MAGDI M. MOSSOBA, IONEL ROSENTHAL,¹ AND PETER RIESZ

Laboratory of Pathophysiology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20205, U.S.A. Received September 4, 1981

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The reactions of hydroxyl radicals with methylamine, dimethylamine, trimethylamine, diethylamine, sec-butylamine, ethylenediamine, 1,3-diaminopropane, putrescine, cadaverine, 1,7-diaminoheptane, ornithine, spermidine, spermine, agmatine, and arcaine in aqueous solutions have been investigated by spin-trapping and esr. Hydroxyl radicals were generated by the uv photolysis of H₂O₂ and 2-methyl-2-nitrosopropane (MNP) was used as the spin-trap. The effects of ionizing radiation on the same polyamines in the polycrystalline state were also investigated. The free radicals produced by γ -radiolysis of these solids at room temperature in the absence of air were identified by dissolution in aqueous solutions of MNP. The predominant reaction of \dot{O} H with amines and polyamines below pH7 was the abstraction of hydrogen atoms from a carbon that is not adjacent to the protonated amino group. For agmatine and arcaine which contain guanidinium groups abstraction occurred from the α -CH. Dimethylamine was oxidized to the dimethylnitroxyl radical by H₂O₂ in the dark. γ -Radiolysis of polyamines in the polycrystalline state generated radicals due to H-abstraction from either the α -CH or from a carbon atom in the middle of the alkyl chain. The deamination radical was obtained from ornithine.

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Faisant appel à la rpe et à l'utilisation de piegeurs de spin, on a étudié la réaction des radicaux hydroxyles avec des solutions aqueuses des amines suivantes: méthylamine, diméthylamine, triméthylamine, diéthylamine, *sec*-butylamine, éthylènediamine, diamino-1,3 propane, putrescine, cadavérine, diamino-1,7 heptane, ornithine, spermidine, spermine, agmatine et arcaine. Les radicaux hydroxyles furent produits par la photolyse uv de H_2O_2 et on a utilisé le méthyl-2 nitroso-2 propane (MNP) comme piégeur de spin. On a également étudié les effets des radiations ionisantes sur les mêmes polyamines à l'état polycristallin. On a identifié les radicaux libres produits par radiolyse- γ de ces solides à la température ordinaire en l'absence de l'air en les dissolvant dans des solutions aqueuses de MNP. L'élimination d'atomes d'hydrogène de l'atome de carbone non adjacent au groupe amino protoné est la réaction principale du radical ÒH avec les amines et les polyamines à un pH inférieur à 7. Dans le cas de l'agmatine et de l'arcaine, qui contiennent des groupes guanidiniums, l'élimination se produit au niveau du CH en α . On a oxydé la diméthylamine en radical diméthylnitroxyde par H₂O₂ à l'obscurité. La radiolyse γ des polyamines à l'état polycristallin produit des radicaux par suite de l'élimination d'hydrogène soit du CH en α ou de l'atome de carbone qui se trouve au centre de la chaîne alkylée. À partir de l'ornithine, on a obtenu le radical de désamination.

[Traduit par le journal]

Introduction

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Polyamines, which consist of hydrocarbon chains with multiple amine groups, are intimately involved in the control of normal and malignant growth processes (1, 2). Polyamines are especially useful as biochemical markers of cancer patient response to radiation, surgery, immunotherapy, and chemotherapy (2). They are found in elevated concentrations in physiological fluids of patients and appear to be markers of pathology related to overproliferation and cell death (2).

In this work, we have investigated the effects of γ -radiolysis in the solid state and the reactions of OH radicals in aqueous solutions with a number of biologically significant polyamines such as putrescine (1,4-diaminobutane), cadaverine (1,5-di-aminopentane), spermidine (H₃ $\overset{+}{N}$ —(CH₂)₃— $\overset{+}{N}$ H₂--(CH₂)₄—NH₃⁺), spermine (H₃ $\overset{+}{N}$ —(CH₂)₃—

 $\ddot{N}H_2$ —(CH₂)₄— $\dot{N}H_2$ —(CH₂)₃— $\dot{N}H_3$), etc., as well as several primary, secondary, and tertiary amines.

