Sites of Attack of Hydroxyl Radicals on Amides in Aqueous Solution. II. The Effects of Branching α to Carbonyl and to Nitrogen

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Abstract: The reaction in aqueous solution of OH radicals with a number of amides has been studied by the technique of pulse radiolysis–kinetic absorption spectroscopy. Compounds investigated include $CH_3CONHC(CH_3)_3$, $CH_3CON(CH_3)C(CH_3)_3$, $CH_3CON(C_2H_5)_2$, $CH_3CH_2CONH_2$, $CH_3CH_2CONHCH_3$, $(CH_3)_2CHCONH_2$, $(CH_3)_2CHCONHCH_3$, $(CH_3)_2CHCON(CH_3)_2$, $(CH_3)_3CCCONH_2$, $(CH_3)_3CCONHCH_3$, $(CH_3)_3CCONHC(CH_3)_3$, $(CH_3)_3CCON(CH_3)_2$, $(CH_3)_3CCON(C_2H_5)_2$, and $C_6H_5CONH_2$. The chloroamides $CH_3CHClCONH_2$, $CH_2ClCH_2CONH_2$, and $CH_2ClCONHC(CH_3)_3$ were allowed to react with hydrated electrons to generate specific radicals by displacement of chloride. The generality of the spectral features of radicals of the type $RCON(R')\dot{C}<$ in the wavelength range 230–600 nm has been verified. These include a peak with λ_{max} in the region 235–248 nm and ϵ_{max} in the range 7000–9000 M^{-1} cm^{-1}, and another with λ_{max} at 340–390 nm and ϵ_{max} 1600–2600 M^{-1} cm^{-1}. The absorption spectra of radicals produced by abstraction of an α hydrogen consist of single peaks with $\epsilon_{max} \sim 1000$ M^{-1} cm^{-1} and λ_{max} at >340 nm, and are shifted bathochromically by N-alkylation and hypsochromically by α-alkylation. Radicals produced by abstraction of hydrogen from methyl groups which are β to either carbonyl or amido nitrogen absorb at short wavelengths, with λ_{max} <230 nm. Combination of spectral data with rate constant values of k(OH + amide) provides values of specific rates of attack at different sites. It is seen that for these reactions, the rates of which are only one or two orders of magnitude below the diffusion-controlled limit, reactivity varies systematically with molecular environment; *e.g.*, α-methylation increases and N-alkylation decreases the rate of abstraction of α hydrogen. Isolation of $CH_3CON(CH_3)CH_2CH_2N(CH_3)COCH_3$ from reaction of aqueous $CH_3CON(CH_3)_2$ with OH generated by steady radiolysis confirmed previous assignment of the principal site of attack on this molecule.

An investigation by means of pulse radiolysis and kinetic spectroscopy of the reaction of OH radicals with aqueous formamide, acetamide, and their N-methylated derivatives was recently reported.[3] It was found that radicals produced by abstraction of hydrogen from methyl bound to the carbonyl group have a single characteristics absorption maximum with λ_{max} in the range 380–500 nm and $\epsilon_{max} \sim 1000$ M^{-1} cm^{-1}. Radicals produced by abstraction of hydrogen from methyl bound to nitrogen were found to have two characteristic intense absorption bands with λ_{max} respectively in the range 235–250 and 340–380 nm and with $\epsilon_{230}/\epsilon_{350} \sim 3$. The rate of attack at an *N*-methyl group was found to be at least an order of magnitude greater than the rate of attack at an α-methyl, a result which is in agreement with a study[4] of the sites of attack of free radicals on simple peptides. The research reported here explores the effects of branching at the carbon atoms bound to carbonyl or to the nitrogen atom upon the reaction of OH radicals with aqueous amides, and upon the absorption spectra of the resulting radicals.

