HIGH ENERGY HALOGEN ATOM REACTIONS ACTIVATED BY NUCLEAR TRANSFORMATIONS

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PROJECT ABSTRACT

High energy halogen atoms or ions, activated by various nuclear transformations are studied in gaseous, high pressure and condensed phase saturated and unsaturated hydrocarbons, halomethanes and liquid and solid aqueous solutions of biomolecules in order to better understand the mechanisms and dynamics of high energy monovalent species. The experimental and theoretical program and its goals remain the same, consisting of five interrelated areas: (1) The stereochemistry of high energy ^{18}F , $^{34\text{m}}\text{Cl}$, and ^{76}Br substitution reactions involving enantiomeric molecules in the gas and condensed phase are studied. This is a continuation of a joint project with A.P. Wolf at Brookhaven National Laboratory. (2) The gas to condensed state transition in halogen high energy chemistry, involving chlorine, bromine, and iodine activated by the (n, γ) and (I.T.) processes in halomethanes, saturated and unsaturated hydrocarbons is being investigated in more detail. Special attention is given to defining the nature of the enhancement yields in the condensed phase. High energy halogen reactions in liquid and frozen aqueous solutions of organic and biomolecular solutes are studied in an attempt to learn more about these reactions. (3) The applications of high energy chemistry techniques and theory to neutron activation analysis of biological systems are being continued. Special attention is given to developing procedures for trace molecular determinations in biological systems. The applications of hot halogen atoms as indicators of solute-solute interactions in liquid and frozen aqueous solutions of halogenated bases and nucleosides are being developed. Experiments are designed to explain

the mechanisms of the radioprotection offered biomolecular solutes trapped within the frozen ice lattice. (4) Reactions of bromine and iodine activated by isomeric transition with halogenated biomolecular solutes in liquid and frozen aqueous solutions are studied in an attempt to learn more about the activation event in the condensed phase. (5) The high energy reactions of iodine with the isomers of pentene have been studied in low pressure gaseous systems employing additives and rare gas moderators and liquid systems. Special attention is given to the reactivity of excited complex formation and structural effects of electrophilic iodine attack on the pi-bond systems.

FACILITIES

A. Triga Mark I Reactor

All neutron irradiations were made in the Triga Mark I "swimming pool" nuclear reactor at the Veteran's Administration Medical Center in Omaha, Nebraska. A flux of 1×10^{11} thermal neutrons $\text{cm}^{-2} \text{sec}^{-1}$ was present at an operating power of 15.5 kilowatts. Various positions in the "lazy susan" sample holder were employed and the assembly was rotated to ensure that all samples received the same neutron flux and radiation dose. For very short irradiations, the assembly was not rotated and samples were irradiated in the same position. The radiation dose was approximately $3 \times 10^{17} \text{ eV g}^{-1} \text{ min}^{-1}$ using Fricke dosimetry.

For the past year, the nuclear reactor operated routinely for at least four eight-hour days a week at 15.5 kilowatts. The radiochemistry group used for the period from October 1, 1979 to September 30, 1980, 340 hours (integrated time in reactor) at 15.5 kilowatts power, making 1700 irradiations.

B. Radiochemistry Laboratory

All sample preparations were performed in a well-equipped, specially-designed radiochemistry laboratory in Hamilton Hall Chemistry building. The two hot laboratories contain four six-foot "Oak Ridge-Type" hoods, several radioactive waste sinks, radiation safety equipment, seven separate vacuum lines for preparing gas, high pressure gas, liquid and solid state systems, and the usual laboratory facilities. The counting room is equipped with one radiogas chromatograph, three single-channel analyzers with several 2" X 2" NaI crystals, four GM counting stations, four gas-

flow counters, and a Nuclear-Data 128-channel analyzer with a 3" x 3" NaI crystal specially housed in a concrete, cadmium, and lead cave.

Two complete radiogas chromatographs have been built and are located in the radiochemistry room of the reactor facility, allowing us to analyze routinely many more samples containing ^{128}I , ^{130}I , ^{80}Br , ^{82}Br , and ^{38}Cl . This is quite necessary for the study of ^{128}I , ^{80}Br , and ^{38}Cl reactions activated by the (n, γ) process in the unsaturated hydrocarbons, precluding the necessity of making severe corrections for radiation damage and thermal reactions occurring during lengthy neutron irradiations. An ISCO Model 1440 High Performance Liquid Chromatograph with sample collector is located at the reactor facility. This location enables us to study efficiently the high energy reactions of halogens with aqueous liquid and frozen systems of organic molecular and biomolecular solutes. We have increased our data-gathering ability by having our equipment located at the reactor site.

SUMMARY OF PRESENT PROGRAM

A. Background of Project

Hot atom, high energy or "hot" chemistry, is an important tool for basic research in areas now considered vital-energy, environment and medical or related technology. "Hot" chemistry is a probe, an interactive science which embraces many fields; from hot atom reactions in simple hydrocarbon systems to theoretical development of high energy particle reactions. Utilizing reactive species possessing non-Boltzmann energy distributions, high energy chemists have discovered and characterized new reaction channels in organic and inorganic systems; contributed to the theories of energetics, dynamics and systematics; developed new techniques of chemical detection and analysis; and aided biological and medical sciences.

High energy distributions of atoms and/or ions can be produced via two classes of activation: chemical accelerators and bulb techniques. Each type of experiment produces reactions that can contribute to the characterization of high energy species. Each experimental class investigates properties unique to its technique.

Chemical accelerators impart kinetic energy to atoms, ions or molecules by use of electromagnetic, pressure differential or ultrasonic gradients. The particles are accelerated in a straight line (linear or tangential, hence the name "beam" experiment) with a resultant kinetic energy distribution of narrow bandwidth (generally a Boltzmann distribution centered about the terminal accelerator energy). The atomic-, ionic- or molecular-beam is produced in a near vacuum and permits the examination of atom-molecule

and/or ion-molecule single collision reactions. The data obtained reveal information on intrinsic properties of reactions; e.g., reactive cross sections as functions of scattering angle and energy. However, chemical accelerators are limited in their abilities to measure endoergic reactions, to have (energy) resolution and (product) identification simultaneously, to orient molecules (dynamics), and to study the effect of environment (even 1 Torr pressure) and multiple collisions on reactivity.