Free radical formation from aliphatic amines has been investigated previously by a number of methods. For studies of the solid state, electron spin resonance was used to observe radical species produced by X-rays (3) and γ -radiolysis (4–6) in single crystals or by uv photolysis (7, 8) in frozen glasses. Optical absorption was used to follow the radicals produced by pulse radiolysis (9-12) in aqueous solutions that were saturated with N₂O to convert e_{aq}^{-} to $\dot{O}H$. The radicals generated by $\dot{O}H$ (or H) attack formed by steady-state radiolysis of aqueous solutions (13, 14) or by the $Ti^{3+}-H_2O_2$ flow system (15–17) were detected by direct, in situ esr observation. The flow method is limited by the requirement of considerable amounts of substrate to be investigated.

In the single crystal studies, H-abstraction from carbon as in $\cdot CH_2 \dot{N}H_3$ (5) and from nitrogen (e.g., $Me_3 \dot{N}^+$ (6)) was produced by ionizing radiation.

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¹On leave of absence from the Department of Technology, Agricultural Research Organization, Volcani Center, Bet-Dagan, Israel.

N-centered radicals were also formed by ultraviolet irradiation of glassy samples of mono-, di-, and trialkyl amines at low temperatures (7, 8). However, in the reaction of OH radicals with aliphatic amines in aqueous solution (9–14, 17), H-abstraction from the nitrogen as well as from the carbon adjacent to it occurred in alkaline medium. In acid solution, abstraction was observed to take place only from those carbons which were not adjacent to

the $-\bar{N}H_3$ group.

In this work electron spin resonance and spintrapping (18–21) were used to identify the free radicals. The reactions of OH radicals were investigated by uv photolysis of aqueous solutions containing hydrogen peroxide and the amine or polyamine. The direct effects of ionizing radiation on the polyamines in the solid state were investigated by γ -radiolysis of the polycrystalline solids followed by dissolution in a solution containing the spin-trap (22, 23).

In principle, a spin-trap, such as 2-methyl-2nitrosopropane (MNP), Me₃CN=O, reacts with short-lived radicals, R[•], to produce longer-lived spin-adducts, Me₃CN(R)O, whose structures can conveniently be identified by esr. The α , β , and γ positions are defined with respect to the nitrogen of the nitroxyl group as illustrated for the spinadduct of methylamine:

[1]
$$O = N - CMe_3 + CH_2\dot{N}H_3 \rightarrow O^- - \dot{N}^+ - C^{\alpha}H_2^{\beta} - \dot{N}^{\beta}H_3^{\gamma}$$

$$\downarrow \\ CMe_3$$

Experimental

Polyamines as well as primary, secondary, and tertiary amines were purchased from Sigma Chemical Company. 2-Methyl-2-nitrosopropane (MNP) was obtained from Aldrich Chemical Company and D_2O (99.8%) was acquired from Bio-Rad Laboratories.

Aqueous solutions of the MNP were prepared in water by adding 50 mg of the spin-trap to 10 mL of D_2O and stirring in the dark at 45°C for 2 hours (24).

In the γ -radiolysis experiments, solid samples of polyamines were irradiated in a ⁶⁰Co γ -source to a dose of 120 kGy in the absence of air at room temperature. The irradiated samples were subsequently dissolved in the spin-trap solution.

For the study of OH radical reactions in aqueous solution, the amines and polyamines were dissolved in the spin-trap solutions to which 25 μ L of 30% H₂O₂ per mL were added just prior to uv illumination. The radicals were generated by photolysis *in situ* at room temperature in the standard aqueous quartz cell (60 × 10 × 0.25 mm) placed in the esr cavity, using a Schoeffel 1000 W high-pressure Hg-Xe lamp coupled with a grating monochromator. The excitation light had a maximum centered at 260 ± 10 nm and the irradiation time ranged from 5 to 30 seconds.

The esr measurements were made on a Varian E-9, X-band (9.4 GHz) spectrometer. The esr spectra from spin-trapped radicals were recorded at room temperature as first derivatives. The esr scans were traced with a 100 kHz modulation of 0.05 or 0.1 G amplitude and the microwave power level was maintained

at 10 mW to avoid saturation of the esr signals. Thermal decay studies of the spin-adducts were performed at room temperature and proved helpful in analyzing overlapping spectra due to the presence of more than a single radical species. The magnetic field was calibrated with an nmr Gauss Meter.