Experimental Section

The pulse radiolysis of aqueous solutions in the presence of N_2O (1 atm to convert >98% of the hydrated electrons into OH radicals) was used to generate OH radicals. Reactions of chloro derivatives of amides with hydrated electrons were effected by pulsing solutions containing an excess of *tert*-butyl alcohol (to scavenge all OH radicals) under an atmosphere of argon. A Febetron 705 (Field Emission Corp.) pulsed-radiation source was used to produce single ~30-nsec pulses of 2.3-MeV electrons. The 450-W xenon lamp used as monitoring light was pulsed for short durations of 1–2 msec to increase the output of light. A double monochromator reduced the scattered light at wavelengths below ~260 nm. The details of the experimental conditions have been described elsewhere.[3,5-7]

The amides used in this work were either synthesized or repurified from commercially available sources. The following amides, obtained from Eastman, were recrystallized from the indicated solvents: $CH_3CH_2CONH_2$, ethyl acetate, mp 80–80.5°; $(CH_3)_2CHCONH_2$, ethyl acetate, mp 127–128°; *tert*-$BuCONHCH_3$, petroleum ether, mp 89–90°; $CH_3CON(C_2H_5)_2$, utilized as received; $CH_3CH_2CONHCH_3$, distilled, bp 66° (0.2 Torr). Amides obtained from Aldrich, the solvents used in their recrystallization, and their melting points are: $ClCH_2CH_2CONH_2$, benzene, 102–102.5°, and *tert*-$BuCONH_2$, acetone, 157–157.5°. Benzamide was recrystallized twice.

Several amides were prepared by adding 0.1 *M* ethereal acyl chloride drop by drop at −5° to a stirred ethereal solution of the appropriate amine, storing the resulting solution at room temperature for 2 hr, refluxing for 1 hr, filtering the precipitated amine hydrochloride, washing it with ether, evaporating the combined dehydrated (with anhydrous Na_2SO_4) filtrate and washings to dryness, and recrystallizing from ether–petroleum ether or distilling. The amides prepared in ethereal solution and their melting or boiling points are: $CH_3CONHC(CH_3)_3$, ether–petroleum ether, mp 96–97.5°; $CH_3CON(CH_3)C(CH_3)_3$, bp 50° (0.7 Torr); $ClCH_2CONHC(CH_3)_3$, mp 82–83°; $(CH_3)_3CCONHC(CH_3)_3$, mp 118–118.7°. Other amides were prepared by adding a 0.1 *M* aqueous

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(2) National Academy of Science–National Research Council Research Associate at the Natick Laboratories.

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solution of the acyl chloride dropwise to a stirred aqueous solution of the amine or ammonia at −5°, storing the resulting solution at room temperature for 2 hr, extracting continuously with ether, and distilling the amide under reduced pressure or recrystallizing it from ether–petroleum ether. Where ir spectra indicated small amounts of carboxylic acid impurity, the product was stored over sodium bicarbonate and redistilled. The amides prepared in aqueous solution were $(CH_3)_2CHCONHCH_3$; $(CH_3)_2CHCON(CH_3)_2$; $(CH_3)_3CCON(CH_3)_2$, bp 56° (0.9 Torr); $(CH_3)_3CCON(C_2H_5)_2$, bp 79°, (0.9 Torr); $CH_3CHClCONH_2$, mp 78–79.5°. The structure and purity of all the synthesized amides were verified by ir and nmr spectroscopy.

A 0.1 *M* aqueous solution of $CH_3CON(CH_3)_2$ was exposed to a dose of $\sim 10^7$ rads of ^{60}Co γ rays under 1 atm of N_2O. The resulting solution was concentrated under reduced pressure to 2% of its original volume, extracted with cold ether to remove starting material, and extracted several times with hot 2:1 ether–acetone. The white needles which precipitated from the latter extract upon standing were identified as $CH_3CON(CH_3)CH_2CH_2N(CH_3)COCH_3$ by their elemental analysis and by comparison of their melting point (93–94°) and ir and nmr spectra with those of authentic material synthesized from CH_3COCl and $CH_3NHCH_2NHCH_3$, as well as by the melting point of mixed radiolytic and synthetic products.

