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REACTIONS AT SIDE-CHAIN LOCI IN MODEL SYSTEMS

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W.M. Garrison

November 1983

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REACTION MECHANISMS IN THE RADIOLYSIS OF PEPTIDES,
POLYPEPTIDES AND PROTEINS II REACTIONS AT SIDE-CHAIN LOCI
IN MODEL SYSTEMS

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*Consultant

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Abstract

The major emphasis in radiation biology at the molecular level has been on the nucleic acid component of the nucleic acid-protein complex because of its primary genetic importance. But there is increasing evidence that radiation damage to the protein component also has important biological implications. Damage to capsid protein now appears to be a major factor in the radiation inactivation of phage and other viruses. And, there is increasing evidence that radiation-chemical change in the protein component of chromatin leads to changes in the stability of the repressor-operator complexes involved in gene expression. Knowledge of the radiation chemistry of protein is also of importance in other fields such as the application of radiation sterilization to foods and drugs. Recent findings that a class of compounds, the α, α' -diaminodicarboxylic acids, not normally present in food proteins, are formed in protein radiolysis is of particular significance since certain of their peptide derivatives have been showing to exhibit immunological activity. The purpose of

* Consultant

this review is to bring together and to correlate our present knowledge of products and mechanisms in the radiolysis of peptides, polypeptides and proteins both aqueous and solid-state. In part 1 we presented a discussion of the radiation-induced reactions of the peptide main-chain in model peptide and polypeptide systems. Here in part 2 the emphasis is on the competing radiation chemistry at side-chain loci of peptide derivatives of aliphatic, aromatic-unsaturated and sulfur-containing amino acids in similar systems. Information obtained with the various experimental techniques of product analysis, competition kinetics, spin-trapping, pulse radiolysis, and ESR spectroscopy are included.

1. Introduction

A detailed understanding of reaction products and reaction mechanisms in the radiolysis of proteins and related substances is becoming of increasing importance in radiation biology and related areas of radiation research.

The major emphasis in radiation biology at the molecular level has been on the nucleic acid component of the chromosome because of its primary genetic importance.^{1,2} But there is increasing evidence that radiation damage to the conjugated nuclear proteins also has important biological implications. Damage to capsid protein now appears to be an important factor in the inactivation of phage and other viruses by both the indirect and the direct actions of ionizing radiations.³⁻⁶ Other studies have shown that radiation-chemical damage to the protein component is also a factor in both the direct and indirect actions of radiation on chromatin.⁷⁻¹³ Such chemical damage leads to changes in the protein-nucleic acid (repressor-operator) complexes involved in gene expression.¹⁴⁻¹⁷

Knowledge of the radiation chemistry of proteins and related compounds is also of basic importance in other fields such as the application of radiation sterilization to foods, drugs and other medical products. Recent findings that a class of compounds, the α, α' -diaminodicarboxylic acids, not normally present in food proteins, are produced in protein radiolysis¹⁸ has re-emphasized the need for more extensive information on radiation-chemical change in high-protein foods.¹⁹ The α, α' -diamino acids occur naturally in the

glycoprotein (peptidoglycan, chemotypes components I and II) of the bacterial cell wall.^{20,21} Simple peptide derivatives of the α,α' -diaminodicarboxylic acids have recently been shown to have immunological activity.²²

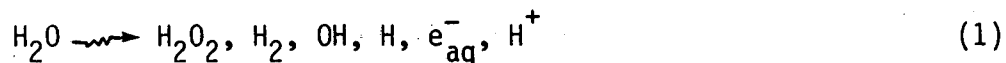
The purpose of this review is to bring together and to correlate our present knowledge of reaction products and reaction mechanisms in the radiolysis of peptides, polypeptides and proteins in both aqueous and solid-state systems. In part 1 we presented a discussion of the various radiation-induced reactions of the peptide main-chain in model peptides and polypeptides.²³ Here in part 2 the emphasis is on the competing radiation chemistry of side-chain loci of peptide derivatives of the aliphatic, aromatic-unsaturated and sulfur-containing amino acids in related model systems. Information obtained with the various experimental techniques of product analysis, competition kinetics, spin trapping, pulse radiolysis and ESR spectroscopy is included. In part 3, this information on model systems will be incorporated in a discussion of the mechanisms of radiation chemical change in proteins--fibrous, globular and nuclear--in aqueous solution and in the solid state.

2. Reactions of Peptide Derivatives of Glycine and Alanine

In considering the comparative radiation chemistry of peptide derivatives of the various aliphatic, aromatic-unsaturated and sulfur-containing amino acids it is useful to briefly summarize the principle and characteristic reactions of glycine and alanine in the peptide form since the radiation chemistry of these systems is confined almost exclusively to the peptide main-chain both in aqueous solution and in the solid state.²³

2.1 Oxygenated solutions

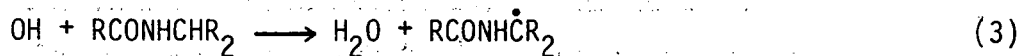
Radiation-chemical change in dilute aqueous solution is initiated by the radiation decomposition of water²⁴



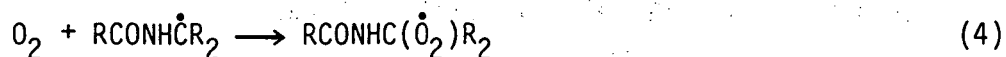
where e_{aq}^- represents the hydrated electron. For γ -rays and fast electrons the 100 eV yields, (G), of the radical products corresponds to $G(\text{OH}) \approx 2.8$, $G(\text{e}_{\text{aq}}^-) \approx 2.7$, $G(\text{H}) \approx 0.55$. In oxygenated solution the reducing species e_{aq}^- and H are scavenged preferentially by O_2 to give O_2^- and HO_2 which are related by the equilibrium



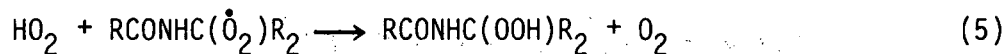
The reactions of OH with N-acetyl, oligo, and polypeptide derivatives of glycine and alanine occur almost exclusively in the peptide main-chain via



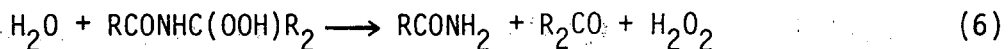
Reaction 3 was first identified by steady-state product analysis studies^{25,26} and has since been extensively studied by pulse radiolysis²⁷ and ESR²⁸ techniques in a large number of peptide systems. In oxygenated solution this leads to formation of the peroxy radical



Subsequent removal of the peroxy radicals, $\text{RCONHC}(\dot{\text{O}}_2)\text{R}_2$ has been interpreted in terms of