Results and discussion

In spin-adducts the free-electron spin density is mostly localized on the nitrogen and oxygen atoms of the nitroxyl group and the interaction of the unpaired electron with ¹⁴N (I = 1) of the nitroxyl group generates a primary triplet. Some of the electron spin is also delocalized on the atoms of the trapped radicals and produces hyperfine structures, referred to as secondary splittings, which are most useful in identifying the structure of the spin-adducts. The primary and secondary hyperfine splitting constants of the spin-trapped radicals of the polyamines and amines investigated are listed in Table 1. The esr spectra of photolyzed aqueous solutions of MNP usually show a 17.2G triplet from the di-tert-butylnitroxyl radical. This spectrum is marked S in the figures.

Initially, the simple amines were studied as models for more complex polyamines. Aqueous solutions of several primary, secondary, and tertiary amines were uv-photolyzed in the presence of MNP and H_2O_2 at room temperature. The esr spectrum produced by the spin-trapped radicals of diethylamine showed detailed hyperfine structure. Figure 1(a) displays the observed spectrum which has a primary nitrogen hyperfine coupling constant of 16.2 G and a secondary structure consisting of a 1:2:1 triplet of 13.6 G which is further split into another 1:2:1 triplet of 0.4 G. Only radical **1** is

$$CH_2 - CH_2 - \overset{+}{N}H_2 - CH_2 - CH_3$$

consistent with this observation and is formed by H-abstraction from a terminal carbon. Radical **1** has been previously detected by esr in the reaction of $\dot{O}H$ with diethylamine using a $Ti^{3+}-H_2O_2$ flow method (17).

Figure 1(b) shows the spectrum obtained from the spin-adducts of *sec*-butylamine which is due to the presence of two radial species. Radical 2 is due

to H-abstraction, as in diethylamine, from a terminal carbon except that the middle lines of the 11.5 G secondary triplet overlap with the more intense 2.0G secondary doublet arising from the spinadduct of radical **3**. This doublet is clearly observed

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DIETHYLAMINE

⊦5G-

sec-BUTYLAMINE

≻5G-

sec-BUTYLAMINE

≻5G-•



Fig. 2(a) and arises from the spin-adduct of radical 4 since it consists of a 1:2:1 triplet of 8.3 G, due to two equivalent hydrogen atoms, which is further split into a 1:1:1 triplet of 3.0 G due to the nitrogen atom. Radical 4 has been previously observed in alka-

·CH₂N(CH₃)₂

line medium (9, 13). During radiolysis of acid solutions of trimethylamine, a minor product, the aminium radical Me₃N⁺ was detected by esr at pH 1 and 3 (14). This radical has also been observed in γ -irradiated single crystals of tetramethylammonium chloride (6). However, the aminium radical could not be detected by spin-trapping under our experimental conditions.





FIG. 1. The esr spectrum from uv-photolyzed aqueous solutions containing MNP, H_2O_2 , and (a) diethylamine, (b) sec-butylamine, (c) sec-butylamine after decay.

(a)

(b)

(c)

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in Fig. 1(c) since the spin-adduct of radical 2 decayed in about 10 min at room temperature.

The spectrum of the spin-trapped radicals of trimethylamine obtained by OH attack is shown in

FIG. 2. (a) The esr spectrum from uv-photolyzed aqueous solutions containing MNP, H_2O_2 , and trimethylamine; (b) esr spectrum from aqueous solutions containing H_2O_2 and dimethylamine in the dark.