Solutions for pulse radiolysis were prepared in water purified by triple distillation, radiolysis, and photolysis. Absorbances were measured 0.5 μsec or less after the electron pulse, using quartz optical cells of 2-cm optical path length.

The results presented here indicate that H atoms do not contribute to the transient absorptions observed.

Results

The rates of reaction of OH radicals with various amides in aqueous solution were determined at pH 5–6 by competition with 10^{-2} *M* thiocyanate, in the presence of 1 atm of N_2O, as has been described previously.[3]

$$OH + CNS^- \longrightarrow CNS\cdot + OH^- \quad (1)$$

$$CNS\cdot + CNS^- \rightleftharpoons (CNS)_2^- \quad (2)$$

$$OH + \text{amide} \longrightarrow \text{radical}$$

The resulting rate constants are presented in Table I along with those previously reported[3]. Not surprisingly for reactions as rapid as these, the variation in k(OH + amide) is not great, amounting to an overall range of a factor of 20. However, when the rate data are considered in conjunction with the spectra of the transients, rates of attack at specific molecular sites can be estimated. These estimates and their variation with structure are taken up in the Discussion section.

Table I. Rates of Reaction of OH Radicals with Aqueous Amides at pH 5–6, Determined by Competition with Thiocyanate[a]

Amide	Concn range, m*M*	k_1/k_2[b]	k(OH + amide), M^{-1} sec^{-1}
$HCONHCH_3$[c]	25–100	9.2	1.2×10^9
$HCON(CH_3)_2$[c]	5–100	6.5	1.7×10^9
CH_3CONH_2[c]	20–100	58.0	1.9×10^8
$CH_3CONHCH_3$[c]	25–100	6.9	1.6×10^9
$CH_3CON(CH_3)_2$[c]	24–72	3.1	3.5×10^9
$CH_3CH_2CONH_2$	20–150	15.7 ± 1.6	7.0×10^8
$CH_3CH_2CONHCH_3$	20–130	7.7 ± 0.5	1.4×10^9
$(CH_3)_2CHCONH_2$	25–150	7.0 ± 0.4	1.6×10^9
$(CH_3)_2CHCONHCH_3$	9–70	5.7 ± 0.3	1.9×10^9
$(CH_3)_3CCONH_2$	10–100	7.6 ± 0.6	1.4×10^9
$(CH_3)_3CCONHCH_3$	10–60	4.6 ± 0.4	2.4×10^9
$(CH_3)_3CCON(CH_3)_2$	5–55	2.8 ± 0.2	4.0×10^9
$CH_3CONHC(CH_3)_3$	10–60	9.7 ± 0.9	1.1×10^9

[a] k(OH+SCN$^-$) taken as 1.1×10^{10} M^{-1} sec^{-1} (ref 6). [SCN$^-$] = 10^{-2} *M*. [b] Based on measurements at four or five different concentrations of amide. Uncertainties are mean deviations. [c] Taken from ref 3.

The rates of reaction of hydrated electrons with a number of amides were determined at pH 9.2, using a borate buffer, and are presented in Table II. In all cases, 0.5 *M* *tert*-butyl alcohol was added to ascertain complete removal of the OH radicals. It is interesting to note that the reactivity of hydrated electrons with formamides is significantly higher than with the corresponding acetamides. A similar effect was observed[8] with acyl derivatives of glycine: $k(e^-_{aq} + HCONHCH_2COO^-) = 2.9 \pm 0.3 \times 10^7$ M^{-1} sec^{-1} and $k(e^-_{aq} + CH_3CONHCH_2COO^-) = 2.6 \pm 0.3 \times 10^6$ M^{-1} sec^{-1}. Since hydrated electrons add[8] to carbonyl peptides, the stronger electron-donating property of the methyl group in an α position reduces the rate of reaction of the acetamides with hydrated electrons.