Bulb techniques are multi-collisionally oriented. The kinetic energy imparted to atoms or ions are the result of nuclear recoil or photochemical recoil activation. While photochemical and some nuclear activation modes produce atoms, ions or radicals within narrow kinetic energy limits, the multi-collisional nature of the technique results in collisional "cooling" of the "hot" entities, producing a broad spectrum of kinetic energies.

Extrinsic properties are readily measured (the hot species or medium taken in bulk) and intrinsic properties are inferred. New reaction channels (both exo- and endoergic) have been observed and characterized. Although molecules cannot be oriented, the ease of product identification (including diastereomers and enantiomers) permits study of reaction dynamics. The effect of the molecular environment on the reaction systems from low pressure gas to solid state gasses and crystals is easily studied in bulb experiments. These studies can significantly contribute to a better understanding of the photo-catalytic cage effects or de-excitation processes, an area that may be important in photochemical energy conversion processes.

In our research work, we are interested in the area of monovalent high energy physical-organic chemistry, concentrating on heavy halogens activated by radiative neutron capture and isomeric transition, and cyclotron produced fluorine, chlorine and bromine. We have also used photochemistry, ion cyclotron resonance and mass spectrometry techniques in our work.

During the period February 1980 to January 1981, three publications appeared in the literature, two are currently in press and one has been submitted for publication. The lead talk "Liquid Phase Hot Atom Chemistry: At Crossroads" which I presented at the 10th International Hot Atom Chemistry Symposium in Loughborough, U.K., appears in a special issue devoted to the lead lectures of the Symposium in Radiochimica Acta. The reader may acquire a flavor of the current work that is being done by the group in the last several years. As much of our progress of the past contract year is contained in publications and manuscripts in-press or submitted, only a brief discussion relating the relevance, progress and significance of the work will be presented.

B. Summarized below is a report of our main progress during the current contract period.

1. **The Stereochemistry of Energetic Halogen Substitution Reactions at Asymmetric Carbon Atoms.**

RELEVANCE. The fundamental question of whether high energy halogen atoms replace another halogen by retention or inversion of configuration at asymmetric carbon atoms,

is important to investigate since it can provide insight into the dynamics of hot atom reactions. The continuing role of simple physical models for hot atoms with molecules such as the "Impact Model" and the "Inertial Model" can be evaluated and refined. These projects are a collaborative effort with Dr. A. P. Wolf of Brookhaven National Laboratory.

(a) High Energy Chlorine-for-Chlorine Substitution Involving Walden Inversion in Gaseous 2-Chloro-1-Propanol.¹

PROGRESS. In a recent study^{2,3} it was reported for the first time that a gas phase high energy substitution reaction occurred mainly by Walden inversion. In gaseous 2(S)-(+) - and 2(R)-(-) - chloropropionyl chloride greater than 80% of inversion in configuration was observed at the chiral center for both ^{34m}Cl and ³⁸Cl substitutions. The extent of inversion being independent of radical scavenging suggested a unique inversion mode for high energy chlorine-for-chlorine substitution. It was concluded that the predominant factor controlling this substitution event was steric in character. It is of obvious importance to test for the presence of Walden inversion in other molecules with single chiral centers. This paper reports the reactions of ^{34m}Cl-for-Cl substitution in gaseous 2(S)-(+) - and 2(R)-(-) - chloro-1-propanol at various system pressures and in the presence and absence of neon moderator and a radical scavenger.

The experimental techniques employed in this study have been previously described.²⁻⁴ The methods described by Lucas et al.⁵ were used to produce 2(S)-(+)- and 2(R)-(-)- chloro-1-propanol. Polarimetric analysis of the R and C chloropropanol showed specific rotations of $[\alpha]_D^{25} = 15.5$ and $[\alpha]_D^{25} = +15.33$, respectively. The resolving agent, 2(S)-(-)- acetoxy-4-methyl valeryl chloride was found to be 86% optically pure. Sample sizes varying from 30-80 μ L were used for the study. The samples were heated to 100°C in quartz irradiation vessels and were irradiated with a 22 MeV proton beam at the BNL 60-inch cyclotron. The samples received an average irradiation of 60 μ As normally producing about 12 μ Ci at E.O.B. Post-irradiation derivatization and separations of diastereomers were accomplished by the methods previously described.²⁻⁴ Control experiments³ in which derivatization was run in the presence of externally generated ^{34m}Cl in admixture with the substrate showed that post-irradiation ^{34m}Cl -for-Cl exchange reactions were not significant under the conditions employed for the derivatization of the diastereomers.

Presented in Table I are the absolute yields and percent inversion of ^{34m}Cl -for-Cl substitution at the chiral center of 2(S)-(+)- and 2(R)-(-)- chloro-1-propanol at various pressures and in the presence and absence of neon moderator. These results show a predominant inversion of configuration at the chiral center for ^{34m}Cl -for-Cl substitution of the propanol in agreement with the results previously obtained in the study of ^{34m}Cl -and ^{38}Cl -for-Cl substitution in the gas phase enantiomers, 2(S)-(+)- and 2(R)-(-)- chloropropionyl chloride. The percent inversion and the absolute

TABLE I. Yields of ^{34m}Cl -for-Cl Substitution at the Asymmetric Carbon of 2(S)-(+)- and 2(R)-(-)- Chloro-1-Propanol in the Gas (at +100°C) Phase.