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	n n	Primary 14N	Second splitting	tary s (G)			
Compound	value ^b	splitting (G)	β	γ	Method	Radical	_
Diethylamine	6	16.2	13.6 (2H) ().4 (2H)	юн	\cdot CH ₂ CH ₂ $\stackrel{+}{N}$ H ₂ CH ₂ CH ₃	1
sec-Butylamine	5.2	16.5	11.5 (2H) ().6 (2H)	.он	CH2-CH2-CH-CH3 NH3	2
		15.8	2.0 (H)		юн	CH ₃ ĊHCH ₃ I NH ₃	3
Trimethylamine	11	15.7	8.3 (2H) 3.0 (N)		•ОН	•CH ₂ —N(CH ₃) ₂	4
Methylamine	5.3	15.2	11.7 (2H) 2.2 (N)		юн	$CH_2 - NH_3$	5
Dimethylamine	12	17.0	14.6 (6H)		H_2O_2	ON(CH ₃) ₂	6
Ethylenediamine	3.5	13.7	3.0 (N) 1.3 (H)		γ, ÖH	H ₃ N ⁺ CHCH ₂ N ⁺ H ₃	7
1,3-Diaminopropane	6.4	16.0	1.3 (N) 1.3 (H)		γ, Ο Η	$H_3 \dot{N} - \dot{C} H - (CH_2)_2 - \dot{N} H_3$	8
		15.4	1.8 (H)		Ċн	$H_3 \overset{+}{N}$ — CH_2 — $\dot{C}H$ — CH_2 — $\overset{+}{N}H_3$	9
L-Ornithine H ₃ $\stackrel{+}{N}$ —(CH ₂) ₃ —CH— $\stackrel{+}{N}$ H ₃ COO ⁻	5	15.6	4.5 (H) ().5 (2H)	γ	H ₃ Ň—(CH ₂) ₃ —ĊH—COO ⁻	10
1,4-Diaminobutane (Putrescine)	5.1	15.2	2.0 (H)		γ, ÖH	$H_{3}\dot{N}$ —CH ₂ — $\dot{C}H$ —(CH ₂) ₂ — $\dot{N}H_{3}$	11
		14.2	2.8 (N) 1.4 (H)		ĊН	H ₃ N ⁺ ĊH(CH ₂) ₃ NH ₃	12
		15.7	8.8 (2H)		ŎН	CH_2 CH ₂ NH ₃	13
1,5-Diaminopentane (Cadaverine)	4.6	15.5	2.0 (H)		γ, ÖH	\sim CH ₂ -CH-CH ₂ - \sim	14
		14.3	2.7 (N) 1.5 (H)		ĊН	H_3N — $\dot{C}H$ — $(CH_2)_4$ — $\dot{N}H_3$	15
		15.7	8.8 (2H)		ÓН	·CH ₂ —CH ₂ —NH ₃	16
1,7-Diaminoheptane	4.5	15.8	2.0 (H)		ÓН	\sim - CH ₂ -CH ₂ -CH ₂ - \sim	17
1,8-Diaminooctane	12.1	16.1	2.5 (N) 1.5 (H)		γ	H_2N — $\dot{C}H$ — $(CH_2)_7$ — NH_2	18
Spermidine	5.4	15.9	1.4 (N) 1.4 (H)		γ	~~N—ĊH—CH ₂ —~	19
$H_3N - (CH_2)_3 - NH_2 - (CH_2)_4 - NH_3$		15.2	2.0 (H)		ÓН	$\sim -CH_2 - CH_2 - CH_2 - \sim$	20
		15.7	8.8 (2H)		ÓН	·CH2-CH2-NH3	21

TABLE 1. Hyperfine coupling constants^a of the spin-trapped polyamines and amines radicals

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		TABLE 1.	(Conclude	(p			
		Drimory 14N	Second splitting	lary s (G)			
Compound	value ^b	splitting (G)	β	٨	Method	Radical	
Spermine	5.6	15.9	1.4 (N)		γ	₩►N—ĊH—CH2—	22
$H_{3}\overset{h}{h}-(CH_{2})_{3}-\overset{h}{h}H_{2}-(CH_{2})_{4}-\overset{h}{h}H_{2}-(CH_{2})_{3}-\overset{h}{h}H_{3}$		15.5	1.4 (n) 2.0 (H)		фн	··· —СН₂—ĊH—СН₂ — ····	23
Agmatine	4.8	15.5	2.8 (N)		γ, ởH	~~NĊHCH ₂ ~~	24
H ₂ N—Ç—NH—(CH ₂) ₄ — [†] H ₃		15.5	2.0 (H) 2.0 (H)		ЧŅ	~~−СН ₂ −ĊН−СН ₂ −~	25
$^{\mathrm{L}}_{\mathrm{+}}$							
Arcaine H ₂ N—C—NH—(CH ₂) ₄ —NH—C—NH ₂	5.1	15.5	2.8 (N) 1.9 (H)		γ , ỞH H ₂ N	С¦NHС́H(СН₂)₃NHС¦NH	² 26
H_{12} H_{2} H_{2} H_{2}						H_2 H_2 H_2 $+$ $+$	
^a Accurate to ± 0.1 G. ^b pD = observed pH + 0.4 (31).							

