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REVIEW ARTICLE

Fundamentals of Interaction of Ionizing Radiations with Chemical, Biochemical, and Pharmaceutical Systems

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The effects of ionizing radiations produced by radioactive isotopes, particle accelerators, nuclear reactions, and X-ray generating devices upon matter have been of interest in chemistry and biology for several decades. Ionizing radiations are known to produce highly reactive ionic and free radical species in chemical substances, which lead to stable chemical products, usually very different from those obtained from the normal chemical reactions of these substances. In biological systems, the reactions caused by ionizing radiations are usually detrimental to the organism, resulting in mutagenesis, incapability to reproduce, organic damage, and even death. However, some aspects of radiation effects are beneficial. Studies of the effects of ionizing radiations upon solids elucidated the nature of the defect solid state and assisted advances in solid-state electronic components. The modification of polymeric materials by treatment with ionizing radiations often enhances the mechanical and thermal stabilities of these materials and has already been exploited commercially.

Interest in the chemical and biological effects of ionizing radiations in the pharmaceutical sciences has never been great, probably as a result of the lack of application of radiation science to pharmaceutical science. However, in recent years there has been a surge of interest in toxicology, drug interactions, and clinical pharmacy in general. A significant fraction of the population is exposed to substantial levels of ionizing radiations in the form of X-rays, γ-rays (cancer patients), or a variety of high-energy nuclear radiations (workers in nuclear research and in fields utilizing radioisotopes). The author believes that the effects of ionizing radiations on the biochemical systems in living organisms, particularly man, constitute a branch of toxicology. Moreover, in cancer patients who are subjected to unusually high dosages of ionizing radiations while they may be taking substantial dosages of a variety of drugs regularly, the direct or indirect effects of ionizing radiations upon the drug (*in vivo*) and ultimately upon the patients themselves constitute a special area of drug interactions. Virtually no definitive research has been undertaken in these areas, and very little has even been accomplished with regard to the effects of ionizing radiations upon pure drugs. This review was written to introduce the pharmaceutical community to the fundamental principles underlying the interactions of ionizing radiations with matter in the hope that interest will be stimulated in this area.

The intent of this work is not all inclusiveness; rather, it is a concise exposition of the fundamental principles underlying radiation chemistry and contains a representative selection of references to works of major interest throughout the history of the subject. Several excellent review articles already in the literature were freely drawn upon in preparing this review.

THEORETICAL CONSIDERATIONS

This section deals with the fundamental nature of the interactions of high energy radiations with matter, from the absorption of the radiation to the eventual establishment of chemical equilibrium in the system. The overall process may be divided into three stages (1):

1. The physical stage, entailing the dissipation of the radiant energy in the system. Its duration is of the order of 10^{-15} sec., the time scale representative of electronic absorption in molecules.

2. The physicochemical stage, consisting of processes that lead to the establishment of thermal equilibrium in the system. Its duration is of the order of 10^{-14}–10^{-12} sec., the time scale of vibrational and other thermal relaxation phenomena in molecules.

3. The chemical stage, consisting of diffusion and chemical reaction of the reactive species leading to chemical equilibrium. It lasts upward of 10^{-8} sec., depending on the rate constants and diffusion coefficients of the reactive species and the lifetimes of the reactive species.

Physical Stage—The interaction of ionizing radiation with a medium results initially in ionization and electronic excitation. At very high energies or with very heavy ionizing particles, it is also possible to effect nuclear excitation and dislocation. These processes occur regardless of the nature of the radiation. The mechanism of excitation and ionization by charged particles is different, however, from that by high energy photons. These mechanisms are, therefore, discussed separately.

Charged Particles—The interaction of charged particulate radiations, such as protons, α-particles, and β-rays, with a medium consists predominately of electrostatic coulomb excitation and ionization of the atomic and molecular electrons in the medium. According to Bethe's (2) semiclassical treatment, the energy transferred per unit length of path to the medium by a heavy particle of charge Ze and velocity v is:

$$\frac{dE}{dx} = \frac{4\pi Z^2 e^4 n}{mv^2} \ln \frac{2mv^2}{I} \qquad \text{(Eq. 1)}$$

where n is the mean electron density (number of electrons per unit volume) of the medium, m is the electronic mass, I is a mean excitation potential for the medium ($I = 11.5Z$ ev. for $Z \leq 30$, $I = 8.8Z$ ev. for $Z \geq 30$ where Z is the mean atomic number of the medium), and dE/dx is the energy gained by the medium per unit path length. The latter term is generally referred to as the linear energy transfer (LET) of the radiation. If electrons (β-rays) are the ionizing particles, the expression for LET is changed slightly to:

$$\frac{dE}{dx} = \frac{4\pi Z^2 e^4 n}{mv^2} \ln \left(\frac{mv^2}{2I} \sqrt{\frac{\epsilon}{2}} \right) \qquad \text{(Eq. 2)}$$

where ϵ is the basis of the natural logarithms.

Equations 1 and 2 yield some interesting conclusions about the transfer of energy by charged particles. First, the rate of energy loss of a charged particle in a given medium is proportional to the electron density in the medium. Second, because the factor v^2 outside the logarithmic term is more important than that inside, the rate of energy loss increases as the particle slows down. Third, if two particles of equal energy but different mass are compared, the heavier one will have a smaller velocity and hence a higher LET. As a consequence, an α-particle will produce many more excitations and ionizations per unit path length than a β-particle of the same energy. This is important in the interpretation of effects due to different types of radiation.

High Energy Electromagnetic Radiations—When high energy photons such as X-rays and γ-rays pass through matter, they lose energy by three mechanisms: (*a*) photoelectric absorption, in which the photon transfers its entire energy to an electron; (*b*) Compton scattering, in which the photon transfers part of its energy to an electron; and (*c*) pair production, in which the photon disappears and a high energy electron and positron are formed. The relative contribution of each mechanism to the total energy loss depends upon the energy of the photon. For photons in the 100-kev.–2-Mev. range, the principal mode of absorption by the medium is Compton scattering (3); much higher photon energies favor pair production (at least 1.02 Mev. is required to produce a pair) while lower energies favor photoelectric absorption. The principal effect of the absorption of high energy photons is the production of energetic electrons, which then dissipate their energies by the mechanism already discussed. In addition, ions are produced, the fate of which will be discussed.

In general, the effect of transfer of energy from an energetic particle to the medium is to produce along its path a variety of electronically excited molecules and ions as well as free electrons. Secondary electrons are also formed along with the ions. The electronic transitions resulting in the formation of these species occur in short times (10^{-15} sec.) compared to molecular vibration times (10^{-14} sec.). Little is known about the relative amounts of these species in the several electronic states, especially in the liquid and solid states.

Physicochemical Stage—This stage lasts about 10^{-14}–10^{-12} sec., which is of the order of magnitude of molecular vibration times, during which internal molecular rearrangements can take place.