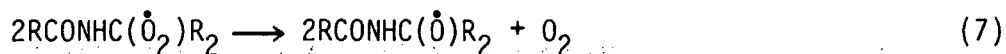


followed by the hydrolysis step

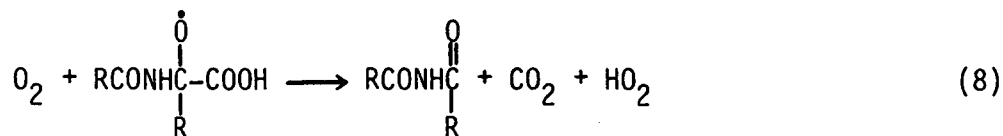


to give amide and keto acid as final oxidation products.^{29,30}

A major competing path for removal of $\text{RCONHC}(\dot{\text{O}}_2)\text{R}_2$ radicals appears to involve the formation of alkoxy radicals via^{30,31}



With the N-acetyl amino acids and the lower molecular-weight oligopeptides, the alkoxy radicals are removed in turn, e.g.,

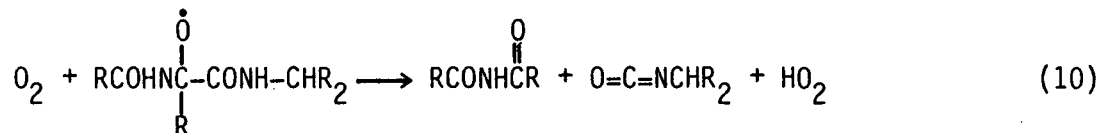


to give the diamide RCONHCOR which hydrolyzes to yield amide and the lower fatty acid

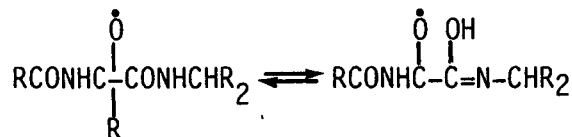


In the γ -radiolysis of N-acetylalanine (0.1 M) in O_2 -saturated solution, $G(RCONH_2) \approx 3 \approx G(OH)$, $G(RCOCOOH) \approx 1$, $G(RCOOH) \approx 2$, $G(CO_2) \approx 2$.³⁰

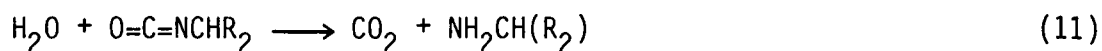
With the higher molecular weight oligopeptides and polypeptides, OH attack is not confined to the C-terminal amino acid. Under these conditions the analogue of reaction 8 involves the adjacent peptide bond (enol form)* i.e.^{30,31}



*Reaction 10 is more readily seen as an analogue of reaction 8 if the peptide bond adjacent to the alkoxy radical site is formulated in terms of the enol form, i.e.,

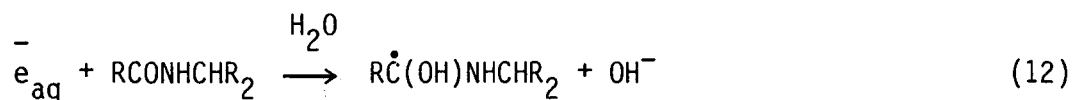


followed by the hydrolysis step 9 and



2.2. De-aerated Solutions

The carbonyl group of the peptide bond represents the principle trapping center for e_{aq}^- in oxygen-free solutions of peptide derivatives of glycine, alanine and most other aliphatic amino acids³²⁻³⁸



Chemistry of the $\text{RC}(\text{OH})\text{NHCHR}_2$ radical (reaction 12) has been studied under a number of experimental conditions. Detailed product-analysis studies of γ -irradiated N-acetylalanine solutions at pH 7 indicate that the major process for removal of $\text{RC}(\text{OH})\text{NHCHR}_2$ radicals involves the back-reaction (reconstitution)



where $\text{RCONN}\dot{\text{C}}\text{R}_2$ corresponds to the product of OH attack via reaction 3. It was concluded that main-chain cleavage via dissociative deamidation



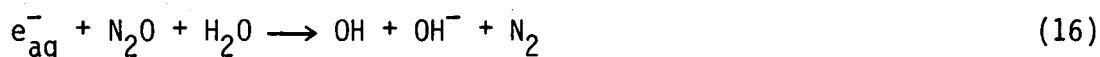
was relatively unimportant with $G \leq 0.3$ under the experimental conditions employed.³² Pulse radiolysis studies of the addition of e_{aq}^- to the carbonyl group of the peptide bond do not show any evidence for main-chain cleavage via reaction 14.^{27,37}

However, ESR studies of the reactions of photogenerated electrons with simple peptides in aqueous glasses at low temperatures show the addition reaction 12 which is followed by the dissociation reaction 14 as the system is warmed.^{35,36} Reaction 14 has also been observed in a wide variety of aqueous peptide systems through use of spin-trapping techniques involving *t*-nitrosobutane as the spin trap, i.e.,³⁸



The differences in these findings probably involves a dose-rate effect. If the rate of the first-order dissociation reaction 14 is relatively slow, then the second-order reconstitution reaction 13 would be favored at the higher dose-rates. Both the product-analysis studies and the pulse-radiolysis studies were done at dose-rates $\geq 10^{18}$ eV/gm min. The spin-trapping studies were done at a dose rate a factor of 10 lower. In the low-temperature glasses, dissociation of the "matrix-isolated" RC(OH)NHCHR_2 radical would be greatly favored over any diffusion controlled recombination reaction.

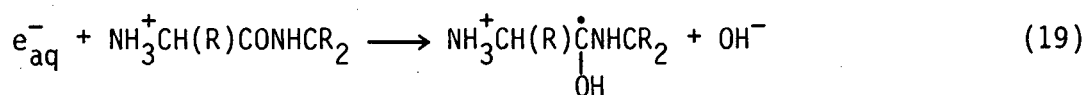
Addition of electron scavengers such as N_2O and H_3O^+



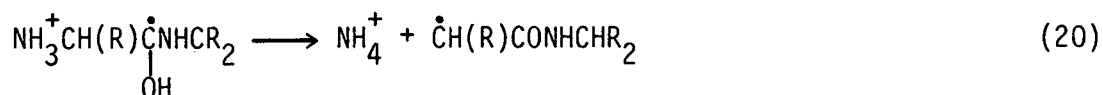
eliminates the possibility of the back reaction and results in the formation of the α, α' -diamino succinic acid derivatives through cross-linking at the main chain^{26,34}