Enantiomer	Pressure (Torr)	Mole % Neon	Absolute Yield %	Inversion %
S-(+)	290	--	1.2 $\pm$ 0.1	79 $\pm$ 10
R-(-)	290	--	1.2 $\pm$ 0.4	80 $\pm$ 5
S-(+)	340	--	1.3 $\pm$ 0.8	78 $\pm$ 7
R-(-)	340	--	1.7 $\pm$ 0.7	74 $\pm$ 10
S-(+)	390	--	2.1 $\pm$ 0.8	59 $\pm$ 6
R-(-)	390	--	2.1 $\pm$ 0.6	56 $\pm$ 4
S-(+)	500	--	2.5 $\pm$ 0.5	47 $\pm$ 6
R-(-)	500	--	2.4 $\pm$ 0.4	54 $\pm$ 10
S-(+)	750	--	3.1 $\pm$ 0.4	44 $\pm$ 5
R-(-)	750	--	3.4 $\pm$ 0.3	40 $\pm$ 5
S-(+)	340	7.7	1.1 $\pm$ 0.3	76 $\pm$ 4
S-(+)	340	21.1	1.0 $\pm$ 0.4	60 $\pm$ 7
S-(+)	340	50.2	1.0 $\pm$ 0.5	50 $\pm$ 3
S-(+)	340	63.4	0.8 $\pm$ 0.2	44 $\pm$ 7

yield of ^{34m}Cl -for-Cl substitution in 2(S)-(+)- chloro-1-propanol decreases with increasing mole % neon suggesting that ^{34m}Cl -for-Cl substitution at the chiral center of 2(S)-(+)- chloro-1-propanol, resulting in inversion, involves high energy (hot) chlorine atoms. While it may be argued that 20% of the inversion is actually due to racemization there is a remaining 60% of the substitution reaction that must result from an inversion reaction. The effect of 1,3-butadiene on the ^{34m}Cl -for-Cl substitution in 2-chloro-1-propanol has also been investigated. In the presence of 5 mole % of 1,3-butadiene the observed percent inversion was 73 $\pm$ 4 %. As noted previously in the 2-chloropropionyl chloride, the observed percent

inversions are similar within experimental error. Based on the absence of any effects on the observed percent inversion in the presence of the 1,3-butadiene radical scavenger, it is suggested that reactions involving thermal or hot radicals which can react with the butadiene are not involved in the inversion mode.

As can be seen in Table I, the percent inversion appears to decrease with increasing pressure. Ache et al.⁴ who have studied chlorine-38 for chlorine substitution in liquid 2-chloro-1-propanol found a partial retention or a racemic mixture depending on which solvent system was used. The next system showed partial retention. It is known from infrared spectroscopy studies⁶⁻¹³ that alcohols can readily hydrogen bond. In fact it has been shown^{14,15} by infrared and thermal conductivity techniques that there is molecular association or aggregation in an alcohol such as methanol in the vapor phase. In order to investigate further correlation between the extent of inversion and the system pressure, the state of aggregation in the chloro-alcohol was investigated. The IR spectra at 100°C in the pressure range of 340-740 Torr were studied. With a system pressure of 390 Torr a small absorption band at 3470 cm^{-1} -- absent at 340 Torr pressure -- and a sharp absorption band at 3600 cm^{-1} were observed. The absorption bands at 3600 cm^{-1} and 3470 cm^{-1} have been shown to be the free fundamental valence stretching vibrations of the hydrogen-oxygen bond and the fundamental stretching vibration of the O-H in the dimer in which the hydrogen participates in the bridge between its own oxygen and the oxygen of another molecule,¹⁰ respectively. Increasing the

system pressure resulted in an appearance of the 3470 cm^{-1} dimer absorption band with a concomitant decrease of the 3600 cm^{-1} monomer absorption band. The presence of the 3470 cm^{-1} absorption band suggests molecular aggregation at these system pressures. As seen in Table I, unlike the chlorine-for-chlorine substitution in 2-chloropropionyl chloride, there is a definite pressure effect on the extent of inversion in the chlorine substitution with 2-chloro-1-propanol. With increasing total system pressure the extent of inversion decreases. This evidence suggests a relationship between aggregation and the extent of inversion. As the extent of aggregation increases the number of molecules allowing a relatively unhindered backside attack leading to inversion decreases. This can be readily seen from scale molecular models. This again suggests the importance of steric factors in hot atom substitution reactions.

SIGNIFICANCE. This study demonstrates that an inversion reaction mode involving high energy chlorine substitution is not unique for the 2-chloropropionyl chloride but also occurs in chlorine-for-chlorine substitution with 2-chloro-1-propanol vapor. The neon moderator data suggest that excess kinetic energy is necessary for the inversion channel, the extent of its yield decreasing with increasing moderator concentration. Unlike the halo-acyl-chloride the chloro-alcohol forms aggregates or clusters via hydrogen bonding at higher pressures. This would vitiate any conclusions regarding the mechanism and dynamics of the substitution process in higher pressure systems, especially those involving the condensed

phase⁴ and would suggest that care must be taken in comparing liquid or "high" pressure results with those of low pressure systems.

(b) High Energy Fluorine-for-Fluorine Substitution Reactions in Gaseous 2-Fluoropropionyl Fluoride.

PROGRESS. One of our goals in the study of halogen-for-halogen substitution reactions is the role of hot atom size, enantiomer ligand atom size, nature of hot atoms on whether predominant substitution with retention of configuration or inversion of configuration occurs. We choose to study the ^{18}F -for-F substitution at the asymmetric carbon of 2(S)-(+) and 2(R)-(-)- fluoropropionyl fluoride in the gas phase. For reasons described in the previous section, our enantiomer of choice was the acyl fluoride rather than the alcohol. The experimental details are similar to those previously employed in the chlorine project.³ The nuclear activation reaction of choice was the $^{19}\text{F}(\text{p,pn})^{18}\text{F}$ reaction.

Presented in Table II are the absolute yields and percent inversion of ^{18}F -for-F substitution at the chiral center of 2(S)-(+) and 2(R)-(-)- fluoropropionyl fluoride at various pressures and in the presence and absence of 1,3-butadiene scavenger. Unlike the 2-chloropropionyl chloride system,³ these results show a predominant retention of configuration at the chiral center ^{18}F -for-F substitution of the acyl fluoride. The percent inversion and its absolute yield, appear independent of the system pressure and 1,3-butadiene additive.

SIGNIFICANCE. While it is too early to define the parameters responsible for the differences in the substitution processes between the chlorides and fluorides, it appears that there is a sub-

stituent inertial effect involved. Our experiments involving ^{18}F and ^{76}Br will assist us in understanding better the substituent processes.