During the physicochemical stage, the excited molecules and ions dissipate their excess energy by bond rupture, internal conversion, energy transfer to neighboring molecules, *etc.* Therefore, an understanding of these processes is fundamental to radiation chemistry (4). Also, during this stage the low energy secondary electrons produced during the physical stage interact with the environment. There are two divergent theoretical views on this phenomenon as it occurs in pure water. One theory (5, 6) assumes that secondary electrons lose kinetic energy due to attraction by the parent ion and by inelastic collisions with other molecules. After several collisions, these electrons, when they are sufficiently slowed, are recaptured by the parent ions. The recapture process transforms the parent ion into an excited neutral molecule which can then decompose into hydrogen ions and hydroxyl radicals produced close together.

According to the other view (6, 7), the electron loses

its kinetic energy through vibrational and rotational excitation of the medium. The dipole vibration loss lowers the energy of the electron to about 0.2 ev. in about 10^{-12} sec. at a distance larger than 50 Å from the parent ion. It is then surrounded by water molecules corresponding to the IR value of the dielectric constant of about 5 and, thereafter, it is thermalized by rotational excitation of water in about 10^{-11} sec. Since that is the relaxation time of the water dipole, the electron cannot be recaptured by the parent ion; it becomes solvated and produces a hydrogen atom according to: $e_{aq}^- + H_2O \rightarrow H\cdot + OH_{aq}^-$. The parent ion dissociates according to: $H_2O^+ \rightarrow H^+ + OH$.

Consequently, according to the latter model, the hydrogen ions and hydroxyl radicals that result from a given primary ionization are quite far apart; according to the former model, they are quite close. The difference between the initial distribution of these radicals is important for the chemical stage of radiolysis (6).

Chemical Stage—During this stage, the reactive intermediates (ions and radicals) produced in the previous stages diffuse away from their sites of production and undergo chemical reactions. Two subjects are of great importance in the chemical stage: (*a*) the relative importance of ionic *versus* free radical reactions, and (*b*) the rates of diffusion and reaction of the chemically reactive species.

Ionic versus *Free Radical Reactions*—Current theory and experiments indicate that ionic processes are most important in the radiation chemistry of gases (8–12). These processes consist mainly of ion-neutral molecule reactions in which collisions between these entities result in secondary ionization, neutralization, and cluster formation. In condensed systems, however, the main reactive species produced in the physicochemical stage, which react in the chemical stage, are believed to be free radicals. Their primary modes of reaction are atomic abstraction, radical recombination, and addition to π-bonds.

Diffusion Kinetics—The treatment of the rates of disappearance of reactive species has been effected, to a fair degree of accuracy, through the "radical diffusion model" (13). This model is based upon the assumption that the macroscopic laws of diffusion and reaction kinetics are applicable to the system in spite of the spatial inhomogeneity of the "spurs" (localized sites) in which the radicals are formed (3, 5). To compensate partially for the grossness of this assumption, the kinetic equations are expressed in terms of probability densities rather than concentrations of the various reactive species (13). The probability densities describe the average behavior of a statistical ensemble of radical spurs ($\geq 10^{14}$ spurs). The rate of disappearance of a reactive species (x_i) from the medium in which it is formed is given by:

$$\frac{\partial c_i(r,t)}{\partial t} = D_i\nabla^2 c_i - k_i c_i - \sum k_{ij} c_i c_j + \sum_1 \bar{k}_1 c_1 + \sum_{m,n} \bar{k}_{m,n} c_m c_n \quad \text{(Eq. 3)}$$

where $c_i(r,t)$ is the probability density of x_i at time t after the onset of the chemical stage and a distance r from the spur in which it is formed, D_i is the diffusion coefficient of x_i, ∇^2 is the three-dimensional Laplacian operator, k_i is the first-order rate constant for the disappearance of x_i, k_{ij} is the second-order rate constant for the reaction of x_i with x_j, $\bar{k}_1$ is the first-order rate constant for the appearance of x_i from the radiolysis of x_1, and $\bar{k}_{m,n}$ is the second-order rate constant for the appearance of x_i by reaction of x_m with x_n, whose probability densities are c_m and c_n, respectively. Given the initial distributions $c_i(r,0)$, it is possible in principle to integrate numerically the simultaneous, nonlinear, differential equations obtained for each species involved in the process. Once the functions $c_i(r,t)$ are known, one can calculate the amounts of chemically stable products formed.

The radical diffusion model has been criticized on the grounds that: (*a*) the use of probability densities instead of concentrations neglects interactions between nonreacting molecules (correlation) (14), (*b*) it is merely an assumption that the reactive species are in thermal equilibrium with the medium at the onset of the chemical stage (1), and (*c*) too many unknown parameters (rate constants) must be determined (13). Nevertheless, it does provide a reasonable working model of the chemical stage of radiolysis and will have to suffice until it is replaced with a better theoretical treatment.

GASES

The irradiation of gases results in the ionization of the gas molecules (8). Since the distances between molecules in a gas are great, there is a good chance that the ion may escape its counterelectron and engage in reactions of its own (6). This is not a likely process in a condensed medium, because the medium will exert a retarding effect upon ejected electrons and slow them enough to be recaptured rather quickly (6).

A free ion in a gas may be in a vibrationally excited state. The excited ion may possibly have sufficient excess vibrational energy to dissociate during the lifetime of a single vibration ($\sim 10^{-14}$ sec.). This has been observed occasionally in the case of small molecules but is a very rare process in molecules of molecular weight greater than 44 (15).

Free positive ions appear to react in gas media by three principal modes. First, a positive ion may attract other molecules to itself by dipole induction as the ion is thermalized (11). This has the effect of forming an ion cluster in which the charge and excess energy of the ion are delocalized over the entire cluster. This situation is similar to exciton formation in solids. The cluster then may be neutralized by absorbing an electron from the medium. Chemical reaction ensues, resulting in the formation of molecular products. An example of reaction *via* cluster formation is the formation of cuprene from the gas phase radiolysis of acetylene (16) according to the sequence:

$$C_2H_2 \xrightarrow{\alpha} C_2H_2^+ + e^-$$

$$C_2H_2^+ + 20C_2H_2 \rightarrow (C_{42}H_{42})^+ \xrightarrow{e^-} \underset{\text{cuprene}}{C_{42}H_{42}}$$

Second, the ion may capture a neutral molecule by constraining the molecule to move in an orbit around

it. Neutralization may occur, resulting in a complex molecule. For example, consider the interaction between methane and the methane ion to form ethane and hydrogen (17):

$$CH_4^+ + CH_4 \rightarrow (CH_4)_2^+$$

$$(CH_4)_2^+ + e^- \rightarrow H_2 + C_2H_6$$

Alternatively, ion molecule reactions may result in catastrophic processes as, for example (18):

$$H_2O^+ + H_2O \rightarrow H_3O^+ + OH\cdot$$

$$H_2^+ + H_2 \rightarrow H^+ + H + H_2$$

and:

$$CH_3^+ + CH_4 \rightarrow C_2H_5^+ + H_2$$

Third, an ion may become thermalized and recapture an electron, resulting in the formation of an excited neutral molecule which can then dissociate into free radicals by several different mechanisms (depending upon which excited states are involved). The free radicals then react with other molecules in the system to begin a chain of reactions leading to the final products. An example of this type of process is the formation of ozone by the radiolysis of oxygen (19):

$$O_2 \xrightarrow{\alpha} O_2^+ + e,\ O_2^+ + e^- \rightarrow (O_2^*) \rightarrow 2O\cdot$$

$$O\cdot + O_2 \rightarrow 2O_3$$

This is an example of a one-component gas reaction. In multicomponent reactions, common processes are oxidation, hydrogenation, polymerization, and reverse reactions.