Table II. Rates of Reaction of Hydrated Electrons with Amides in Aqueous Solution, Determined at pH 9.2

Amide	$k(e^-_{aq} + \text{amide})$, M^{-1} cm^{-1}
$HCONH_2$	6.3×10^7 (4.2×10^7)[7]
$HCONHCH_3$	7.1×10^7
$HCON(CH_3)_2$	4.6×10^8 [a]
CH_3CONH_2	3.5×10^7 (1.7×10^7)[7]
$CH_3CON(CH_3)_2$	2.1×10^7
$CH_3CON(C_2H_5)_2$	8.0×10^6
$CH_3CH_2CONH_2$	5.4×10^7
$(CH_3)_3CCONH_2$	1.5×10^7
$(CH_3)_3CCON(CH_3)_2$	1.2×10^7
$CH_3CONHC(CH_3)_3$	1.2×10^7

[a] Fresh spectrograde DMF was used; impurities might account, however, for the unexpected high rate constant.

Spectra of the transients produced by attack of OH radicals on the various amides are presented in Figures 1–8. Assignments of spectral features to particular radicals as well as values of λ_{max}, ϵ_{max}, and specific rates for radical–radical disappearance are summarized in Table III. Estimation of the latter two quantities is taken up in the Discussion section.

Figure 1 shows that the transient spectra produced from $CH_3CH_2CONH_2$ at pH 5.3 and 11.8 are identical. These spectra can be compared with those of $CH_3\dot{C}HCONH_2$ and $\dot{C}H_2CH_2CONH_2$ produced by reaction of hydrated electrons with $CH_3CHClCONH_2$ and $ClCH_2CH_2CONH_2$, eq 3 and 4. That attack of

$$CH_3CHClCONH_2 + e^-_{aq} \longrightarrow CH_3\dot{C}HCONH_2 + Cl^- \quad (3)$$

$$CH_2ClCH_2CONH_2 + e^-_{aq} \longrightarrow \dot{C}H_2CH_2CONH_2 + Cl^- \quad (4)$$

OH radicals occurs at both the α and β positions is apparent. Approximately 45% of the attack occurs at the α position. Absorption below 250 nm is due to the $\dot{C}H_2CH_2CONH_2$ radical, with some contribution from $CH_3CH_2C\dot{O}NH$.[3] It is noteworthy that the spectrum of the β radical has no maximum within the experimentally accessible wavelength range above ~230 nm. The transient spectrum produced by attack of OH on $CH_3CH_2CONHCH_3$ is shown in Figure 2. This spectrum is characterized by two maxima, similar to those observed with the *N*-methyl derivatives of formamide and acetamide, and assigned primarily to

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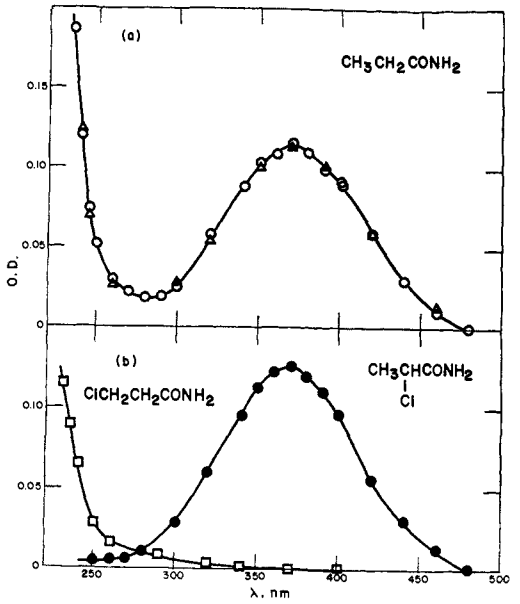

Figure 1. Transient spectra from the pulse radiolysis of aqueous solutions of (a) 5×10^{-2} *M* $CH_3CH_2CONH_2$ in the presence of N_2O (1 atm) at pH 5.3 (○) and 11.8 (△) and (b) 10^{-2} *M* $CH_3CHClCONH_2$ (●) and 10^{-2} *M* $ClCH_2CH_2CONH_2$ (□) in the presence of 1.0 *M* *tert*-BuOH and argon (1 atm) at pH 9.2. Dose per pulse ~19 krads.