2. Gas to Liquid to Solid Transition in High Energy Chemistry.

RELEVANCE. While the gas phase studies of any system may lead to discovery of new high energy reaction channels, the gas phase quite often does not resemble the final, technological end product to which the system can be applied. The liquid or solid phase system is often ideally suited for chemical, technological or environmental application on an industrial scale. The dilemma lies in the often too complex nature of condensed phase systems. Dynamic, systematic and energetic information is more difficult to extract from high density data than the low pressure gas counterparts. The gas to liquid to solid transition provides a continuity between simpler research (gas phase) systems and their applicable end-product (often the condensed phase).

By systematic use of the gas to condensed phase transition, the effects of a collapsing molecular environment on high energy atoms or ions and their reaction channels can be observed. The resulting data contribute information as to the nature and importance of various reaction channels; the emergence of new reaction products (channels), not found in the gas phase; and the relative importance of molecular versus enhancement reactions in the condensed phase.

The nature of condensed phase enhancement reactions has been a controversial subject since the beginning of hot atom chemistry.

The interplay of the gas to liquid to solid transition experiments with theoretical chemistry provides a realistic link between observation and postulation. The characterization of phase transitions of any system provides feedback for refinement of enhancement yield theories. However, we realize that care must be employed not to over-interpret gas to condensed phase data. We do not employ the density-variation technique as a kinetics tool to extract quantitative information but as a mechanistic probe to develop reaction schemes as seen in Section 5, and to observe the effects of a collapsing molecular environment on high energy reaction products.

In the same manner, the gas to condensed phase transition studies on diastereomers and enantiomers provide information for the refinement of current concepts of molecular dynamics of hot atom or ion reactions with organic substrates.

(a) High Energy Reactions of Iodine in Liquid and Aqueous Solutions of Biomolecular Solutes.

PROGRESS. In a recent communication¹⁶, we suggested caging effects by an ice lattice on high energy iodine geminate recombination with the biomolecules diiodotyrosine (DIT) and moniodotyrosine (MIT). This suggestion was based on the observation that the only observed products from neutron irradiation of frozen dilute aqueous solutions of MIT and DIT were the ¹²⁸I-labeled iodide and MIT or DIT, respectively. Over a 100-fold concentration range the labeled MIT or DIT product yields were not only relatively large but constant in value. This behavior of the frozen aqueous state

was quite different than that of the liquid where the labeled biomolecular product yields appeared to decrease with decreasing biomolecule solute concentration. In order to make the suggestion that the events responsible for the high constant biomolecular yields over a large concentration range in the frozen aqueous mixture are the result of geminate recombination of a hot ^{128}I species produced by radiative neutron capture with the original radical caged by the ice lattice, it is necessary to establish that the biomolecule solute exists as a monomolecular dispersion trapped in the empty spaces within the ice lattice. The water molecules in ice at -77°C are arrayed¹⁷ in hexagonal arrangements of oxygen atoms (isomorphous with the wurtzite form of zinc sulfide) by hydrogen bonding with much empty space between the molecules.

The biomolecular solute can exist as microcrystals, small clusters or aggregates of the biomolecules or as individual molecules trapped within the ice lattice. There is no a priori reason to assume that all biomolecules are trapped in a monomolecular dispersion within ice. Since the ^{128}I -labeled MIT or DIT yields decreased with decreasing solute concentration in the liquid aqueous solutions, it may indicate a decrease in the extent of aggregation with decreasing solute concentration.

In this study the product distributions of ^{128}I activated by radiative neutron capture were determined in dilute aqueous solutions in both the liquid and frozen states and the neat form of 1-iodoaniline (2IA), 3-iodoaniline (3IA), 4-iodoaniline (4IA), 5-iodouracil (5IU), 3-iodo-L-tyrosine (MIT), 5-iodo-2'-deoxyuridine

(IUDR), 5-iodo-5'-deoxyadenosine (5IdA) and 3,5-diiodo-L-tyrosine (DIT). These results suggest to us that a "hot atom" such as ^{128}I , activated by radiative neutron capture, can be utilized as an "interactive tracer" to find site information in liquid solutions, as well as frozen aqueous mixtures. This can only be accomplished if the hot atom has distinctively different chemical reactivities with solute aggregates and water.

The main purpose of this study was to determine the nature of organic or biomolecule solute aggregation in liquid and frozen aqueous systems in order to understand better the high labeled product yields in neutron irradiated aqueous systems. Whether in the liquid or frozen aqueous state the organic or biomolecular solute can exist as clusters or aggregates, microcrystals or solute aggregates of a preferred size within the ice lattice, or as a monomolecular dispersion. The nature of the solute can, of course, depend on its concentration. If aggregates or clusters of the solute molecules exist in the liquid or frozen aqueous systems, then the hot atom reaction products observed should be characteristic of the neat solute in the crystalline state. Unfortunately there are in the literature no studies reporting hot atom reactions in crystalline biomolecular systems.

Iodine reactions produced by radiative neutron capture must probably involve positively charged iodine ions in ground or electronically excited states. Iodine-128 formation in all the crystalline systems must involve hot hydrogen abstraction reactions producing H^{128}I either with biomolecules in the crystalline lattice, or if trapped in the metastable states within the crystals,

with water molecules in the dissolution process prior to product analysis. In the aqueous system iodine will of course exist as $^{128}\text{I}^-$. It would be quite informative to have crystal structures for all the crystalline biomolecules studied. Unfortunately all of the structures are not available. Even so, because of the molecular complexity of the biomolecules, it probably would be difficult to perform computer simulation studies of (n, γ) recoil of iodine as performed by Rössler et al.¹⁸ for hexahalogenate crystals. Crystal structures have only been determined for IUdR¹⁹ and DIT $\cdot$ 2H₂O.²⁰ While it may be tempting to ascribe the large differences in yield among the eight systems studied to hydrogen availability (considering the range of the recoil iodine within the crystal) and orientation of the biomolecules within the crystal, any such suggestions must be delayed until more crystal data, annealing studies, etc. are at hand.

Of major importance to our studies of iodine reactivity in the liquid and frozen aqueous systems of biomolecular solutions is the result that the major organic product is the ^{128}I -labeled parent chemical form, whose yield is relatively high for all the crystalline compounds, ranging from 10.2% for IUdR to 87.2%.