The irradiation of a system containing oxygen can result in the formation of species such as O_2^+, formed by ionization, or O_2^-, formed by electron capture. These ions can dissociate according to the reactions (19):

$$O_2^+ \rightarrow O\cdot + O^+$$

$$O_2^- \rightarrow O\cdot + O^-$$

Species such as O^+ and $O\cdot$ are strongly oxidizing and react with hydrogen to form water and hydrogen peroxide. Carbon monoxide reacts with oxygen to form carbon dioxide; hydrocarbons react with oxygen to form carbon dioxide, water, and partial oxidation products; and ammonia reacts with oxygen to form water and oxides of nitrogen.

If oxygen is mixed with a gas that by itself undergoes some specific radiolytic reaction, the effect of the oxygen generally predominates over the usual path of radiolysis. This is known as "exclusivity of oxidation" (15).

The presence of hydrogen in a gas system that is being irradiated results in the formation of hydrogen ions which are not as reactive as oxygen positive ions. Hence, hydrogenation does not proceed with the exclusivity seen with oxidation. The irradiation of ethylene in the presence of hydrogen results in the formation of some ethane, but the principal product is still polyethylene (15).

Gas phase polymerization of unsaturated hydrocarbons proceeds by the formation of ions which then attack π-bonds in a chain reaction. Small polymers (3–20 monomer units) are formed independent of temperature and pressure conditions, while the formation of long-chain polymers is dependent upon temperature and pressure as well as the presence of foreign "initiator" species (15). Polymerization of saturated molecules can also occur with elimination of hydrogen; *e.g.*:

$$2CH_4 \rightarrow H_2 + C_2H_6$$

and:

$$2C_2H_6 \rightarrow CH_4 + C_3H_8$$

In some radiolyses of unicomponent or multicomponent gases, the product yields are considerably lower than would be expected from the ion yields measured by dosimetry. The low yields may often be accounted for by the occurrence of reverse reactions. The products formed by radiolysis can react with each other to give the starting material back (15).

In addition to ionization, two other processes may occur in gas phase radiolysis. One, electron capture, has already been mentioned in connection with oxidation. The other is the splitting of a neutral molecule into positive and negative ions; *e.g.*:

$$CHCl_3 \rightarrow CHCl_2^+ + Cl$$

Both of these processes have a reasonable chance of occurring only if the molecules being irradiated contain electronegative atoms (20).

LIQUIDS

The irradiation of liquids results in the formation of ions in the same way as it does in gases. The ejected electrons are usually thermalized within the electric field of the parent ion. Most of these ion-pairs culminate in recapture of the ejected electrons leaving the molecules in a highly excited state, which may return to the ground state or the lowest allowed excited state by internal conversion, luminescence, or energy transfer (21–23). Alternatively, the highly excited neutral molecules may split into free radicals (24). In addition to these processes, some ion-pairs may be sufficiently longlived to diffuse away from the site of production and react ionically with the surrounding medium (6). However, the free radicals are currently believed to be the most important reactive species formed. Once free radicals are formed along the track of an ionizing particle, they may combine with each other while they are in close proximity, or they may diffuse away from the spur and react with molecules in the bulk of the liquid medium. Those that recombine within the spur react so rapidly that they cannot be detected by physical or chemical methods. They form stable molecular products, which are known as the molecular yield. Those radicals that diffuse away from the spur and react with medium can be detected by physical methods, such as electron spin resonance spectroscopy (25), and chemical methods, such as compound formation with radical scavengers (*e.g.*, iodine and diphenylpicrylhydrazine), and are called the radical yield. The mechanisms of chemical radiation effects are frequently

determined by comparison of relative molecular and radical yields. The radiation chemistry of liquids has developed along two distinct paths—that of water and aqueous solutions (26–28) and that of organic liquids (29, 30). Each area has enough distinction to warrant separate discussion.

Water and Aqueous Solutions—The irradiation of pure water is believed to result in two dissociative processes. The first is the direct dissociation of water into hydrogen atoms and hydroxyl radicals:

$$H_2O \rightarrow H\cdot + OH\cdot$$

The second reaction is the ionization of water to yield a hydrogen ion, a hydroxyl radical, and a hydrated electron:

$$H_2O \rightarrow H^+ + OH\cdot + e_{aq}^-$$

The second mechanism was identified through the detection of the absorption spectrum of the hydrated electron. The hydrated electron is an extremely powerful reducing agent and reduces water according to:

$$e_{aq}^- + H_2O \rightarrow H\cdot + OH^-$$

It reduces the hydrogen ion according to:

$$e_{aq}^- + H^+ \rightarrow H\cdot$$

Since the latter two reactions result in the same products as direct radiolysis, and since the products of reduction by the hydrogen atom and the hydrated electron are identical, it is frequently impossible to determine whether the hydrated electron or the hydrogen atom is the principal reducing species in aqueous solutions. In acid solutions, it is reasonable to assume that the hydrated electron will reduce hydrogen ions (H^+) almost exclusively and that hydrogen atoms ($H\cdot$) will therefore be the predominant reducing species; but, in neutral and basic solutions, the hydrated electron may be assumed to predominate. The ultimate molecular products of the radiolysis of pure water are hydrogen gas and hydrogen peroxide, formed by the reactions:

$$H\cdot + H\cdot \rightarrow H_2$$

$$OH\cdot + OH\cdot \rightarrow H_2O_2$$

Of course, hydrogen atoms can react with hydroxyl radicals ($OH\cdot$) to form water, but this process is impossible to detect experimentally.

The radiation chemistry of aqueous solutions may be considered from two points of view. The first, called "target theory," considers the direct effect of ionizing radiations upon the solute molecules. The second approach regards transformations in the solute molecules to be due to interactions with the reactive intermediates formed by the radiolysis of water. Since most aqueous systems are relatively dilute, the latter approach seems to be more reasonable on a purely statistical basis. Kinetic studies of dilute aqueous systems have indeed borne out this supposition. The radiation chemistry of aqueous solutions then becomes the free radical and redox chemistry of $H\cdot$, $OH\cdot$, and e_{aq}^-.

The effectiveness of radicals in producing chemical changes, other than formation of molecular hydrogen and hydrogen peroxide, in aqueous systems depends upon the LET of the ionizing radiation which produces these radicals. A high LET particle, such as an α-particle or a proton, produces a large concentration of radicals along its short track. These radicals are likely to recombine, forming molecular products, before they can diffuse away from the spurs in which they are formed. Low LET particles produce low radical concentrations along their tracks, minimizing the probability of recombination so that the radicals can diffuse away from the spurs and initiate chemical reactions. Protons and α-particles, therefore, result in high molecular yields while β- and γ-rays result in high radical yields.