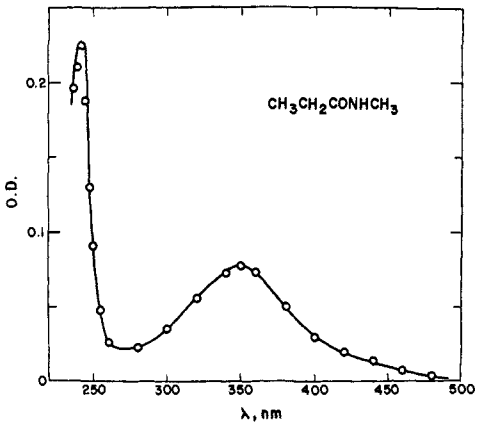

Figure 2. Transient spectrum from the pulse radiolysis of N_2O-saturated (1 atm) aqueous solutions of 5×10^{-2} *M* $CH_3CH_2CONHCH_3$ at pH 5.9. Dose per pulse ~3.9 krads.

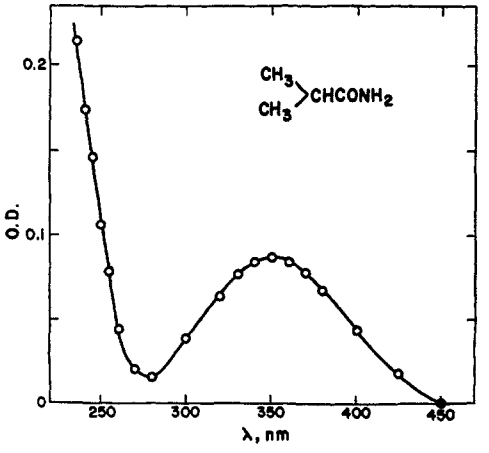

Figure 3. Transient spectrum from the pulse radiolysis of N_2O-saturated (1 atm) aqueous solutions of 2×10^{-2} *M* $(CH_3)_2CHCONH_2$ at pH 6.2. Dose per pulse ~19 krads.

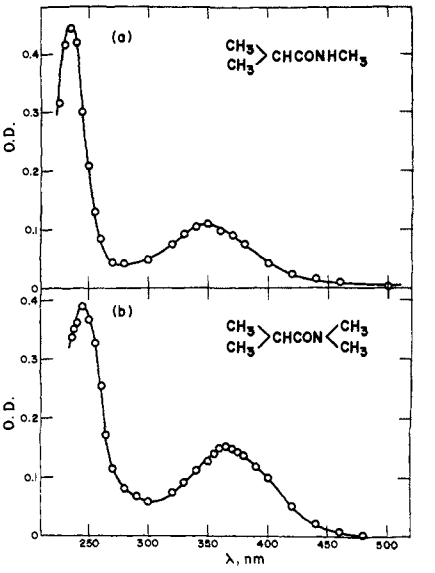

Figure 4. Transient spectra from the pulse radiolysis at pH 5.0 of N_2O-saturated (1 atm) aqueous solutions of (a) 5×10^{-2} *M* $(CH_3)_2CHCONHCH_3$ and (b) 5×10^{-2} *M* $(CH_3)_2CHCON(CH_3)_2$. Dose per pulse ~8 krads.

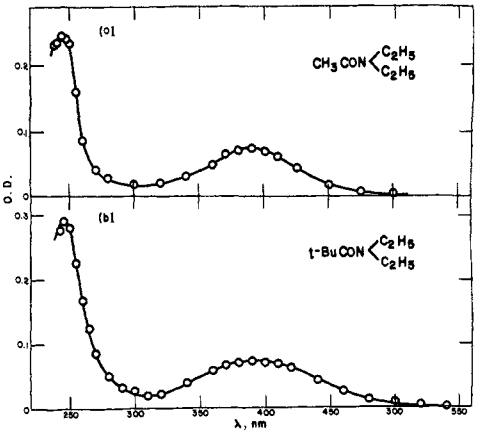

Figure 5. Transient spectra from the pulse radiolysis of N_2O-saturated (1 atm) aqueous solutions at pH 5.8 of (a) 5×10^{-2} *M* $CH_3CON(C_2H_5)_2$ and (b) *tert*-$BuCON(C_2H_5)_2$. Dose per pulse ~3.9 krads.