$^{128}\text{I}^-$ was a product for all the iodinated biomolecules. Its absolute yield varied from 3.6% for crystalline DIT to 88.5% for 5IdA. For crystalline 2IA and crystalline and liquid 3IA, the $^{128}\text{I}^-$ yields were similar ranging between 62.2% and 70.3%. However, the $^{128}\text{I}^-$ yield for 4IA was only 40%. No evidence was found in any crystalline systems for the formation of ^{128}I -labeled diiodine.

Depicted in Figures 1 and 2 are the absolute product yields of the ^{128}I -labeled parent plotted versus solute concentrations in liquid aqueous solutions of iodinated biomolecules. For the sake of clarity some of the yields at higher solute concentration are not included. Three important observations can be made. Compared to the crystalline systems the labeled biomolecular yields are small. As the concentration of the biomolecule solute decreases in the aqueous solution the labeled biomolecule yields decreases. Interestingly, as the solute concentration decreases to zero the $^{128}\text{I}^-$ concentration approaches one hundred percent. It would appear that the only interpretation consistent with these data is that the biomolecules exist in some kind of cluster or aggregate form, perhaps of the kind postulated for aggregation of nucleic acid bases and their derivatives in aqueous solutions.

It would also seem that aqueous water does not offer much caging for geminate recombination of hot iodine or its reaction with organic radical debris. Apparently there is a high tendency for diffusion away from the initial site of formation of the hot atom organically bound to the biomolecule in monomolecular dispersion. This suggestion of a monomolecular dispersion is consistent with the $^{128}\text{I}^-$ yields increasing to 100% at low biomolecular solute concentrations. In the liquid state at low solute concentrations the most probable tendency for the recoil iodine species is to undergo a hydrogen abstraction reaction with a nearby water molecule forming H^{128}I .

Figure 1: Effect of biomolecule solute concentration on the percent yield of ^{128}I -labeled parent in the neutron-irradiated liquid aqueous solutions. The biomolecule solutes are 2IA $\bigcirc$, 3IA $\square$, 5IdA $\blacktriangle$ and IUDR $\blacksquare$. Yields for solute concentrations above 10×10^{-3} mole percent solute are not included.

Figure 2: Effects of biomolecule solute concentration on the percent yield of ^{128}I -labeled parent in the neutron-irradiated liquid aqueous solutions. The biomolecule solutes are 4IA $\triangle$, MIT $\odot$, DIT $\blacktriangledown$, and 5IU $\triangledown$. Yields for solute concentrations about 10×10^{-3} mole percent solute are not included.

From inspecting Figures 1 and 2 it can be seen that three aqueous systems, those containing IUdR, SIU and DIT, have ^{128}I -labeled parent yields increasing with solute concentration initially at a greater rate than that of the other systems. If the biomolecule solute does form clusters or aggregates whose size somehow increases with increasing solute concentration and the cluster sizes are sufficiently large to trap most of the recoiling hot atoms for reaction within the aggregate, the product yields and distribution should be similar to that of crystalline systems. In dimers and larger aggregates, the hot atoms can react within the aggregate as well as with surrounding water molecules. This would give rise to a parent yield whose extent would increase with increasing solute concentration. Except for some of the minor products which are not present in the liquid systems this is essentially the case. As seen in figures 1 and 2 which describe the effects of solute concentration on the percent yield of ^{128}I -labeled parent, it can be seen that there are three regions to the curves for all eight systems studied. At concentrations approaching zero mole percent solute, the ^{128}I -labeled parent yield tends to approach zero. As mentioned previously, this effect coupled with the yields of $^{128}\text{I}^-$ increasing to 100% for all systems as evidence that state of solute aggregation was predominately as the monomer at very low concentrations. Except for the IIA and 3IA systems, there is an initial rapid parent product yield increase with increasing solute concentration followed by a third region of linear segments, or in the case of IUdR, a plateau of no further change in parent

yield with concentration. This effect of the behavior of solute concentrations on yield is quite similar to the effect²¹ of CH_3I concentration on the organic yield of ^{128}I produced by the $^{127}\text{I}(\text{n},\gamma)^{128}\text{I}$ reaction. Perhaps the IUdR system best demonstrates the experimentally observed effect. The extent of stacking the monomer units and the effect of concentration on their formation will depend on the nature of biomolecule solute-solute, solute-water solvent interactions, the limited solubilities of the halogenated biomolecules, and the extent of the ^{128}I -labeled parent yield in the crystalline solute. If an isodesmic model is assumed for vertical stacking²² of monomer units and if each successive stage of aggregation governed by an equilibrium $\text{B}_n + \text{B}_1 \xrightleftharpoons{k_n} \text{B}_{n+1}$ in which B_n is an aggregate containing n monomers, the effect of concentration on the ^{128}I -labeled parent yield can be explained. At very low concentrations, monomers should predominate. As the concentration increases, so should the population of dimers and higher polymers. This has been reported for association of 6-methylpurine and 5-bromouridine in aqueous solutions.²² If at very low solute concentrations the ^{128}I -labeled yield is zero or near zero (as is the case) and if, in crystalline solids the parent yield is generally quite high, then we can employ the ^{128}I recoil species as an "interactive tracer" to determine specific site information on the aggregation of the solute monomers at various concentrations. This interactive tracer technique can be employed in solutions whose solute concentration is too low for the thermodynamics and spectroscopic techniques.

SIGNIFICANCE. This information, along with thermodynamics and spectroscopic studies²² can relate to solute-solute, solute-solvent interactions of biomolecules and water molecules. Actually the nature of these aggregations in aqueous solutions of bases, nucleosides and nucleotides is still not well understood. Its study is quite important in explaining the stability of the secondary structure of DNA and other polynucleotides and perhaps to the question of prebiological evolution.

There appears to be promise for using hot atoms in liquid aqueous solutions of halogenated biomolecular solutes as an "interactive tracer", especially involving slightly soluble solutes which are not available for study by thermodynamic and spectroscopic techniques and for systems whose states of aggregation are implied by that data.

(b) High Energy Reactions of Iodine in Frozen Aqueous Solutions of Biomolecular Solutes.