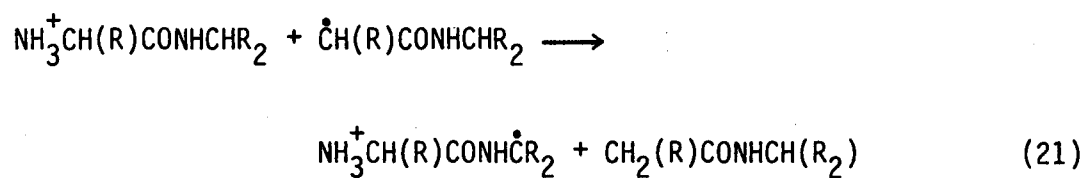
High yields of main-chain cross linking with formation of α, α' -diamino acid derivatives are also observed in the radiolysis of the low molecular-weight linear oligopeptide derivatives of glycine^{26,34} and alanine.³⁹ In these systems, the addition of e_{aq}^- occurs preferentially at the C=O bond of the N-terminal residue.³³⁻³⁸



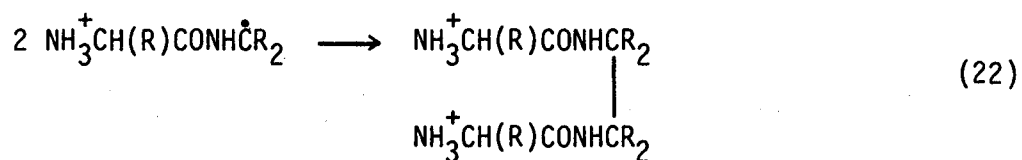
and this leads to deamination via



Reactions 19,20 are characteristic of compounds containing the amino group in the α -position to the carbonyl function i.e., $\text{NH}_3^+\text{CH(R)COX}$ where $X = \text{O}^-$, OH , OR , NHR etc.^{26,27,33} Subsequent steps include



and



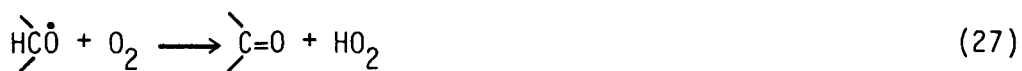
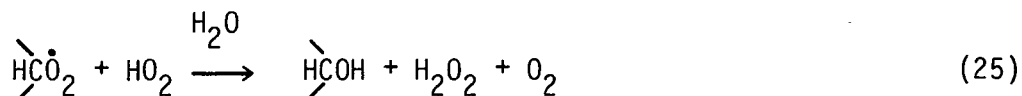
3. Reactions of Peptide Derivatives of the Other Aliphatic Amino Acids

3.1 Oxygenated Solutions

Although OH attack at the glycine and alanine residues occurs almost exclusively at the α C-H position along the peptide main-chain (reaction 3), with all other amino acids the side-chain represents a major competing locus of OH reaction^{28,40,41}. With the alkyl series, α -aminobutyric, valine, leucine, etc., the yield for oxidative degradation of the main-chain via reactions 3-8 to yield amide, keto acid and fatty acid functions decreases with increasing number of C-H bonds in the hydrocarbon chain.^{25,26,40} Competing side-chain chemistry leads to hydroxyl and carbonyl substitution via

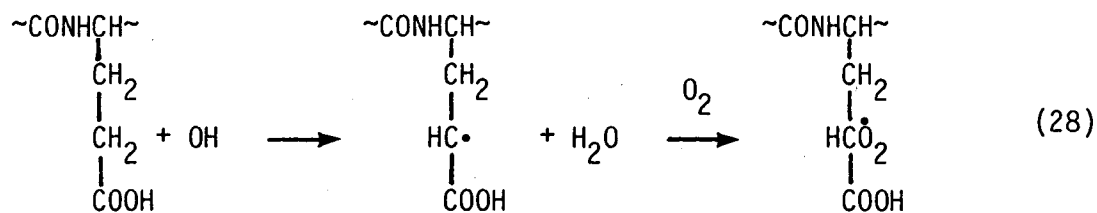


followed by the characteristic reactions of alkyl peroxy radicals^{30,42}

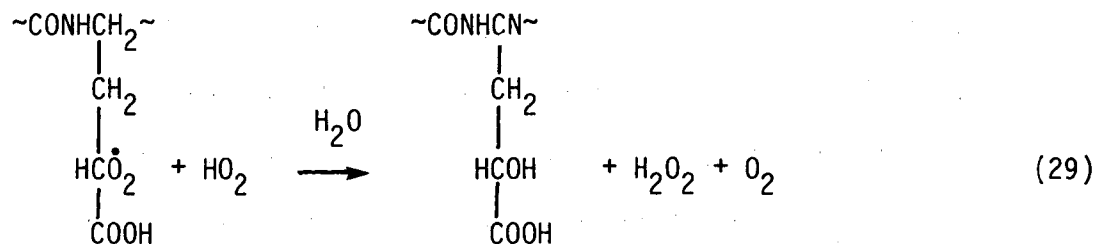


Oxidation can occur at any C-H position along the chain. Valine and leucine yield 3-hydroxy valine and 3-hydroxy plus 4-hydroxy leucine respectively as major products. Detailed chemical identifications and quantitative determinations of the various hydroxy and carbonyl products formed through OH attack at side chain loci of α -amino-butyric, valine and leucine have been made.⁴⁰

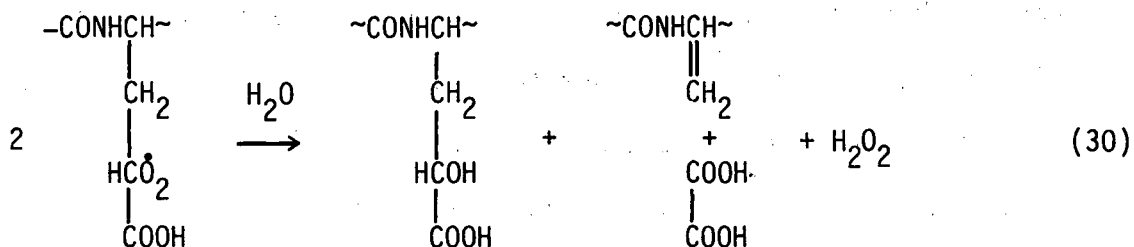
With the dicarboxylic amino acids aspartic and glutamic the C-H bond α to the side-chain carboxyl group represents the principal locus of OH attack in competition with the main-chain reaction 3-8 as observed by both product analysis and spin-trapping methods.^{28,43} With N-acetylglutamic acid in oxygenated solution, main-chain degradation via reactions 3-8 to yield amide and α -ketoglutaric acid functions accounts for ~30 percent of the OH radicals.⁴³ The remainder attack at the side chain via