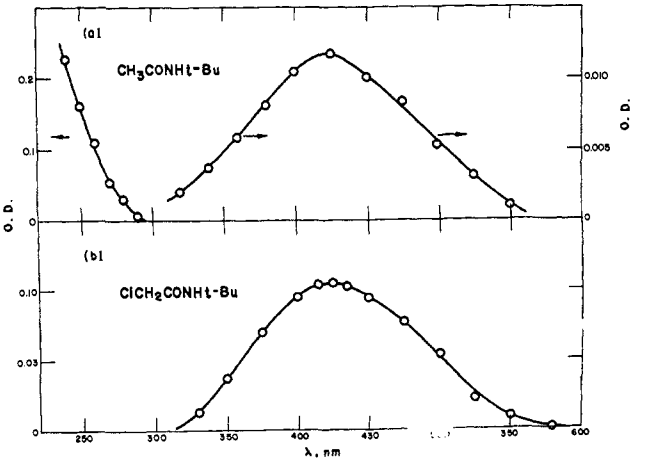

Figure 6. Transient spectra from the pulse radiolysis of aqueous solutions of (a) 5×10^{-2} *M* CH_3CONH-*tert*-Bu, N_2O (1 atm), pH 5.5, and (b) 10^{-2} *M* $ClCH_2CONH$-*tert*-Bu in the presence of 1.0 *M* *tert*-BuOH, argon (1 atm), pH 5.0. Dose per pulse ~19 krads.

Table III. Absorption Maxima, Extinction Coefficients, and Rate Constants for Decay of Transient Species Produced from the Reaction of OH Radicals with Amides at pH 5–6

Amide	Suggested radical	λ_{max}, nm	ϵ, M^{-1} cm^{-1} [a]	$2k$, M^{-1} sec^{-1}
$CH_3CH_2CONH_2$	$CH_3\dot{C}HCONH_2$	370	1180[b]	3.2×10^9
	$\dot{C}H_2CH_2CONH_2$	<235[d]	>1080[c]	
$CH_3CH_2CONHCH_3$	$CH_3CH_2CONH\dot{C}H_2$	350	>1800	2.1×10^9
	$CH_3CH_2CONH\dot{C}H_2$	242[e]	>5200	
$(CH_3)_2CHCONH_2$	$(CH_3)_2\dot{C}CONH_2$	350	>820	$>2.2 \times 10^9$
	$\dot{C}H_2(CH_3)CHCONH_2$	<235[f]	>2101	
$(CH_3)_2CHCONHCH_3$	$(CH_3)_2CHCONH\dot{C}H_2$	350[g]	>1200	$>1.3 \times 10^9$
	$(CH_3)_2CHCONH\dot{C}H_2$	235	>5050	$>1.2 \times 10^9$
$(CH_3)_2CHCON(CH_3)_2$	$(CH_3)_2CHCON\dot{C}H_2(CH_3)$	365[h]	>1700	$>1.5 \times 10^9$
	$(CH_3)_2CHCON\dot{C}H_2(CH_3)$	245	>4400	$>1.6 \times 10^9$
$(CH_3)_3CCONH_2$	$\dot{C}H_2(CH_3)_2CCONH_2$	<240	>1100	1.3×10^9
$(CH_3)_3CCONHCH_3$	$(CH_3)_3CCONH\dot{C}H_2$	340	>1030	$>1.6 \times 10^9$
	$(CH_3)_3CCONH\dot{C}H_2$	240[i]	>4350	$>2.6 \times 10^9$
$(CH_3)_3CCON(CH_3)_2$	$(CH_3)_3CCON\dot{C}H_2(CH_3)$	370	>1750	1.4×10^9
	$(CH_3)_3CCON\dot{C}H_2(CH_3)$	247	>6400	
$(CH_3)_3CCON(C_2H_5)_2$	$(CH_3)_3CCON\dot{C}HCH_3(C_2H_5)$	390	1700	1.2×10^9
	$(CH_3)_3CCON\dot{C}HCH_3(C_2H_5)$	243	6700	1.1×10^9
$(CH_3)_3CCONHC(CH_3)_3$	*j*	<250	> 800	
$CH_3CONHC(CH_3)_3$	$\dot{C}H_2CONHC(CH_3)_3$	425	1000[k]	2.2×10^9
	$CH_3CONHC\dot{C}H_2(CH_3)_2$	<240	>1100	1.1×10^9
$CH_3CON(CH_3)C(CH_3)_3$	$CH_3CON(\dot{C}H_2)C(CH_3)_3$	370	>1100	$>1.5 \times 10^9$
	$CH_3CON(\dot{C}H_2)C(CH_3)_3$	248[l]	>5300	$>1.5 \times 10^9$
$CH_3CON(C_2H_5)_2$	$CH_3CON\dot{C}HCH_3(C_2H_5)$	390	1750	1.6×10^9
	$CH_3CON\dot{C}HCH_3(C_2H_5)$	242[m]	5700	1.6×10^9
$C_6H_5CONH_2$	$OH\dot{C}_6H_5CONH_2$	~335	3500	1.0×10^9