One popular device for measuring radiation dosage, the Fricke dosimeter, is based upon the oxidation of the ferrous ion by hydroxyl radicals produced in the radiolysis of a dilute aqueous solution of ferrous sulfate:

$$Fe^{+2} + OH\cdot \rightarrow Fe^{+3} + OH^-$$

The presence of dissolved oxygen alters the nature of the redox properties of irradiated water as a consequence of the "radical scavenging" property of oxygen. Molecular oxygen has two unpaired electrons. One of these can form a covalent bond with a hydrogen atom, forming the hydroperoxy radical ($HO_2\cdot$). This species can act either as an oxidizing or as a weak reducing agent:

$$HO_2\cdot + Fe^{+2} \rightarrow Fe^{+3} + HO_2^-$$
(oxidizing)

and:

$$HO_2\cdot + Cu^{+2} \rightarrow Cu^+ + H^+ + O_2$$
(reducing)

The main consequence is that while solutions in pure irradiated water have about equal oxidizing and reducing capabilities, the presence of oxygen in these solutions can result, in some cases, in very strong oxidizing properties due to the conversion of the reducing hydrogen atom to the predominately oxidizing hydroperoxy radical. In general, the presence of oxygen in aqueous solutions leads to alterations of the mechanisms of radiolyses due to the "exclusivity of oxidation." A brief summary of some representative free radical reactions in aqueous solution follows.

Hydrogen Atom—

$$H\cdot + D_2 \rightarrow HD + D\cdot$$

$$H\cdot + H_2O_2 \rightarrow OH\cdot$$

$$H\cdot + O_2 \rightarrow HO_2\cdot$$

$$H\cdot + Fe(H_2O)_n^{+2} \rightarrow Fe^{+3}(H_2O)_{n-1} + OH^- + H_2$$

$$H\cdot + Ce^{+4} \rightarrow Ce^{+3} + H^+$$

$$H\cdot + Fe^{+3} \rightarrow Fe^{+2} + H^+$$

$$H\cdot + Cu^{+2} \rightarrow Cu^+ + H^+$$

$$H\cdot + I_2 \rightarrow H^+ + I^- + I\cdot$$

$$H\cdot + NO_2^- \rightarrow NO\cdot + OH^-$$

$$H\cdot + CH_4 \rightarrow CH_3\cdot + H_2$$

$$H\cdot + HCOOH \rightarrow H_2 + \cdot COOH$$

$$H\cdot + CH_3COOH \rightarrow H_2 + \cdot CH_2COOH$$

Hydroxyl Radical—

$$OH\cdot + H_2 \rightarrow H_2O + H\cdot$$

$$OH\cdot + D_2 \rightarrow HOD + D\cdot$$

$$OH\cdot + H_2O_2 \rightarrow H_2O + HO_2\cdot$$

$$OH\cdot + Fe^{+2} \rightarrow Fe^{+3} + OH^-$$

$$OH\cdot + HSO_4^- \rightarrow OH^- + HSO_4\cdot$$

$$OH\cdot + Ce^{+3} \rightarrow Ce^{+4} + OH^-$$

$$OH\cdot + Tl^+ \rightarrow Tl^{+2} + OH^-$$

$$OH\cdot + I^- \rightarrow OH^- + I\cdot$$

$$OH\cdot + NO_2^- \rightarrow OH^- + \cdot NO_2$$

$$OH\cdot + CH_4 \rightarrow H_2O + CH_3\cdot$$

$$OH\cdot + HCOOH \rightarrow H_2O + \cdot COOH$$

$$OH\cdot + CH_3COOH \rightarrow H_2O + \cdot CH_2COOH$$

Hydroperoxy Radical—

$$HO_2\cdot + HO_2 \rightarrow H_2O_2 + O_2$$

$$HO_2\cdot + OH \rightarrow H_2O + O_2$$

$$HO_2\cdot + H_2O_2 \rightarrow H_2O + O_2 + OH\cdot$$

$$HO_2\cdot + Fe^{+2} \rightarrow Fe^{+3} + HO_2^-$$

$$HO_2\cdot + Fe^{+3} \rightarrow Fe^{+2} + H^- + O_2$$

$$HO_2\cdot + Ce^{+4} \rightarrow Ce^{+3} + H^+ + O_2$$

$$HO_2\cdot + Cu^{+2} \rightarrow Cu^+ + H^+ + O_2$$

Organics—An important difference between the radiation chemistry of water and of organic liquids is that the concept of the spur, a reasonably well-defined volume in which the formation of the reactive species occurs along the track of the ionizing particle, becomes somewhat hazy (31). The reason for this is that the radicals formed in water show a preference for recombination rather than reaction with the environment immediately after formation. The volume in which recombination is likely defines the spur. The radical products of irradiated organic liquids, however, are more likely to interact with their immediate environment than to undergo recombination. This is evidenced by the low molecular yields of hydrogen from irradiated organic systems.

The radiation chemistry of hydrocarbons and their derivatives has been extensively investigated (32). An important difference between gas phase and liquid phase radiolysis of hydrocarbons exists in that the breaking of carbon–carbon bonds is an important primary process in the gas phase, while the rupture of carbon–hydrogen bonds is almost exclusive in the liquid phase. Another important difference between analogous reactions in gas and liquid phases occurs in the polymerization process. In gas phase polymerizations, the presence of radical scavengers, such as iodine and benzoquinone, does not appreciably alter the yields of polymeric products. In the liquid phase, however, the yields of the polymers obtained from the irradiation of materials like vinyl chloride are seriously curtailed by the addition of radical scavengers. This indicates that polymerization in the liquid state occurs primarily by a free radical mechanism, whereas in the gaseous state it occurs by an ionic mechanism. The irradiation of polymeric materials results in cross-linking of polymer chains and grafting of dissimilar polymeric materials. This treatment of polymers contributes considerable tensile strength and heat resistance to the irradiated polymers and is already being exploited commercially.

Irradiation of saturated aliphatic compounds typically results in unsaturation, polymerization, and isomerization. The radiolysis of cyclohexane illustrates all three processes. The initial step in the radiolysis of cyclohexane results in the formation of energetic cyclohexyl radicals and hydrogen atoms. If the radicals produced are very energetic, cyclohexane can be formed by the abstraction of hydrogen from a cyclohexyl radical either by a hydrogen atom or by another cyclohexyl radical. If the radicals become thermalized, recombination of radicals can occur to give bicyclohexyl. A less frequent process occurring in the thermalized cyclohexyl radical is rearrangement followed by hydrogen atom capture to yield methylcyclopentane.

The irradiation of alkyl halides results in cleavage of the carbon halogen bond. The radiolysis of methyl iodide, for example, yields ethane and molecular iodine.

Alcohols, upon radiolysis in the liquid state, yield aldehydes and vicinal glycols (33–35). For example, consider the radiolysis of methanol:

$$CH_3OH \rightarrow \cdot CH_2OH + H\cdot$$

$$\cdot CH_2OH \rightarrow H_2C{=}O + H\cdot$$

and:

$$2\cdot CH_2OH \rightarrow CH_2OHCH_2OH$$

Although it would be expected that high LET radiations would favor glycol formation and low LET radiations would favor aldehyde formation, the opposite is true. This indicates that the mechanisms involved are not as simple as the schemes would lead one to believe.