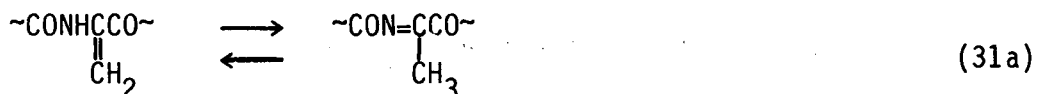
Part of the subsequent chemistry ($\text{RO}_2 + \text{HO}_2 \longrightarrow$) is similar to that formulated in equation 25 i.e.,



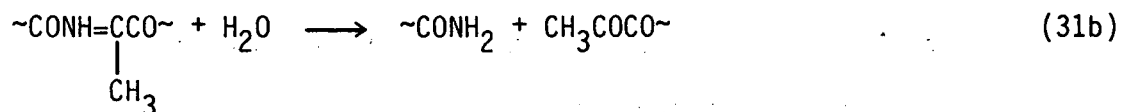
However, the analogues of the competing reactions ($2R\dot{O}_2 \longrightarrow$) takes a more complicated form than that shown in equations 26,27 i.e.,



Reactions akin to the degradation reaction 30 have been observed in other systems.^{42,43} The unsaturated degradation product formed in reaction 30 corresponds to a class of compounds referred to as dehydropeptides.



These compounds are easily hydrolyzed to yield amide and keto acid functions



We have here an example of a case in which OH attack at a side chain locus can lead to oxidative degradation of the peptide main chain.

Product yields in the γ -radiolysis of N-acetylglutamic acid (0.1 M, O_2 -sat) are essentially independent of pH over the range pH 3 to 8 with $G(\text{amide}) \approx 2.3$, $G(\alpha\text{-ketoglutaric}) \approx 0.8$, $G(\text{pyruvic}) \approx 0.9$.

Similar product yields are obtained with polyglutamic acid solutions (0.15%, O_2 -sat) over the pH range 6-8. But, the amide and pyruvic acids yields from PGA decrease abruptly as the pH is lowered from 6 to 4 whereas the α -ketoglutaric yield remains essentially constant over the entire pH range 8 to 3.

In interpreting these pronounced pH effects in the polyglutamic system, it has been pointed out that one of the unique characteristics of the radiation chemistry of macromolecular substances in aqueous solution is that each (macro)molecule undergoes reaction with a relatively large number of OH radicals even at the lowest practicable dosages.⁴³ For example, with a 0.15% solution of PGA, a γ -ray dose of 3×10^{18} eV/g produces only one OH per 100 glutamic acid residues, but, at the same time this corresponds to about 20 OH radicals per PGA molecule (MW 140,000). Since PGA above pH 6 has the random coil configuration, the various segments of the macromolecule are free to interact both intermolecularly and intramolecularly, and we find at pH > 6 no essential differences between the macromolecule and the low molecular weight model from the standpoint of product yields. But, as the pH of the solution is decreased, PGA undergoes a coil \rightarrow helix transition over the pH range 6 to 4.5. This is the range over which there is an abrupt decrease in the amide and pyruvic acid yields. With PGA in the helix form, the peroxy radicals RO_2 are frozen in a fixed spatial arrangement and it is obvious that the probability of reaction 30 ($2RO_2 \rightarrow$) is greatly reduced, reaction 29 ($RO_2 + H_2O \rightarrow$) is favored and as a result the yield of main chain degradation decreases as observed experimentally.

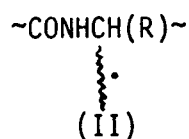
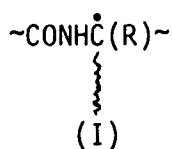
The loci of OH attack with asparagine and glutamine are analogous to those observed with the parent compounds aspartic acid and glutamine acid as formulated above.²⁸ Serine and threonine residues also undergo main-chain and side-chain oxidation to β -hydroxy α -keto acid and β -keto, α -amino acid functions respectively.^{28,40}

The reactions of OH radicals with peptide derivatives of the aliphatic amino acids, outlined above, all involve the formation of carbon-centered radicals through H abstraction. Such reactions are of intermediate velocity with $k \approx 10^8 - 10^9 \text{ M}^{-1} \text{ sec}^{-1}$.^{27,44}

3.2 Evacuated Solutions

The available data from product analysis,²⁶ pulse radiolysis²⁷ and spin-trapping studies³⁸ in irradiated aqueous solutions and from ESR studies^{36,37} of photogenerated electrons in aqueous glasses indicate that the carbonyl bond of most aliphatic amino-acid residues represents the major trapping center for e_{aq}^- via the addition reaction 12. This applies to (a) the alkyl amino acids, glycine, alanine, valine, leucine etc., (b) the dicarboxylic acids, aspartic, glutamic and their respective amides, asparagine and glutamine, (c) the basic amino acids, lysine and arginine, (d) the hydroxy containing amino acids, serine and threonine. These addition reactions are of intermediate velocity with k values in the $10^8 - 10^9 \text{ M}^{-1} \text{ sec}^{-1}$.^{26,27,45}

Both main-chain and side-chain radicals



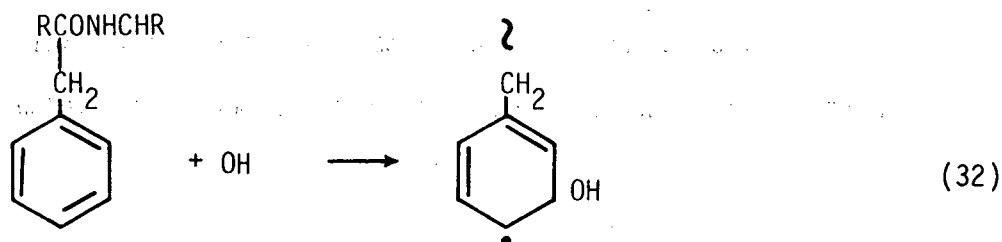
formed through OH attacks in these systems undergo dimerization to yield, α,α' -diaminodicarboxylic derivatives. The dimerization of type I radicals from glycine and alanine residues to give α,α' -diaminosuccinic and α,α' -diaminodimethyl succinic acids respectively has been discussed in Sec. 2.2. Higher molecular-weight dimers such as α,α' -diaminopimelic and α,α' -diaminosuberic formed through dimerization of type II radicals have also been identified.⁴⁰ The formation of unsaturated dimers through combination of side-chain radicals derived from phenylalanine and tyrosine are discussed below.