PROGRESS. Unlike the comparable liquid state systems where the ^{128}I -labeled parent yields tend to decrease to zero and $^{128}\text{I}^-$ yields tend to increase to 100% with decreasing solute concentration, frozen aqueous system product yields remain constant over the solute concentration range employed. That is, the concentration range extends from that of saturated solutions to those very dilute solutions whose ^{128}I activity is near the limit of detection.

The ^{128}I -labeled parent yields for the frozen aqueous systems of 2IA and 3IA are larger than those of the crystalline systems. The ^{128}I -labeled MIT, IUdR and 5IdA yields appear comparable in both systems. In addition to labeled I^- and parent, minor products, mainly unidentified, were found in all of the frozen aqueous systems except MIT and DIT. Since the formation of only labeled I^- and parent are found only for MIT and DIT, the question arises as to whether solute molecules exist within the open ice lattice as monomers or as polymers as suggested for various concentrations in the liquid systems. At the temperatures of the neutron irradiation of the frozen aqueous solutions (-77°C) and atmospheric pressure, ice exists as Ice I. Detailed features can be found.²³ The structural features of Ice I are well known. The oxygen atom is at the center of a tetrahedron formed by four oxygen atoms $2.76 \text{ \AA}$ away. Cell water molecules are hydrogen bonded to their nearest neighbors. This aggregation results in an open hexagonal lattice about $4.4 \text{ \AA}$ between the farthest oxygen atoms and about $2.767 \text{ \AA}$ for nearest neighbor oxygen atoms. This effect leads to long tunnels in ice, an open-ended cage, which can effectively trap monomers or aggregates of molecules.

While there are no clear-cut rules to assist us in determining whether a solute exists as single monomers or polymers trapped in ice, several guidelines may be helpful. Ideally, it would be expected for a system whose halogenated biomolecular solute exists as monomers trapped within an ice lattice cage that after neutron irradiation the hot halogen atom or ion would 1) either recoil from its site in the ice and react with a neighboring water molecule

Table II. Yields of ^{18}F -for-F Substitution at the Asymmetric Carbon of 2(S)-(+)- and 2(R)-(-)- Propionyl Fluoride in the Gas Phase.

Enantiomer	Pressure (Torr)	Mole % 1,3-Butadiene	Absolute Yield %	Approximate Inversion %
S-(+)	300	--	1.5 ± 0.5	34 ± 1
R-(-)	300	--		31 ± 3
S-(+)	500	--	1.6 ± 0.2	31 ± 3
R-(-)	500	--		30 ± 3
R-(-)	750	--	1.7 ± 0.1	33 ± 3
R-(-)	500	16.7		26 ± 2
R-(-)	500	48.0		32 ± 1
2(R)-(-)-fluoro-propionylchloride		500	--	24 ± 1

forming HI , or 4) be trapped by the ice cage walls and return and combine with its radical (geminate recombination). The only two labeled products should be the iodide ion and the parent, whose yield would be constant and independent of solute concentration. On the other hand, if solute-solute interactions are sufficiently strong and the solute forms aggregates of constant size (resulting in observed constant yields at various solute concentrations), then the product spectrum, if not its yields, should be similar to that of neutron-irradiated crystalline systems.

Of the eight systems studied only the DIT system presents the best evidence for monomolecular dispersion of DIT molecules within an ice lattice. In the frozen aqueous systems where DIT concentration is less than 4×10^{-3} mole percent, only ^{128}I -labeled I^- and DIT were observed. At higher concentrations of DIT in the frozen

systems, fractional crystallization was suspected because of the appearance of labeled MIT and increasing DIT yields with increasing concentration. This is apparent if it is realized that the DIT yield in the crystalline system is 87.3% and MIT is a minor product (3.3%). Therefore, it is suggested that at DIT concentrations less than 4×10^{-3} mole percent, DIT exists as single monomers trapped within the ice lattice. In Figure 2 it was seen that the DIT yield decreased with decreasing concentration; whereas, at 8.1×10^{-5} mole percent DIT, its labeled yield was 3.2% as compared to the DIT yield which is constant below 4×10^{-3} mole percent. In the previous section it was suggested that with decreasing concentration the monomer population increased as evidenced by labeled product yields decreasing to zero with decreasing concentration. It would appear that ice offers a more effective cage than liquid water because of its unique crystal structure. It is suggested that the constant DIT yield over a large concentration range represents the yield for geminate recombination for ^{128}I with DIT in an ice lattice.

Based on the guidelines discussed above, it can be suggested that only one other system has solutes which exist as monomers in ice, MIT. For this system, the frozen aqueous product spectrum is different than that for the crystalline system. Its labeled parent product yield is constant over the solute concentration ranges studied. For MIT, its yield is 16.9%. As in the DIT system, the ice lattice offers a unique cage for geminate recombination reactions.

SIGNIFICANCE. For the frozen aqueous systems containing the solute 2IA, 3IA, 4IA, IUdR, and 5IdA, the product spectra are similar to those of neutron irradiated crystalline systems. That is, in addition to labeled iodide and parent, various minor products are found in frozen aqueous systems, similar to those in neutron irradiated crystalline compounds. Based on these results it is suggested that for these frozen aqueous systems the solute molecules exist as aggregates $(X)_n$ of a preferred size "n". It had previously been suggested by us in studies of neutron-irradiated solutions of iodine and hydrocarbons²⁴ that regions of constant ^{128}I organic yield over a large concentration range suggest formation of preferred $(\text{I}_2)_n$ cluster sizes of iodine molecules at sites in the polycrystalline organic matrices. It was suggested that these iodine organic yields could act as an indicator of clustering, complexing and fractional crystallization for frozen systems. Because of efficient caging effects by the ice lattice, it is difficult to estimate the sizes of these clusters. It is apparent from a comparison of the data that the parent yields of the 2IA and 3IA frozen aqueous systems are larger than those for the crystalline compounds. This suggests that the ice lattice is, perhaps, a more efficient cage for the recoiling hot iodine than the crystal lattice itself. An interesting result is that the yields and product spectra for crystalline, frozen aqueous, and concentrated liquid aqueous systems of IUdR are similar. This would suggest large aggregates of comparable size, probably exceeding eight monomer units in number. Apparently solute-solute forces between IUdR monomers are larger than water-solute hydrogen bonding forces.