The irradiation of alcohols frozen to glasses at liquid nitrogen temperature results in deep coloration of the glasses (36). Methanol turns a brilliant purple while ethanol turns blue. These colored glasses are stable if kept in the dark at low temperatures. Exposure to visible or UV light results in bleaching of the alcoholic glasses as well as elimination of the electron spin resonance signal observed in the colored glasses. The nature of the colored glasses is not well understood, but the colors are believed to be due to the absorption spectra of trapped free radicals in the glasses. The product yields from the bleached glasses are different from those of irradiated glasses that have not been exposed to light. This indicates that the trapped radicals might be photolyzed by visible and UV light.

The irradiation of aromatic compounds generally results in considerably lower yields of radiolysis products than does irradiation of aliphatic compounds of similar molecular weight and functional group composition (37–39). This has been attributed to the effectiveness of the delocalized π-orbitals in these compounds in accommodating excitation energy without permitting the molecule to dissociate. Nevertheless,

some radiolysis does occur. Benzene is known to yield biphenyl, phenylcyclohexadiene, and a polymeric material of average composition $(C_6H_7)_x$, which behaves like an unsaturated hydrocarbon. The low yields of hydrogen molecules (H_2) observed in benzene radiolysis are due to attack of hydrogen atoms upon the benzene ring to form phenylcyclohexadiene and the polymer. Dimerization and polymer formation are also characteristic of the radiation chemistry of other aromatic hydrocarbons. The resistance of polystyrene $(-C_6H_5CHCH_2-)_n$ to cross-linking, compared with polyethylene, is further evidence of the stability of aromatics to radiation effects. Nitrobenzene is also very stable to radiation damage.

In addition to being stable to radiation, aromatic compounds frequently protect other, more radiosensitive compounds from radiolysis (40). An example of this is the protection of liquid cyclohexane from extensive radiolysis by the addition of a small amount of benzene. This protective effect of benzene is probably due to energy transfer from cyclohexane to benzene, followed by dissipation of the excitation energy by the aromatic π-system.

Finally, one important general feature of the radiation chemistry of liquids is that excited or reactive molecules are formed in close proximity and are quite likely to react with one another. This situation is not encountered in photochemistry, and it is this phenomenon that makes liquid phase radiation chemistry so interesting.

SOLIDS

Because of the "fixed" positions of atoms in crystalline lattices, the effect of irradiation of solids (41, 42) includes atomic displacements as well as electronic excitation and ionization. While electronic alterations of materials affect their chemical behavior, atomic displacements in solids have a much more pronounced effect upon the physical properties of crystals. To dislodge an atom from its normal lattice position, a certain amount of energy must be transferred to the atom by an irradiating particle. Because of the large mass of the atoms, electrons and photons are relatively ineffective in producing substantial numbers of atomic dislocations. The heavier particles—α-particles, protons, deuterons, and neutrons—are much more effective in this process. Furthermore, unlike the primary effect of ionizing radiations in producing electronic disturbances through electrostatic effects, the predominant effect that is required to produce atomic dislocations is the direct knock-on process.

Two basic types of lattice defects, point defects and line defects, occur in all real crystals and at very high concentrations in irradiated crystals. Point defects result from the displacements of atoms from their normal lattice sites. These displaced atoms usually occupy a site not in the lattice framework and are then known as "interstitials." The empty lattice site left behind by the interstitial is called a "vacancy." A vacancy produced by displacement of an anion or cation, along with its interstitial ion, is called a Frenkel pair or simply a Frenkel defect. In some cases, the displaced ions are removed so far from their vacancies that they form a new layer at the crystal surface. The vacancies left behind are called Schottky defects. Frenkel and Schottky defects play very important roles in the properties of solids altered by radiation damage.

Line defects (dislocations) are produced by slippage or shear of the crystal lattice. If the slippage is perpendicular to a face of the crystal so that the lattice planes on either side of the dislocation are parallel but displaced with respect to one another, the defect is called an edge dislocation. If the slippage is angular, as if produced by rotation about the shear axis, so that lattice planes on either side of the defect are not perpendicular, the defect is called a screw dislocation.

A consideration of the effects of irradiation of crystalline materials requires that the nature of the crystal be understood. There are four broad classifications of crystal types, according to the nature of the interatomic forces holding the crystal together. In metallic crystals the atoms are thought to form a quasi-ionic lattice arrangement with the valence electrons, which bind the lattice delocalized throughout the crystal so that they cannot be identified with any one atom. Valence crystals, such as diamonds, consist of a lattice in which the atoms are bonded by conventional covalent interaction throughout the lattice. This implies that a valence crystal could be considered a giant molecule. Molecular crystals (*e.g.*, naphthalene and water) are regular arrangements of well-defined molecules which are bound together in the lattice by van der Waals' and hydrogen bonding forces. Finally, the ultimate in electronic localization occurs in ionic crystals, in which the lattice is composed of alternating positive and negative ions held together by strong electrostatic attractions. Sodium chloride is a typical example of an ionic crystal. The predominant effects of ionizing radiations on these crystal types will be considered separately, because these effects are manifested as characteristics of the crystal type.

Metallic Crystals—The effects of ionizing radiations upon metals are entirely due to atomic displacement. Because of the delocalization of electrons throughout the crystal, no persistence of ionization can occur; a positive hole formed by an electron ejection is always refilled by an electron from the conduction band. As a result, no chemical decomposition can occur because of ionization. On the other hand, sufficiently energetic radiations can cause atomic displacements. The production of interstitial atoms in the lattice has the effect of "swelling" the crystal. This results in a lowering of the density of the crystal. The irradiation of a crystal of copper increases the critical shear stress considerably (43). This is believed to be due to the migration of thermalized interstitials and vacancies to the sites of naturally occurring dislocations in the copper crystal. These interstitials impede the vibration and slippage of the dislocations, resulting in greater resistance to shear. This "pinning of dislocations" is also used to explain why copper behaves like a tuning fork when struck with a hammer after irradiation while it gives a dull "thud" when struck prior to irradiation.

Perhaps the most obvious evidences of radiation damage in metallic crystals are the increase of electrical

resistivity and the decrease of thermal conductivity in irradiated crystals. This is believed to be due to scattering of electrons and photons by vacancies and interstitials which behave like impurities and destroy the order of the lattice necessary for high conductivity.

The obvious effects of radiation damage in metallic crystals can be reversed by "annealing." This process consists of heating the irradiated materials so that the "energy of activation" required to push an interstitial back into a vacancy is supplied (44).

Valence Crystals—The stable, symmetrical bonding occurring in valence crystals results in the failure of these crystals to demonstrate quasichemical changes such as depolymerization or reaction of the matrix with displaced entities. Unlike metals, however, valence crystals have no conduction electrons and can therefore retain electronic dislocations as well as atomic displacements. The trapping of dislocated electrons in the crystal by potential wells, such as those created by atomic vacancies, results in coloration of the normally transparent valence crystals. This is due to the low excitation energies of trapped electrons as opposed to σ-bonded electrons.

The irradiation of semiconducting valence crystals like silicon and germanium usually drastically decreases the conducting properties of these crystals (45). Large numbers of Frenkel defects are produced and act as traps for conducting electrons and holes, thereby altering the concentrations of conducting species. Bombardment of n-type germanium with deuterons converts the germanium to a p-type semiconductor.