[a] Calculated on the basis of $G(e_{aq}^-) = 2.7$ and $G(OH)_{N_2O} = 5.5$. [b] Determined by reaction of hydrated electrons with $CH_3CHClCONH_2$. [c] Determined by reaction of hydrated electrons with $ClCH_2CH_2CONH_2$. [d] May include contribution from $CH_3CH_2C\dot{O}NH$. [e] May include contribution from $\dot{C}H_2CH_2CONHCH_3$. [f] Includes some contribution from $(CH_3)_2CHC\dot{O}NH$. [g] Includes some contribution from $(CH_3)_2\dot{C}CONHCH_3$. [h] Includes some contribution from $(CH_3)_2\dot{C}CON(CH_3)_2$. [i] Includes contributions from $\dot{C}H_2(CH_3)_2CCONHC(CH_3)_3$ and $(CH_3)_3CCONHC\dot{C}H_2(CH_3)_2$. [k] Determined by reaction of hydrated electrons with $ClCH_2CONHC(CH_3)_3$. [l] May include contribution from $CH_3CON(CH_3)C(\dot{C}H_2)(CH_3)_2$. [m] May include contributions from $CH_3CON(CH_2\dot{C}H_2)C_2H_5$.

radicals produced by abstraction of H from methyl bound to nitrogen, eq 5. Also present is a long-wave-

$$R'CONRCH_3 + OH \longrightarrow R'CONR\dot{C}H_2 + H_2O \quad (5)$$

length tail which is too intense to be ascribed to the α

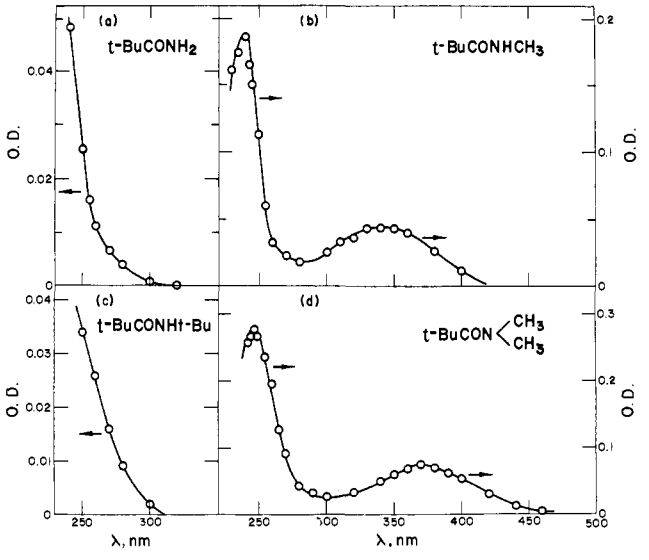

Figure 7. Transient spectra from the pulse radiolysis of N_2O-saturated (1 atm) aqueous solutions at pH ~5.0 of (a) 5×10^{-2} *M* *tert*-$BuCONH_2$, (b) 5×10^{2} *M* *tert*-$BuCONHCH_3$, (c) 10^{-2} *M* *tert*-BuCON-*tert*-Bu, and (d) 5×10^{-2} *M* *tert*-$BuCON(CH_3)_2$. Dose per pulse ~3.9 krads.