4. Reactions of Peptide Derivatives of the Aromatic-Unsaturated Amino Acids

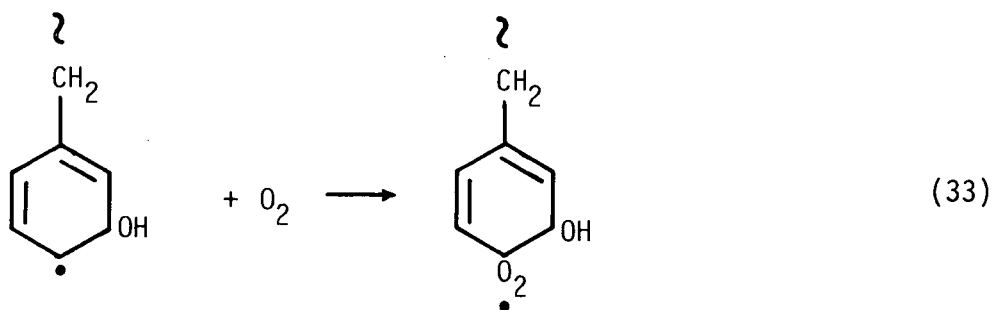
4.1 Oxygenated Solutions

Reactions of OH radicals with the phenylalanine residue include:

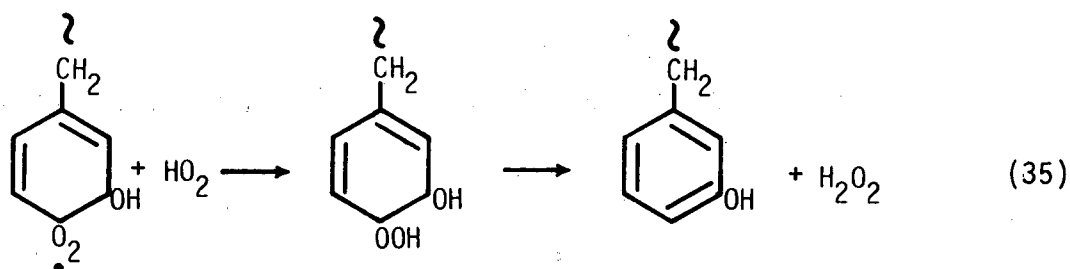
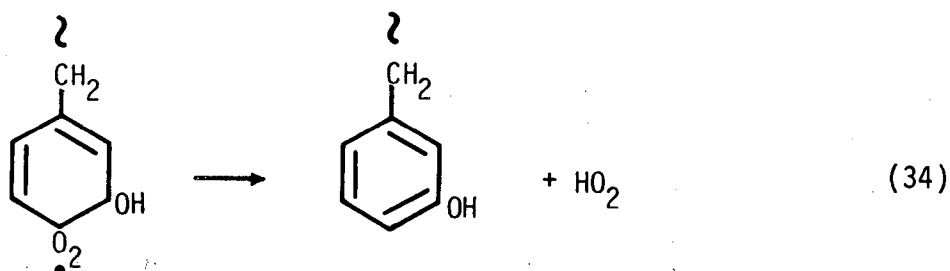
(1) H-abstraction at the main-chain via reaction 3 to give $\text{RCONH}\dot{\text{C}}(\phi)\text{R}$ radicals²⁸ and (2) addition to the aromatic side-chain⁴⁶⁻⁴⁹ e.g.,



where reaction 32 represents the principal path for OH removal. In the presence of O_2 , the main-chain radicals, $\text{RCONH}\dot{\text{C}}(\phi)\text{R}$ undergo oxidative degradation with formation of amide, phenylpyruvic acid and products of higher oxidation through reactions analogous to those formulated in equations 3-9. The hydroxycyclohexadienyl radicals formed through the OH addition reaction 32 react with O_2 to yield peroxy radical intermediates



which undergo the subsequent reactions



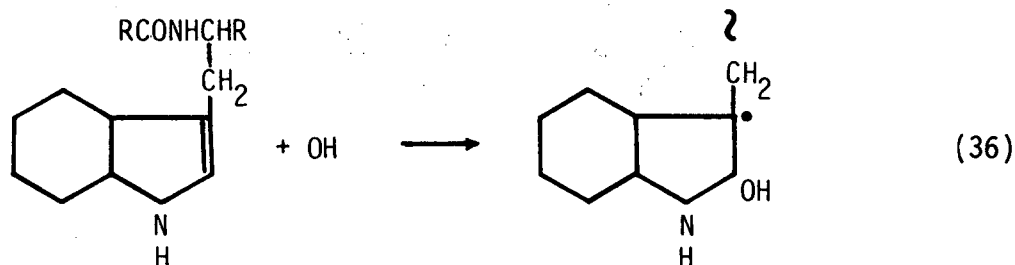
to yield tyrosine (ortho, meta, para) as the major products.^{46,50}

In the radiolysis of aqueous benzene a fraction of the peroxy radicals formed in reaction 32 undergo rearrangement and further oxidation to yield β -hydroxymucondialdehyde.⁵⁰

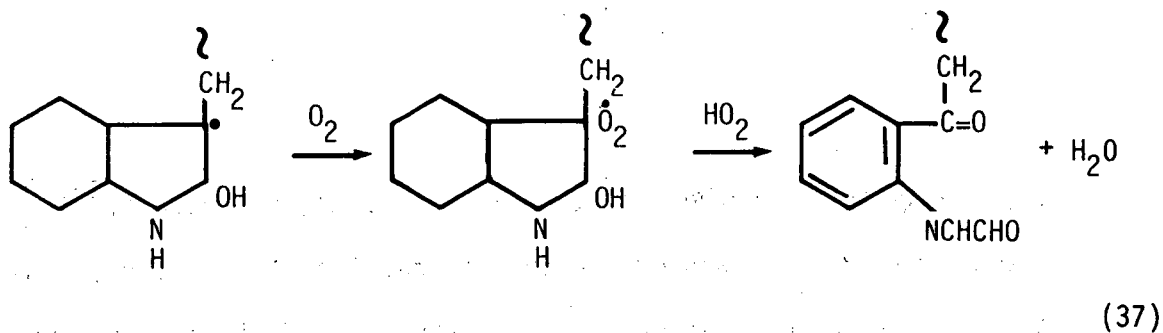
The radiolytic oxidation of tyrosine residues in O_2 -saturated solution appears to involve reactions analogous to those given in equations 32-35 to yield dopa, 3,4-dihydroxyphenylalanine, plus other unidentified products.^{51,52}

The radiolytic oxidation of the tryptophan residue in oxygenated solution arises predominantly through reactions initiated by OH addition to unsaturated bonds of the indole moiety as evidenced by

both product-analysis and pulse-radiolysis studies.⁵⁴⁻⁵⁷ The addition of OH to the C2-C3 double bond of the indole heterocyclic ring e.g.,