Ionic Crystals—Irradiation of ionic crystals results in atomic and electronic dislocations. The trapping of displaced electrons by anion vacancies results in a pseudoatomic system which usually has a manifold of closely spaced, electronic energy levels. This results in the absorption of visible and near UV light which gives these crystals their characteristic colors. These pseudoatomic electrons and their vacancies are called color centers (46). The polarizations of the spectra of these color centers depend upon the symmetry of the electric field produced by atoms surrounding the trapped electron. Some of the color centers commonly produced by irradiation of ionic crystals are: F-centers (octahedral symmetry), consisting of an electron trapped by a simple halide-ion vacancy; M-centers (isoceles, triangular symmetry), consisting of the delocalized coupling of an F-center with an adjacent anion-cation vacancy pair (Seitz defect); and V-centers, consisting of a singly charged halogen molecule anion in a normal lattice site, behaving as a trapped hole by virtue of its molecular bond. The exposure of colored ionic crystals to visible or UV light results in bleaching of the colorations induced by irradiation. While this bleaching is being carried out, the crystals become photoconductive when a potential difference is imposed across them. This implies that the bleaching process is due to annealing of trapped electrons. If a sufficient potential difference is placed across the crystal, the color centers will migrate through it. In some cases where the crystal remains uncolored upon irradiation, thermoluminescence is observed in the annealing process.

The dissolution of a heavily irradiated crystal of sodium chloride in water will result in the evolution of hydrogen and chlorine from the solution. The solution also turns alkaline, presumably due to the reactions of trapped holes and electrons with water (47):

$$e^- + H_2O \rightarrow {}^1/_2\, H_2 + OH^-$$

$$\text{hole}^+ + Cl^- \rightarrow {}^1/_2\, Cl_2$$

Trapped electrons also account for the ability of irradiated sodium chloride to initiate polymerization in acrylonitrile.

Irradiation of nitrates, chlorates, perchlorates, and bromates results in the liberation of oxygen (48, 49). In potassium perchlorate, irradiation results in explosion of the crystal due to internal buildup of oxygen.

Molecular Crystals—The irradiation of substances that form crystals containing discrete molecules, held together by dispersion forces, results in radiolysis in the conventional sense. For example, the radiolysis of aliphatic carboxylic acids in the solid state yields hydrogen, carbon monoxide, and carbon dioxide (50). The relative yields of these gases depend upon the strength of the bonds involved in radiolysis and their frequency of occurrence. These considerations apply as well to liquids and gases and suggest no special solid-state effects. This is the case for the γ-radiolysis of bromotrichloromethane (51), where no difference in the yield of bromine is observed for irradiation of solid or liquid bromotrichloromethane. Differences are observed between the radiolysis patterns of liquids and molecular crystals of the same materials, but these seem to be more the exception than the rule and may generally be attributed to stronger caging effects in the solid than in the liquid (52).

Energy transfer in molecular crystals seems to be a well-established phenomenon. Irradiated crystals of anthracene containing only a trace of naphthacene show the characteristic green fluorescence of naphthacene rather than the violet of the main constituent (53). If the material is dissolved in benzene, the anthracene fluorescence predominates. This phenomenon is often seen in mixed, scintillating crystals (54).

The irradiation of ice results in formation of trapped hydrogen and hydroxyl radicals as well as the hydrated electron (55). Dilute solutions of Cd^{+2}, Zn^{+2}, and Mg^{+2} in ice have been reduced to the unstable Cd^+, Zn^+, and Mg^+, respectively, upon irradiation (56). Apparently, some mobility is enjoyed by some radical species in the ice lattice.

The irradiation of surface catalysts alters the properties of these catalysts through defect production on the surfaces (57). These defects have been observed to enhance and inhibit catalytic activity in specific cases. For example, irradiation of silica gel enhances the rate of hydrogen–deuterium exchange on it (58). On the other hand, irradiation of zinc oxide decreases the rate of hydrogenation of ethylene on it (59).

CHEMICAL PROTECTION FROM IONIZING RADIATIONS

The effects of ionizing radiations upon chemical and biological systems may be minimized or even eliminated by the addition of certain chemical compounds to the system to be irradiated. These compounds react

either directly with the radiation or, more often, with the reactive species produced by the radiations. In so doing, they are themselves transformed into other substances, but their transformation results in the preservation of the integrity of the original chemical or biological system.

At the molecular level, several mechanisms account for the protection of irradiated systems by chemical agents. These are: (*a*) energy transfer and charge transfer, in which an ionized or excited molecule transfers its charge or excess energy to a protecting molecule either by collision or by resonance transfer at a distance; (*b*) scavenging, in which a protecting radical scavenger reacts with radicals from the initial actions of the radiation before they can attack other molecules in the system; and (*c*) complex formation, in which a protective molecule can form complexes that are either more or less susceptible to radiation than the original substance.

Energy and Charge Transfer—The transfer of charge or excitation energy (60) must be fast enough to compete with dissociation processes if protection is to occur. In some cases, an activated molecule can dissociate within 10^{-14} sec., the time for one molecular vibration. However, localization of energy in a particular bond usually requires 10^{-13}–10^{-9} sec. To remove energy or charge from an activated molecule effectively, the protector should have a slightly lower ionization or excitation potential. In fluid systems the rate of charge transfer is limited by diffusion; the donor and acceptor must be in contact. Excitation energy, however, can be exchanged by molecules as much as 70 Å apart by "Förster energy transfer," a dipole–dipole interaction. One requirement of this process is partial overlap of the absorption spectrum of the energy acceptor and the emission spectrum of the energy donor. Energy transfer is radiationless, comparable in rate to molecular vibration and thus more efficient than luminescence in deactivating highly excited molecules. Transfer processes of this type are extremely efficient in crystalline materials where the high degree of order permits excitation energy to travel in excitons which traverse the crystal faster than its vibrational relaxation time. Crystalline structure also facilitates charge transfer by providing conduction bands in which electrons can freely move about.

Energy conversions within a molecule can decrease the probability of decomposition. Energy can be dissipated so rapidly by internal conversion that its localization in any one bond is improbable. Paramagnetic additives such as transition metal ions are useful in this context as strong spin-orbit coupling increases the number of energy states available to the original molecules. Aromatic compounds are protective because they can probably dissipate acquired excitation energy throughout their extensively delocalized π-systems (61–63).

Scavenging Intermediates—The addition of certain compounds that readily react with free radicals can effectively prevent these radicals, which are primary products of ionizing radiations, from causing secondary damage in the system. Molecular iodine is a very effective radical scavenger, forming iodo compounds (64, 65) with radicals and leaving behind iodine atoms to do further scavenging, *e.g.*:

$$CH_3\cdot + I_2 \rightarrow CH_3I + I\cdot$$

$$CH_3\cdot + I\cdot \rightarrow CH_3I$$

Oxygen is a diradical which enhances radiation damage by forming radicals with other radicals. An example of the latter process is the scavenging of hydrogen atoms by molecular oxygen to form the hydroperoxy radical (65):

$$H\cdot + O_2 \rightarrow HO_2\cdot$$

Complexes—Certain compounds may exert protective action by forming molecular complexes with the original molecules of the system. These complexes might be less sensitive to radiolysis or attack by radicals or they may be better able to transfer charge and excitation energy than the original compound. Protection can also result from the formation of complexes across particularly sensitive bonds in the original compound. For example, the degradation of polyisobutylene is reduced about 50% by copolymerization with 20% styrene (66). The radiation resistance of the porphyrin ring is enhanced by complexing it with vanadium and other metals.