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When OH radicals reacted with methylamine a spectrum similar to the one obtained for trimethylamine was observed and the untrapped radical from methylamine has structure 5. The spin-adducts of both radicals 4 and 5 decayed after about 4 min at room temperature.

·CH₂NH₃

Radical 5 has been previously observed by esr in a single-crystal study of methylammonium alum (5). In acid solutions, 5 was detected by pulse radiolysis (9) but not by esr (13, 17) due to line broadening caused by chemical exchange of the ammonium protons (13). Only in the pH range 7-13.5 the conjugate base of 5, \cdot CH₂NH₂, was observed by esr in γ -irradiated aqueous solution of methylamine (13).

Dimethylamine was found to react with H_2O_2 in the dark in the absence of MNP. The observed spectrum (Fig. 2(b)) is characteristic of a 17.0G 1:1:1 triplet which was further split into a 14.6G septet with a relative intensity of 1:6:15:20:15:6:1 due to six equivalent hydrogen atoms. This evidence is consistent with the formation of the nitroxyl radical **6**.



 H_2O_2 -oxidation of dimethylamine has previously been obtained in a 1*N* NaOH solution (25). The oxidation product **6** has also been produced in a titanous ion – hydrogen peroxide flow system (15, 16).

After ethylenediamine dihydrochloride was γ irradiated in the solid state to a dose of 120 kGy, it was dissolved in an aqueous solution of MNP. The observed esr spectrum of the spin-adduct consisted of a secondary 1:1:1 triplet (3.0G) which was further split into a doublet (1.3G). This observation is consistent with the formation of radical 7. The

> H_3 ⁺M⁺CH⁻CH₂⁺NH₃ 7

same radical species was also found when an aqueous solution of ethylenediamine containing MNP and H_2O_2 was photolyzed for 5 seconds at 260 nm as shown in Fig. 3(a).

Solid-state radiolysis of 1,3-diaminopropane dihydrochloride yielded radical 8. The esr spectrum, shown in Fig. 3(b), indicates the equivalence of the β -nitrogen and the β -hydrogen of the spin-adduct

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(a)

(b)



+5G-

1,3-DIAMINOPROPANE

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$$H_3 \overset{+}{N} - \dot{C}H - CH_2 - CH_2 - \overset{+}{N}H_3$$

of radical 8. In the H_2O_2 -photolysis experiment a mixture consisting of radical 8 as well as the one (structure 9) generated by H-abstraction from the C(2) carbon was obtained.

$$H_3 \overset{+}{N} - CH_2 - \dot{C}H_2 - CH_2 - \dot{N}H_3$$

9

The esr spectrum of the spin-adduct generated from γ -radiolysis of polycrystalline L-ornithine hydrochloride and spin-trapping in aqueous solution exhibited a 4.5 G doublet which was further resolved into a 0.5 G triplet (1:2:1). This spectrum is due to the formation of the deamination radical **10**. This result is similar to that obtained for

 γ -irradiated polycrystalline α -amino acids (23). The interaction of OH radicals with L-ornithine did not generate radical 10, but gave rise to an unresolved mixture of H-abstraction radicals.

Similar esr spectra were recorded for 1,4-diaminobutane and 1,5-diaminopentane. Hydrogen abstraction from the middle of the chain was observed by both H_2O_2 -photolysis and γ -radiolysis. The spin adduct of radical **11** shows an esr spec-

$$H_3 \overset{+}{N} - CH_2 - \dot{C}H - (CH_2)_2 - \overset{+}{N}H_3$$

11

trum (Fig. 4(a) and (b)) that consists of a 2.0 G secondary doublet. At higher gain, the esr spectrum (Fig. 4(c)) observed in the photolysis experiment also shows two other sets of lines. The lines labelled A arise from radical 12, while the ones

$$H_{3}\dot{N} - \dot{C}H - (CH_{2})_{3} - \dot{N}H_{3}$$

12

labelled with numbers are tentatively attributed to a \cdot CH₂-type radical which could be obtained from 12 by a β -scission mechanism (26) giving radical 13:

$$[2] H_{3}\overset{+}{N} - \dot{C}H_{2} \xrightarrow{\xi} \dot{C}H_{2} - CH_{2} - \ddot{N}H_{3}$$

$$12$$

$$\overset{\beta\text{-scission}}{\longrightarrow} H_{3}\overset{+}{N} - CH = CH_{2} + CH_{2} - CH_{2} - \ddot{N}H_{3}$$

$$13$$

FIG. 3. (a) The esr spectrum from uv-photolyzed aqueous solutions containing MNP, H_2O_2 , and ethylenediamine; (b, c) esr spectra of spin-trapped radicals from polycrystalline (b) 1,3-diaminopropane, (c) L-ornithine γ -irradiated at room temperature and subsequently dissolved in an MNP solution.

