accomplished in excitation labeling involves the decay of ^{123}Xe in Cl_2 gas resulting in a 100% yield of ^{123}ICl . Another example of labeling is the decay of ^{123}Xe on indocyanine green crystals resulting in a non-specifically labeled product in 20% yield, of potential use as a liver function agent. Fortunately there has already been some excellent basic work done in this area by hot-atom chemists but a great deal more needs to be done before a method as simple as this one is in conception can be routinely realized for large scale production.

An area of great importance in labeled compounds has to do with inorganic compounds, organo-metallics and complexes of all types. The surface of this vast area has hardly been scratched. The application of inorganic hot-atom chemistry is obvious and necessary. For example, the very high yields one sometimes observes in inorganic salts can be made use of for direct application in synthesis. The selectivity of complexes in recoil reactions and the application of annealing may well afford new routes to useful compounds.

Analytical Control

While this may seem far afield from hot-atom chemistry, it must again be pointed out that the particular interests and training of a hot-atom chemist put him in an advantageous position in appreciating the problems.

Radiochemical and radionuclidic purity are of primary interest. The peculiar problems relating to radiochemical and radionuclidic purity are the daily concern of the hot-atom chemist. Trace contaminants and the questions they raise have been addressed in almost every responsible research paper that has appeared in the literature of hot-atom chemistry.

Here again the hot-atom chemist can bring his special talents to bear, in addition to utilizing his expertise in radioassay.

Conclusion

In considering labeling of a radiopharmaceutical and the application of hot-atom chemistry one should not lose sight of the fact that the potential for large scale production of the nuclide should be high (the scale is defined by the medical community need, thus "large" is a subjective term) and the chemical and radiochemical yield of the radiopharmaceutical should be optimized. Much interesting basic research in the biological and medical fields has been done using labeled compounds with no or very limited clinical application. However, the underlying driving force in medical research is to be able to apply any new and useful finding to the treatment of disease in the general population. This is as true of radiopharmaceuticals as it is of any other drug or technique the medical profession ultimately uses. While these comments may be obvious, their substance has been ignored in many of the efforts involving direct use of cyclotron produced nuclides.

The purpose of this report was not to outline in detail each aspect of research and application in radiopharmaceutical production but rather to

touch briefly on just some of the problems that arise ^{in the period} between "beam-on-target" and "delivery-to-the-user". Hopefully some appreciation of the role of the hot-atom chemist has become apparent in this primarily heuristic exercise. The intention was to stimulate discussion rather than to provide an extensive monograph. What is more essential, however, is to note the importance, nay, necessity of a great deal more effort in basic research in hot-atom chemistry as a whole field in order to fully develop the benefits this branch of chemical science can provide for an applied field.