3. Applied Hot Atom Chemistry,

RELEVANCE. While applications of hot atom chemistry techniques or theory may, by themselves, not be energy-related, it is important to realize that the hot atom chemistry approach may be the most efficient method to assist in a problem solution. Our main applied interests have been in neutron activation analysis of biological specimens. This collaboration with the Omaha V.A. Medical Center staff has resulted in a waving of the reactor-irradiation fee and, generally, unrestricted use of the reactor and laboratory facility for our high energy chemistry program.

Our applied hot atom chemistry program consists of three areas (a) trace elemental and molecular activation analysis, (b) preparations of radiopharmaceuticals by Szilard-Chalmers labeling and radioprotection in an ice lattice, and (c) applications of the interactive (hot atom) tracer technique for acquiring information on solute-solute interactions of aqueous solutions of nucleosides and bases.

In our molecular activation analysis program we are in the midst of evaluating the uses of neutron activation as a detector in high-performance liquid chromatography. One of our first goals is to be able to detect trace quantities of halogenated biomolecular in complex biological systems such as urine and blood. While our first results show much promise they are too preliminary to report at this time.

(a) Preparations of Radiopharmaceuticals by Szilard-Chalmers Labeling and Radioprotection in an Ice Lattice.²⁵

PROGRESS. A new and simple method for the labeling of halogenated organic molecules and biomolecules was developed. Dilute aqueous solutions of the halogenated molecule are irradiated with neutrons in the frozen state. The labeling yields are generally high for the 18 molecules investigated and constant over a large concentration range. The only observed labeled organic product is the radiohalogen labeled parent molecule with the halogen at its original site. Unlike neutron-irradiated liquid aqueous solutions of the molecules no radiation damage to the molecules is observed for the irradiation times employed.

SIGNIFICANCE. This technique may have importance for the rapid production of radiohalogen labeled high molecular weight or complex organic molecules or biomolecules which cannot be readily labeled by conventional methods. Employing a reactor irradiation, radiation damage to the labeled molecules is minimized. It is realized that a cyclotron has various clear and unique advantages for the production of radiopharmaceuticals, such as the production of positron emitters allowing utilization of positron emission tomography. It will be of interest to test the application of the Szilard-Chalmers labeling procedure in an ice lattice to cyclotron conditions where the radiation flux is more severe than those present in a nuclear reactor.

(b) Applications of Hot Atoms as Interactive Tracers

PROGRESS. Various workers^{22,26-29} have studied aqueous solutions of nucleosides, bases and nucleotides by spectroscopic and thermodynamic techniques in an attempt to gain insight into the solute-solute and solute-solvent interactions. These studies are important in that they pertain to the stability of the secondary structure of DNA and other polynucleotides, and perhaps to the problem of prebiological evolution. These studies determined the concentration dependence on proton chemical shifts, osmotic and activity coefficients, and ultrasonic velocity. These results suggest (1) successive equilibria involving the monomers, the dimers, forming larger aggregates by vertical stacking, and (2) self-association enhanced by substitution and that the association process is exothermic. These studies are limited to highly soluble biomolecular compounds whose solubilities are in excess of 0.05 M.

In Section 2 we plan to study the reactions of hot halogen atoms in dilute liquid and frozen aqueous solutions of biomolecular reactions. One of the possible applications of these reactions is to employ hot atoms as interactive tracers. This is possible in multiphase systems such as aqueous solutions of biomolecular solutions when the hot halogens have distinctly different reactivity in the phases, the water and the solute aggregates. More information can be found in a preprint³⁰ of our current work. By computer simulation techniques reported previously^{31,32} we hope to calculate ranges of hot halogen atoms in the crystalline biomolecular compounds in order to estimate the labeled parent yields in dimers,

trimers, etc., and to correlate the hot atom data (labeled parent yields as a function of concentration) with thermodynamic calculations of aggregate equilibria experiments, and perhaps estimate dimer, trimer populations of the biomolecular solute at various concentrations. It must be remembered that if a hot atom is born within an aggregate, its product distribution may be similar to that of the neat crystalline system. We have found that the most probable fate of the hot halogen atom in the monomer is reaction with water, forming labeled halide ions. This is the basis of the interactive tracer technique.

The first phase of this work is completed. Depicted in Figures 3-5 are the effects of solute concentrations on the labeled parent yields of liquid aqueous solutions of halouracils, halodeoxyuridines and halouridines. We are now in the process of qualifying our results as described above.

4. Nature of Isomeric Transition Activation in Condensed Systems.

RELEVANCE. As a result of a nuclear activation, a nuclide may be left in a high energy level (metastable nuclear state). The lifetime of a metastable state is usually about 10^{-17} to 10^{-12} seconds. However, a nucleus may exist in a metastable state for a length of time long enough to be measured. A number of these isotopic isomers which have comparatively long half-lives have been found; for example, Co-60m (10.7 min), Br-80m (4.4 hr), Br-82m (6.2 min), I-130m (9.3 min).

Figure 3: Effect of biomolecule solute concentrations on the percent yield of ^{128}I -labeled parent in the neutron-irradiated liquid aqueous solutions. The biomolecule solutes are $\diamond$ 5ClU, $\square$ 5BrU, and ∇ 5IU.

Figure 4: Effect of biomolecule solute concentration on the percent yield of ^{128}I -labeled parent in the neutron-irradiated liquid aqueous solutions. The biomolecule solutes are $\bullet$ ClUdR, $\blacksquare$ BrUdR, and $\blacktriangledown$ IUdR.

Figure 5: Effect of biomolecule solute concentration on the percent yield of ^{128}I -labeled parent in the neutron-irradiated liquid aqueous solutions. The biomolecule solutes are Δ 5BUR and $\circ$ 5IUR.