The most obvious application of chemical protection from ionizing radiations is to biological systems. For a protective agent to be biologically practical, it must be nontoxic at protective concentrations, easily introduced to the organism, widely distributed, and remain intact for long periods of time before irradiation. Many substances of all kinds have been applied to this problem. The most effective to date have been compounds like cysteine, because of the scavenging property of the mercapto (—SH) group and the ease of oxidation of the amino ($-NH_2$) group, and cystamine (67), because of complex formation with, and ease of oxidation of, the disulfide linkage. None of the compounds studied to date has been effective enough for use in man, predominately because of their high toxicities.

MOLECULES OF BIOLOGICAL SIGNIFICANCE

The effects of ionizing radiations on living organisms are frequently observed but not completely understood. There are two distinct theories of the actions of ionizing radiations on the components of living cells that result in chemical transformations leading to mutation or cell death. The first of these is the "target theory" (3, 68). This approach regards only those events that produce ionizations in biologically significant molecules as being important. The main evidence for this simple idea is that, in many cases, the amount of damage to a given organism varies logarithmically with the dose of radiation, implying that the amount of damage possible in a cell is proportional to the number of radiosensitive species remaining undamaged and therefore capable of reacting. A less direct mechanism would not require the proportionality of dose and unaffected material because some of the total dose would be channeled out to processes other than the biologically significant ones.

The other theory is based upon such an indirect relationship between the incident radiation and the af-

fected, biologically significant molecules (69). In this approach, the solvent, water, interacts with the radiation, forming ions and radicals. These reactive species in turn react with the biologically significant molecules, causing radiation damage. Radiation biology, under this approach, is simply a branch of the radiation chemistry of aqueous solutions. As such, the recombination of hydrogen atoms and hydroxyl radicals to form hydrogen and hydrogen peroxide (the molecular yield) effectively competes with the biological molecules for the effects of the radiation. There is evidence that both the target and indirect processes occur and that no one theory accounts for all of the observed biological effects of radiation at the molecular level (4).

This section considers the effects of ionizing radiations on molecules known to have biological significance and the relationship of the radiation chemistry of these molecules to radiation effects observed in living organisms.

Carbohydrates—The irradiation of aqueous solutions of carbohydrates (70–74) has the same effect as it does upon alcohols. The hydroxyl groups are attacked to yield carbonyl compounds. Under anoxic conditions, dimeric products and ultimately polymers are also formed. The primary alcohol groups of carbohydrates are especially radiosensitive. Mannitol is readily oxidized to mannose and sorbitol is oxidized to glucose. While oxidation of primary alcohol groups is favored by aerobic conditions, high yields from the oxidation of secondary alcohol groups are favored by anoxic conditions.

The irradiation of polysaccharides results predominately in their degradation. This explains why fruits and vegetables become soft on irradiation. This degradation occurs both in solution and in the dry state.

Amino Acids and Peptides—The irradiation of amino acids (75) results in transformation of both the amino and the carboxylic functions (76). In the dry state, glycine is decarboxylated to methylamine upon irradiation; in dilute aqueous solution, however, the amino group is hydrolyzed to give glyoxalic acid, acetic acid, and formaldehyde. In solutions of concentrations greater than 2%, methylamine again becomes an important product. The other amino acids are similar to glycine in their radiolytic behavior. Alanine, for example, gives ethylamine and carbon dioxide in the dry state and pyruvic acid and ammonia in aqueous solution (77, 78).

The aromatic amino acids, when irradiated in aqueous solution, show effects that are typical of aromatic compounds and amino acids (79, 80). Phenylalanine is deaminated in aerated solutions with the formation of a ketone. The aromatic ring remains relatively stable to radiolytic decomposition.

The irradiation of peptides results in a chemistry similar to that of the amino acids but also in the breakage of the peptide bond (81). In aqueous solution, all irradiated peptides give ammonia whether or not free amino groups are present.

When irradiated in the dry state, the thiol- and disulfide-containing amino acids degrade to keto acids with the evolution of carbon dioxide and hydrogen sulfide. In solution, however, the thiol and disulfide groups are excellent radical scavengers and free radical attack on these groups precludes deamination. The ultimate result of irradiation of thiol-containing amino acids is their oxidation to disulfides. Thus, irradiation of an aqueous solution of cysteine results in the formation of cystine (82–84). The irradiation of the disulfides results in higher oxidation products. For example, cystine gives cystine disulfoxide in aqueous solution. Reduction of disulfides to thiols is not generally observed.

Proteins and Enzymes—The irradiation of proteins (85) results in the formation of free radicals in the sites of disulfide bonds (86). Aromatic amino acids in the proteins are also particularly susceptible to attack, decarboxylation and deamination being common results of irradiation (87, 88). Rupture of the peptide linkage is characteristic of the radiolysis of proteins (87, 89). In the case of enzymes, the destruction of peptide linkages is accompanied by a decrease in biological activity (90). This decrease continues after irradiation is stopped (91). The mechanisms of radiolysis in the dry state and in solution are different, but the results are usually similar. One important difference between these results is the degradation of proteins by dry state irradiation compared with the increase of molecular weight through cross-linking in solution (92). In general, the radiation chemistry of proteins and enzymes may be considered a special case of the radiation chemistry of peptides and amino acids.

Respiratory Proteins, Vitamins, and Coenzymes—*Respiratory Proteins*—These substances are iron-porphyrin-protein complexes. Irradiation of these substances may produce effects in the porphyrin ring or in the protein, but oxidation or reduction of the iron almost always is involved. The iron in cytochrome c (ferricytochrome c) is reduced to the ferrous state in the presence of benzoate ion (93). Under alcoholic conditions, the ferric form is favored. Hemoglobin and oxyhemoglobin are both oxidized from the ferrous to the ferric state, destroying the property of oxygen transport (94–97). Large radiation doses result in attack on the porphyrin ring and denaturation of the protein. When irradiated in the dry state in the absence of oxygen, hemoglobin becomes insoluble due to protein denaturation. Myoglobin behaves in a similar manner to hemoglobin but is considerably more radiosensitive (94). Hemocyanin is a copper-containing respiratory protein of molecular weight more than 10 times that of hemoglobin. In this case, attack at the protein part of the molecule predominates (98).

Vitamins and Coenzymes—The irradiation of coenzyme I (diphosphopyridine nucleotide) results in reduction of the pyridine carboxamido ring. The product of this reduction is probably a dimer, which is itself radiosensitive (99).

The B-group vitamins, thiamine and riboflavin, are destroyed upon irradiation in dilute aqueous solutions. Riboflavin is reduced in air-free solutions to a semiquinone form (100). Niacin is decarboxylated on irradiation in air-saturated aqueous solutions (101).