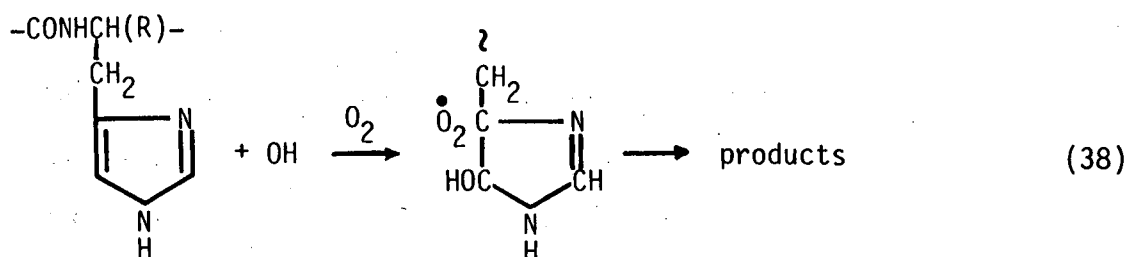


leads to formation of formylkinurenine as a major degradation product in oxygenated solution^{54,55}



The addition of OH to the benzenoid ring leads to formation of phenolic products in lesser yield^{54,55} (cf. reactions 32-35). The attack of OH radicals at the peptide main-chain appears to be minimal in this system.

Product analysis,⁵⁸ ESR,⁵⁹ and pulse radiolysis^{60,61} studies all show that the major mechanism for OH attack at the histidine residue involves addition to the imidazole ring e.g.,



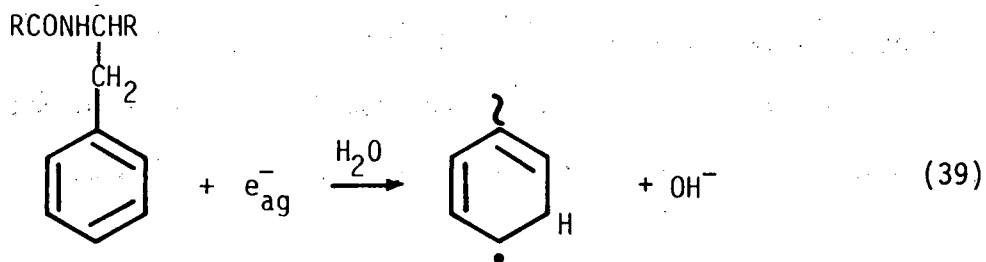
The yield for oxidative degradation of the histidine (imidazole) ring corresponds to $G(-\text{His}) \sim 4$ in dilute O_2 -saturated solutions under γ -rays and a complexity of degradation products are observed.⁵⁸

Among the major products of reaction (38) are asparagine and aspartic acid. The identification of imidazolylpyruvic and imidazolylacetic acids as lesser products indicates that OH attack of the main-chain via reaction 3 (followed by the analogues of reactions 4-9) is also involved in the reaction of OH radicals at the histidine residue.

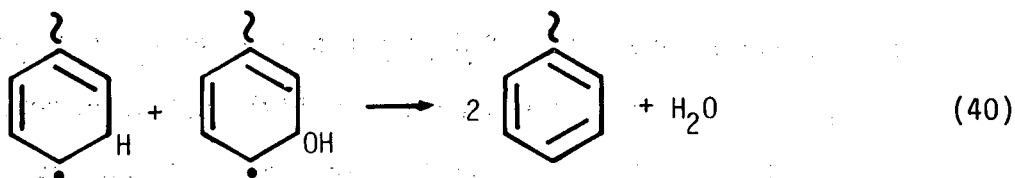
The reactions of OH radicals with the phenylalanine, tyrosine, tryptophan and histidine residues are relatively fast with k -values in the range $10^9 - 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$.^{27,45}

4.2 Oxygen-free Solutions

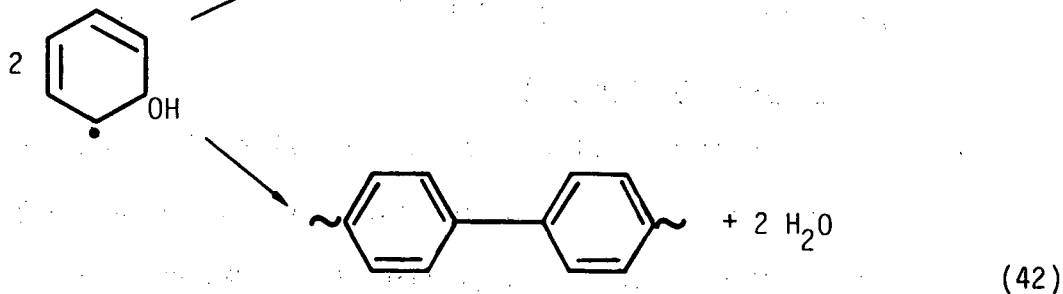
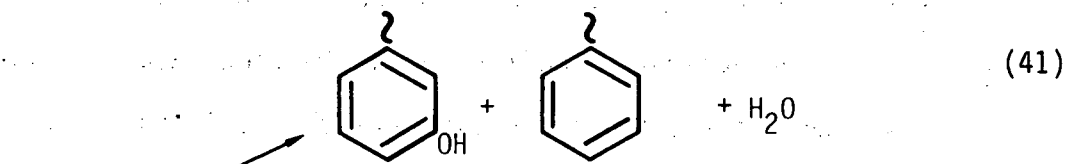
In oxygen-free solutions, both the peptide $\text{C}=\text{O}$ bond and the benzene ring of phenylalanine residue represent major trapping centers for the hydrated electron, e_{aq}^- , via reaction 12 and the reaction^{36,38,61}



Pulse radiolysis studies of aqueous N-acetylphenylalanine indicate that ~50 percent of e_{aq}^- reacts via addition to the peptide C=O bond, the remainder add to the benzene ring via reaction 39.⁶¹ Subsequent reactions of the $\bar{e}(\text{H})$ adduct⁶² formed in step 39 and the OH adduct of step 32 above include the back-reaction



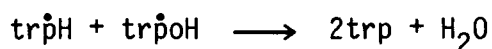
and



where the formation of tyrosine and the phenylalanine dimer via reactions 41,42 are written as analogues of the reaction scheme proposed for the production of phenol and diphenyl in the radiolysis of aqueous benzene.^{63,64} Comparison of the observed yields phenylalanine destruction G(-Phe) with the yields of phenylpropionic and tyrosine formed in the γ -radiolysis of O_2 -free phenylalanine solutions indicate that the phenylalanine dimer is produced as a major product.^{46,47} Direct experimental evidence for the formation of phenylalanine dimers and other cross-linked products from phenylalanine peptides has recently been reported.⁶⁵