De-excitation of a nucleus from its metastable state to the ground state (isomeric transition) often results in internal conversion or release of energy in the form of gamma-rays. During the internal conversion process extranuclear electrons may acquire enough energy to be released from the atom. These ejected electrons are called "Auger electrons". The production of an inner shell vacancy produces an Auger electron cascade during which the energy of excitation of the ionized atom is dissipated by the successive emission of several electrons. The Auger electrons possess a large amount of kinetic energy. Hence each of these electrons will excite and ionize the neighboring molecules. The result of the Auger effect and secondary electron cascade is that the radioactive atom acquires a positive charge of several units. If the radioactive atom is chemically bound to a molecule in the gaseous state, it will be rapidly partially neutralized by intramolecular electron transfer. In doing so, the positive charges can be spread over the neighboring atoms producing extreme Coulombic repulsions and causing the molecules to explode, produced by isomeric transitions from various source molecules.³³ Positively charged fragments possessing high kinetic energy are formed as a result of the molecular explosion. However, if the molecule is rapidly partially neutralized by the intermolecular electron transfer or from both molecules, fragmentation may not take place. Diehm and Thomas³⁴ irradiated liquid iodobenzene with X-rays in order to create a K vacancy in the iodine atom in iodobenzene. As a result of Auger

electron cascade followed by intermolecular electron redistribution, energetic iodine is ejected from iodobenzene. The product analysis showed that no fragmentation of the benzene ring occurred.

There is increasing interest in the consequences of the Auger effect, especially in condensed organic or biochemical systems. For example, the isotope iodine-125 which decays by 100% electron capture demonstrates chemical reactivity associated with the Auger effect. The consequence of an iodine-125 label on a biological molecule can be quite severe biologically because of recoil, electron excitation, charge build-up, chemical identity change and internal radiation effects.³⁵ Actually the role of those processes in condensed systems is not yet clear. These effects account for the experimental evidence that decay of ^{125}I in DNA (incorporated into DNA as a label of thymidine analogue 5-iododeoxyuridine) may be 1-100 times more effective in inactivating cells and phage than is the decay of ^3H in DNA.³⁶ One of the difficulties in obtaining information on the nature of the activation process is that the nuclide can change its identity by virtue of the transformations. For example, iodine-125 decays to xenon-125, which is a stable isotope. As a result it is difficult to analyze for the products formed as a result of the Auger effect. If we incorporate an isomer of a radioisotope into a molecule (any brominated molecule or an ^{129}I -labeled organic molecule) then the daughters of the isomer (ground state ^{82}Br or ^{130}I) can be easily detected if they are radioactive.

There is some question about the applicability of the Auger explosion model. Radiation biologists often cite the well-known

multiple repulsion model, also called the Auger explosion, or Coulomb repulsion model to interpret effects observed when a K-capture nuclide (e.g., ^{125}I) decays in biological systems, neglecting that these systems do not fulfill the requirements originally stated by Carlson and White.³⁵

Our initial experiments involved determining product yields at various biomolecular solute concentrations in liquid aqueous systems. If (I.T.)-activated atoms have negligible kinetic energy, then their labeled parent yield should not be sensitive to solute concentration. As the solute concentration increases the number of larger solute aggregates increases. A comparison of (n, γ) and (I.T.) bromine and iodine yields may prove informative.

Our preliminary results involving a comparison of (n, γ)- and (I.T.)-activated reactions of bromine in neat, liquid and frozen aqueous solutions of 5-bromouracil, 5-bromo-5'-deoxyuridine and 5-bromouridine show that the products produced by these two activations are quite similar. In all these systems the (n, γ)-activated yields of bromine-80 are higher than those of (I.T.)-activated bromine-80. In comparing the yields of the labeled parent as a function of solute concentrations in liquid aqueous systems from both activations, the yield curves are similar, going to zero yield at zero solute concentration. While it may be tempting to speculate at this time about mechanisms, we will wait until we acquire more data and have quantitated our results.

5. Reactions and Systematics of Iodine Reactions with Alkenes and Alkynes.

RELEVANCE. Olefins, acetylene and acetylenic molecules are unsaturated hydrocarbons which, unlike saturated hydrocarbons and halomethanes, are characterized by an electron-rich pi-bond system. High energy (hot) atoms or ions can undergo substitution and abstraction reactions with saturated hydrocarbons and halocarbons. Similar reactions can occur in hot atom-olefin (or acetylene) systems. Furthermore, unsaturated systems can undergo additional reactions to the pi-bond system by electrophilic attack initiated by high energy, electronically excited, or thermal iodine ions resulting in stable organic products.

Activation of iodine species by radiative neutron capture, isomeric transition and other nuclear transformations (and photochemical irradiation) can provide, translationally and electronically, excited as well as charged species, which in reaction can provide direct information for the development of a kinetic theory of "hot" electrophilic attack and indirect dynamics evidence as functions of multiple bond location and steric (spatial) effects.

In a previous publication,³⁷ we presented evidence for an excited reaction intermediate in the (n, γ)-activated reactions of iodine with acetylene. In order to determine the effects of structure on the formation of the electronically excited reaction intermediate, we studied, employing the density-variation technique,³⁸ rare gas additives, oxygen, etc., the reactions of high energy iodine with propyne,³⁸ 1-butyne and 2-butyne.³⁹ In addition, our continuing goals in this project are to evaluate all our existing data

and to attempt to develop rules for high energy ion electrophilic attack on the pi-bond systems, and to determine the importance of steric and bond location effects.

Reactions of Electrophilic Iodine Hot Atoms with Gaseous and Liquid cis-Pentene-2

PROGRESS. We have done systematic studies on the reactions of (n, γ)-activated iodine-128 with all the alkenes from ethene to the isomers of pentene. Although the reactions of iodine with alkenes are indeed complex we have been able to make several generalizations as reported in previous progress reports. One of the important observations was that there is preferential site attack by iodine at the double bond for short chain olefins. One of the results we are looking for in our pentene study is the effect of the additional carbons in the pentene isomers. We have completed the experimental portions of this project and are in the course of proposing possible pathways for the iodine reactions in the pentenes. Our preliminary observations of the iodine reactions in cis-pentene-2 indicate that labeled methyl iodide is the major product. It would appear that the reactive species is a positive iodine ion involving some radical character in product formation. In some respects the reactions are similar to those of iodine with cis-butene-2.⁴⁰

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Papers Read By Principal Investigator During Current Contract Period
Plenary Lecture. "Application of Hot Atom Chemistry Techniques as an Indicator of Solute-Solute Interactions in Liquid and Frozen Water", Las Vegas, Nevada National Meeting, American Chemical Society, August 25, 1980.

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