This type of radical was also observed for spermidine (radical 21 in Table 1). The esr spectrum obtained by H_2O_2 -photolysis of 1,7-diaminoheptane only showed the radical generated by

(c) L-ORNITHINE

ЧЧЧ







(a)

FIG. 4. (a) The esr spectrum of spin-trapped radicals from polycrystalline 1,4-diaminobutane γ -irradiated at room temperature and subsequently dissolved in an MNP solution; (b) esr spectrum from uv-photolyzed aqueous solutions containing MNP, H₂O₂, and 1,4-diaminobutane; (c) like (b) with higher gain (× 5); (*) are the ¹³C satellites of di-*tert*-butylnitroxyl radical (marked S).

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1,4-DIAMINOBUTANE

H-abstraction from the middle of the hydrocarbon chain.

 γ -Radiolysis of the free base 1,8-diaminooctane yielded radical 18. This type of radical was also

found in the γ -irradiation of spermidine and spermine in which the β -nitrogen and β -hydrogen were found to be equivalent since their esr spectra exhibited a secondary 1:2:2:1 pattern. Abstraction of OH from a middle carbon was, however, observed for spermidine and spermine. The radicals obtained from agmatine and arcaine, by γ -radiolysis or H₂O₂-photolysis, exhibited esr spectra with a 6-line secondary pattern due to the nonequivalence of the β -N and β -H and are due to abstraction from a carbon adjacent to a nitrogen. For agmatine a second radical was also observed during photolysis, due to abstraction from the middle of the carbon chain. Radical **26** was generated from the H₂O₂-photolysis of arcaine.

$$\begin{array}{c} H_2 N - C - N H - \dot{C} H - (C H_2)_3 - N H - C - N H_2 \\ \parallel \\ N H_2 \\ \mu H_2 \\ P H_2 \\ 26 \end{array}$$

Previous work has shown that the nature of the radicals produced from the reaction of $\dot{O}H$ radicals with amines is strongly pH dependent (9–12, 27–29). The rate of reactions of $\dot{O}H$ with amines in their basic form, RNH₂, is close to being diffusion controlled and it is one to two orders of magnitude

larger than that with RNH_3 (9, 27). In alkaline solutions, at pH values where the amines are H

deprotonated, R— $\overset{1}{\underset{\downarrow_1}{\text{C}}}$ -NH₂, $\overset{1}{O}$ H radicals abstract

H atoms mainly from $--NH_2$ and α -CH (9). On the other hand, the strong inductive effect of a protonated amino group leads to the transmission of negative charge from the H atoms in the α -position through the carbon atom to the $-NH_3$ group. Hence an electrophilic attack of OH on hydrogen atoms in the position adjacent to the $-NH_3$ group becomes less favorable and abstraction is more likely to occur from positions further away from the ammonium group (9).

In the present study, the observed products in the reaction of OH radicals with amines and polyamines in their protonated form are consistent with the pathways described above. The predominant site of OH attack is not on the carbon attached

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to the ammonium group. This is clearly illustrated in the cases of diethylamine, *sec*-butylamine, 1,4diaminobutane, or spermine. For agmatine and arcaine, which contain one and two guanidinium groups respectively, H-abstraction occurred at a carbon adjacent to a nitrogen, possibly because the proton is shared between the three nitrogen atoms of the guanidinium moiety and the inductive force

of $-\dot{N}H_3$ is no longer present.

The observed radicals from polyamines generated by ionizing radiation in the polycrystalline state were not the same as those obtained by $\dot{O}H$ radicals. It can be seen from Table 1 that radicals due to H-abstraction from either the α -CH or from a carbon atom in the middle of the alkyl chain were produced. A deamination radical was only formed in the γ -radiolysis of ornithine. This result is in agreement with the conclusion of previous studies (30) that deamination requires the presence of a carboxyl group separated by one $-CH_2$ — from the amino group.

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