Chemistry similar to that given in reactions 39-42 appears to be involved in the radiolysis of tyrosine and tyrosine peptides in O_2 -free solution. The large differences between G(-tyr) and the total yield of observed products, principally dihydroxyphenylalanine(dopa), has been interpreted as evidence for polymer(dimer) formation in relatively high yield.^{51,52} In recent chemical and pulse radiolysis studies, a blue-fluorescent product characteristic of dityrosine has been observed in irradiated solutions of tyrosine, glycylytyrosine, polytyrosine and protein.^{53,66,67}

Pulse radiolysis studies indicate that e_{aq}^- reacts with tryptophan almost exclusively through addition to the indole moiety.⁵⁴⁻⁵⁶ The γ -ray yield for tryptophan destruction G(-Trp) is extremely low in O_2 -free solution. The reconstruction reaction



represents the principal radical-removal step in the absence of O_2 .^{54,55}

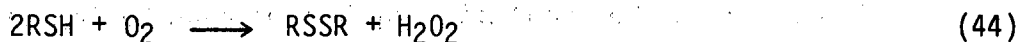
5. Reactions of Peptide Derivatives of the Sulfur-Containing Amino Acids

5.1 Oxygenated Solutions

The reaction of OH at the cysteine residue occurs preferentially at the sulfur moiety



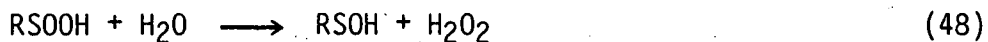
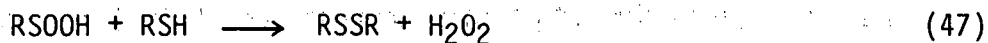
where reaction 43 is essentially diffusion controlled with $k \approx 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$.^{27,44} In acidic oxygenated solution the overall stoichiometry corresponds to⁶⁸⁻⁷¹



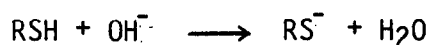
In the γ -radiolysis of 10^{-3} M cysteine in O_2 -saturated solution at pH 3, $G(-\text{RSH}) \approx 10$, $G(\text{RSSR}) \approx 5$, $G(\text{H}_2\text{O}_2) \approx 5$. The mechanism in acidic solution involves a short chain:^{70,71}



The hydroperoxide radical, $\text{HO}_2\cdot$, appears to be unreactive towards RSH. Observed products are formed via the subsequent chemistry



A marked increase in the values of $G(-RSH)$, $G(RSSR)$, $G(H_2O_2)$ is observed with increasing pH above $pH \geq 5$.^{69,71} The evidence is that the thiolate ion



competes with oxygen (reaction 45) for thiyl radicals via



The radical ion reacts in turn with oxygen



which generates additional RS via*



Reactions 50-52 constitute a chain which gives $G(-RSH)$ values as high as 50 in the γ -radiolysis of 3×10^{-3} M cysteine containing 2×10^{-4} M oxygen.

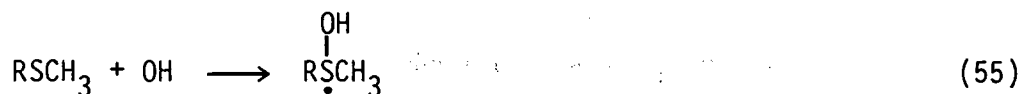
Oxidation of the disulfide linkage of cystine by the hydroxyl radical is also a fast reaction ($k \approx 1 \times 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$) which involves ion-pair formation and dissociative OH addition⁷²⁻⁷³

* Although HO_2 as noted above does not react with RSH, the conjugated base $HO_2 \rightleftharpoons H^+ + O_2^-$ does with $k_{52} \approx 1.8 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$ (ref. 71).



where reactions 53,54 occur with about equal probability. In the presence of O_2 , the principle final oxidation products, the sulfuric and sulfonic acid derivatives, RSO_2H and RSO_3H are formed in the γ -radiolysis of 10^{-3} M cystine with $G \approx 1.7$ and $G \approx 0.7$ respectively.⁷⁴

The reaction of OH with methionine yields an addition product ($k_{55} \approx 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$)



which breaks down in a complex series of reactions to yield a cation dimer and a sulfone.^{72,75} In oxygenated solution the major final products of γ -radiolysis are methionine sulfone, RS(O)CH_3 , and methionine sulfoxide, $\text{RS(O}_2\text{)CH}_3$, with a combined yield of $G \approx 3$.^{76,77}

5.2 Oxygen-free Solutions

The reaction of e_{aq}^- at the cysteine residue



is essentially quantitative with $k \approx 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$ in neutral solution. The e_{aq}^- reaction 56 and the OH reaction 43 lead to the subsequent chemistry



to give $G(\text{cystine}) \approx G(\text{alanine}) \approx G(\text{H}_2\text{S}) \approx 3^{78-81}$ in steady-state γ -radiolysis. Pulse radiolysis studies^{27,81} are in accord with the above formulation.

The reactions of disulfides, cystamine, cystine etc. with e_{aq}^-

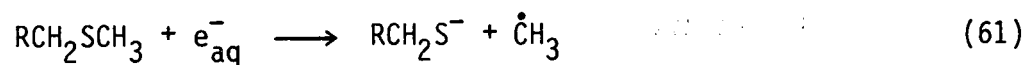
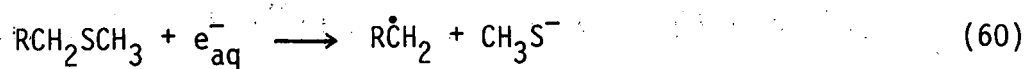


are also fast with $k \sim 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$. The anion radical product absorbs strongly with a band centered at $\sim 410 \text{ nm}$ with an extinction of $\sim 10^4 \text{ M}^{-1} \text{ sec}^{-1}$. The first order constant for the decay reaction



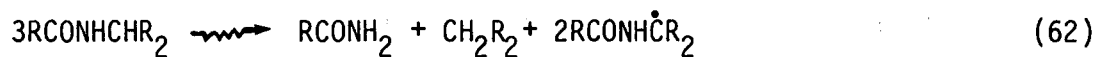
is independent of pH in the range 4-7.5 but rises sharply with decreasing pH.^{82,83}

With methionine and its peptide derivatives the reaction of e_{aq}^- occurs preferentially at the main-chain C=O bond via the addition reaction 12.^{25,26} ESR studies³⁸ of spin-trapped (tNB) radicals indicate a small contribution of



6. Effects of Side-Chain Substitution in the Radiolysis of Solid Peptides

Main-chain cleavage with formation of amide and fatty acid function was established some years ago as a major reaction in the radiolysis of peptides in the solid state.^{23,26,84,85} The overall chemistry was formulated in terms of the stoichiometry