Upon irradiation in aqueous solution, aminobenzoic acid is destroyed by deamination and decarboxylation (102–104). Sulfanilamide and sulfathiazole are inacti-

vated, presumably due to deamination (105). Upon irradiation, the cobalt in vitamin B_{12} is reduced from the cobaltic to the cobaltous state.

The plant hormone auxin has been shown to be radiosensitive. The product of the irradiation of auxin (β-indoleacetic acid) is a polymer similar to that obtained in the radiolysis of indole (106).

Nucleic Acids—The nucleic acids DNA and RNA are responsible for the transmission of genetic information and protein synthesis. Both processes are dependent upon the ordering of purine and pyrimidine bases, which are bound to the main body of the molecule by riboside linkages. The main body of these molecules consists of ribose (5-carbon sugar) molecules linked together by phosphoric acid units to form a long strand. The purine and pyrimidine bases branch off from the chain at the ribose sites. It is believed that the DNA molecule consists of two helically intertwined strands of nucleic acid held together by hydrogen bonding between purine and pyrimidine pairs on opposite strands.

The irradiation of nucleic acids ruptures hydrogen bonds which hold DNA strands together, resulting in polymerization, deamination, and dehydroxylation of purine and pyrimidine bases, fission of sugar base linkage, liberation of the purine bases, destruction of the pyrimidine bases, oxidation of the sugar moiety, and breakage of the nucleotide chain with liberation of inorganic phosphates. In the presence of oxygen, irradiation leads to the formation of hydroperoxides of the pyrimidine bases but not of the purine bases (107–114).

In general, the purine bases appear to be much more stable to radiolysis than the pyrimidine bases (113, 114), probably due to the greater π-delocalization energy of the purines which provides a pathway for nondestructive energy dissipation. Furthermore, the pyrimidine bases are known to undergo free radical reactions more readily than the purine bases. The order adenine > guanine $\gg$ cytosine > uracil > thymine has been established for the relative resistances of the bases to radiolysis. In the presence of oxygen, in aqueous solutions, uracil and thymine form stable hydroperoxides while cytosine forms an unstable hydroperoxide which decomposes to a variety of products (113–116).

Irradiation of DNA in the solid state, at liquid nitrogen temperature, yields radicals in which, as indicated by electron spin resonance measurements, the unpaired spin is delocalized over the entire chain and does not belong to any one unit of the giant molecule (117). Addition of small amounts of water to this system does not alter the nature of the DNA radicals produced, but a two-to-one excess of water results in the annihilation of the electron spin resonance signal for DNA with the appearance of a strong signal due to water radicals. It has been postulated that this protective effect is due to energy transfer which is made possible in an excess of water by structuring of the water, thus providing a pathway for the formation of a delocalized water radical or exciton. Electron spin resonance studies of irradiated nucleoprotein solutions indicate that the protein takes most of the radiation damage, protecting the nucleic acid moiety.

The damages caused by ionizing radiations in nucleic acids and their components are obviously detrimental to the passage of genetic information, which requires specific orders of intact purine and pyrimidine bases in the DNA strands. Alterations in these bases and the DNA molecules in general can lead to mutations and lethal genes. The disruption of RNA molecules interferes with protein synthesis and can result in eventual cell death.

PHARMACEUTICAL SYSTEMS

Most pharmaceutical studies related to the effects of ionizing radiation have been confined to the study of radioprotective drugs. A few studies of the effects of drugs on irradiated organisms and of irradiation on drug-dosed organisms have also been carried out. As mentioned earlier, the effects of ionizing radiation can be minimized by certain chemical compounds. Among the agents employed as radioprotective drugs are the sulfhydryl compounds, notably cysteine, estrogens, and bacterial lipopolysaccharides.

One way in which these protective agents exert their effect is by scavenging free radicals resulting from biological radiation damage. In this instance, the radioprotective agent reacts with a free radical to form a less reactive free radical or a molecule that is insufficiently reactive to interact with cellular components. Aminothiols work well in this context. Grenan and Copeland (118) studied the structure-radioprotective activity relationship of the aminothiols (β-mercaptoethylamine homologs) and found all derivatives to exhibit some radioprotective effect. Vasin (119) found that increasing the length of the alkyl side chains resulted in loss of antiradiation properties. He also found indole analogs of esadrine and ephedrine and the indolylalkylamino alcohols possessing a third amino group to be quite effective in suppressing radiation damage. Recently, Langendorff (120) found that a significant relationship exists between cyclic adenosine monophosphate and radioprotection and hypothesized that cyclic adenosine monophosphate plays a major role in radioresistance.

Organoselenium compounds such as selenocystine, selenomethionine, colloidal selenium, selenoxanthene, selenoxanthone, and selenochromone were found to be similar to, and in some cases superior to, cysteine in radiation protection (121). Dimethyl sulfoxide has also demonstrated radioprotective properties, as has phenylhydrazine (122, 123). Imidazole and erythropoietin were found to increase the survival of irradiated mice, with the highest survival rate being after administering the drug 5 min. prior to irradiation (124). A bile acid sequestrant was also found to be effective in preventing GI effects of whole body irradiation. Parkinson (125) found this to be an effective means of reducing the severity of effects and the morbidity associated with irradiation of the GI tract. To reduce the toxicity seen with the administration of these agents, Vlastislav (126) suggested a causal relationship between radioprotection and immunization by protein antigen interactions with such agents as β-lactin, casein, and human serum albumin.

The interpretations of these phenomena are obviously largely speculative. In this regard, the study of com-

bined influences of drugs and ionizing radiation at the molecular level should prove a most fertile area for future investigation.

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RESEARCH ARTICLES

Chemical Modification of Lincomycin: Synthesis and Bioactivity of Selected 2,7-Dialkylcarbonate Esters

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Abstract □ A series of lincomycin 2,7-dialkylcarbonate esters was synthesized to enhance the pediatric acceptability of lincomycin. Several diester derivatives are sufficiently tasteless to warrant consideration as candidates for pediatric formulations. Preliminary bioactivities [mouse median protective dose (CD_{50}) bioassay] indicated several derivatives to be equivalent in subcutaneous activity to lincomycin hydrochloride. Four diester derivatives exhibited oral bioactivity comparable to that of lincomycin. Serum hydrolysis studies on certain 2,7-diesters of lincomycin established that a high degree of esterase activity is present in the serum of several different rodent species. This phenomenon appeared to be limited to these species.

Keyphrases □ Lincomycin 2,7-dialkylcarbonate esters—synthesis as tasteless derivatives, bioactivity compared to lincomycin hydrochloride □ Carbonate esters of lincomycin—synthesis as tasteless derivatives, bioactivity compared to lincomycin hydrochloride □ Pediatric formulations, potential—synthesis, activity of lincomycin 2,7-dialkylcarbonate esters □ Tasteless lincomycin derivatives—synthesis, activity of 2,7-dialkylcarbonate esters □ Antibacterial agents, potential—synthesis of lincomycin 2,7-dialkylcarbonate esters

The use of bioreversible derivatives for the modification of certain pharmaceutical properties of lincomycin (I) was reported previously (1, 2). This paper represents a continuation of that systematic effort and is concerned with lincomycin 2,7-dialkylcarbonate ester derivatives. The goal of this work was the synthesis of several