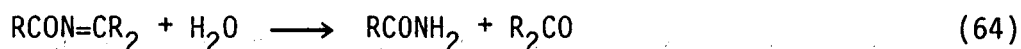


where $\text{RCONH}\dot{\text{C}}\text{R}_2$ corresponds to the long-lived radical products observed at room temperature by ESR spectroscopy.⁸⁶ Dimerization of these radical products occurs on dissolution of the irradiated solid in O_2 -free water via reaction 18.⁸⁷ Detailed chemical separations of products formed in the radiolysis of polyalanine* and N-acetylanine give $G(\text{amide}) \approx 3$, $G(\text{propionic acid}) \approx 2$, $G(\text{pyruvic acid}) \approx 1$, $G(\text{dimer}) \approx 2$.^{84,85} The evidence is that the keto acid is produced through the dehydrogenation

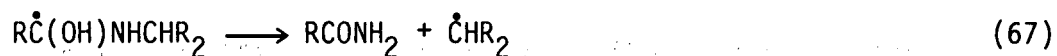
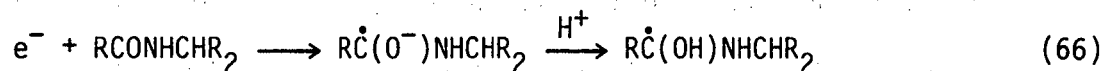
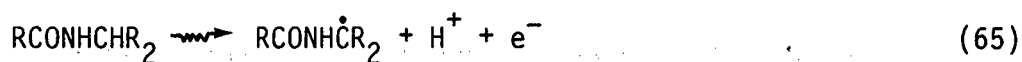


* The authors of a recent study (ref. 88) in which γ -irradiated ("dry") solid polyalanine (and other aliphatic polyamino acids) were simply heated to 100°C for gas-chromatographic analysis have reported that propionic acid (and the corresponding fatty acid from the other aliphatic polyamino acids) are produced only in low yield, $G < 0.1$. These authors seem to have overlooked the fact that the chemistry of equation 62 gives a propionyl(acyl) end group which must undergo hydrolysis to yield the free fatty acid.

The dehydropeptide formed in reaction 63 is readily hydrolyzed to give keto acid and amide

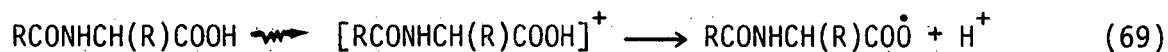


ESR studies indicate that the observed stoichiometries of reaction 62 for polyamino acid derivatives of the simpler α -amino acids results from the intermediate ionic processes⁸⁹⁻⁹²

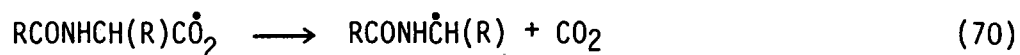


to give the overall stoichiometry given in equation 62.

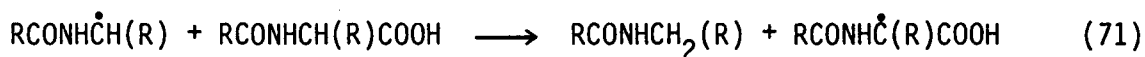
The ESR work also shows that the radiation chemistry of the lower-molecular weight peptides such as the N-acetyl amino acids and the di and tripeptides is somewhat more complicated than that given in the scheme reactions 65-68. In these systems, the carboxyl group represents the major locus of positive-hole formation i.e.,



The ionization step 69 is then followed by



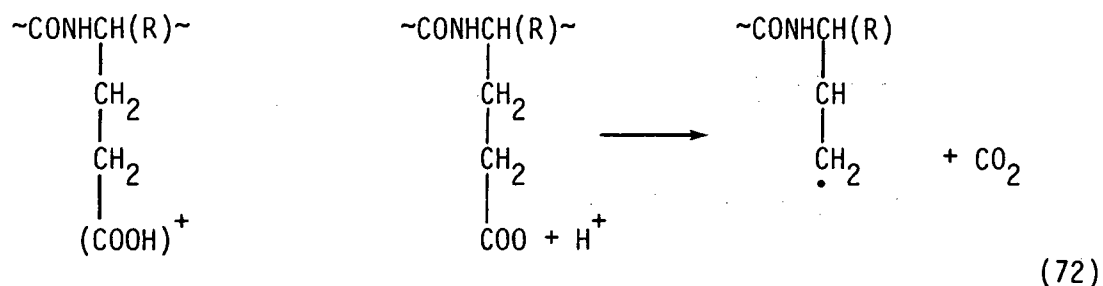
and the abstraction reaction



to yield the long-lived α -carbon radical. Both the decarboxylated radical, $\text{RCONH}\dot{\text{C}}\text{HR}$, and the α -carbon radical, $\text{RCONH}\dot{\text{C}}\text{(R)COOH}$ have been spin-trapped on dissolution of γ -irradiated N-acetyl amino acids and dipeptides in aqueous solution of t-nitrosobutane as the trapping reagent.⁹³

Cleavage of the peptide main-chain with formation of amide and fatty acid functions is a major process in the solid-state radiolysis of peptide derivatives of almost all aliphatic amino acids. Values of $G(\text{amide}) \sim 3$ and $G(\text{fatty acid}) \sim 2$ have been obtained with peptide derivatives of glycine, alanine, α -aminobutyric acid, glutamic acid, leucine, and methionine.^{84,85} The α -carbon radical, $\sim\text{CONH}\dot{\text{C}}\text{(R)}\sim$, is the long-lived radical species in each case as observed by direct ESR measurements of the irradiated solids.^{91,92}

With peptide derivatives of aspartic and glutamic acids, the evidence is that the positive hole is located preferentially at the side-chain carboxyl group (cf reactions 69-71)



where the radical product of reaction then abstracts H from the main-chain to form α -aminobutyric acid derivative as a major product.^{94,95}

Although both methionine and cysteine undergo C-S bond cleavage on reaction with the hydrated electron e_{aq}^- in aqueous solution (reactions 56, 60, 61) the evidence from both product analysis⁹⁵ and ESR^{89,92} studies is that such reactions are relatively unimportant in the solid state. The C=O linkage of the peptide bond appears to be the major trapping center for e^- in the radiolysis of methionine and cysteine peptides as solids.

The yield of main-chain cleavage as measured in terms of amide production is appreciably lower with peptide derivatives of the aromatic amino acids, phenylalanine and tyrosine.⁸⁵ The ESR evidence is that the unsaturated side chains of phenylalanine, tyrosine, and histidine compete effectively with the peptide bond for e^- in the solid state (cf. Sec. 4.2).⁹²

ACKNOWLEDGMENT

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