radical. A similar feature is present in the transient spectrum produced from *N*,*N*-dimethylacetamide.[3] The transient spectrum produced from isobutyramide, shown in Figure 3, is similar to that produced from propionamide. It can be seen that λ_{max} of the α radical shifts

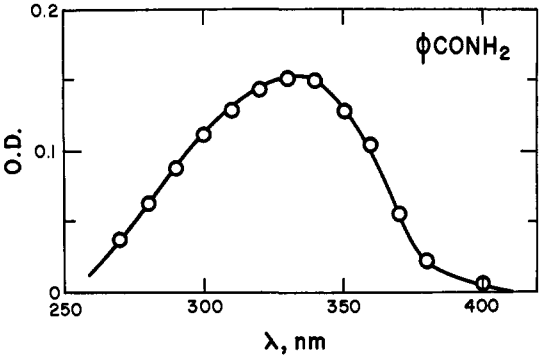

Figure 8. Transient spectrum from the pulse radiolysis of N_2O-saturated (1 atm) 10^{-3} *M* benzamide at pH 5.0. Dose per pulse ~4 krads.

to shorter wavelengths with increasing substitution at that position: $\dot{C}H_2CONH_2$, 400 nm; $CH_3\dot{C}HCONH_2$, 370 nm; $(CH_3)_2\dot{C}CONH_2$, 350 nm. The transient spectra produced from the *N*-methyl and *N*,*N*-dimethyl derivatives of butyramide, shown in Figure 4, possess the two maxima characteristic of radicals produced by abstraction of H from the N-CH_3 group, as well as a long-wavelength tail which cannot be due to the α radical. The transient spectra produced from the *N*,*N*-diethyl derivatives of acetamide and pivalamide, shown in Figure 5, resemble those produced from the N-

methylated amides. They are very similar to each other, suggesting that the principal site of attack is at their common structural feature, the *N*-ethyl group, presumably at the carbon atom adjacent to nitrogen. In Figure 6 the transient spectrum produced by attack of OH on *N-tert*-butylacetamide is compared with that of the $\dot{C}H_2CONHC(CH_3)_3$ radical produced by the reaction of hydrated electrons with $ClCH_2CONHC(CH_3)_3$. These spectra show that only ~5% of the attack of OH occurs at the α position. The transient spectrum produced by the attack of OH on $CH_3CON(CH_3)C(CH_3)_3$ shows the two peaks typical of abstraction of H from the *N*-methyl group (spectrum not given). Figure 7 displays the transient spectra produced by attack of OH on pivalamide and its *N-tert*-butyl, *N*-methyl, and *N,N*-dimethyl derivatives. Only short-wavelength absorption, without a maximum in the accessible region, is observed for the former two and is presumably due to radicals produced by abstraction of H from terminal methyl groups and amido nitrogen. The N-methylated derivatives yield spectra similar to those observed for all the other *N*-methylamides.

The more intense short-wavelength maxima (see also ref 3) of the two bands assigned to $R'CONR\dot{C}H_2$ all fall in a narrow wavelength region: 235–242 nm for *N*-monomethyl derivatives and 245–248 nm for the *N,N*-dimethyl compounds. The less intense longer wavelength maxima are observed over a wide range, 340–380 nm, and λ_{max} obtained with the dimethyl derivative of a given amide falls 10–30 nm higher than that observed with the corresponding monomethyl derivatives. Absorption which can be assigned to the methylene radical bound to saturated carbon, $\geqslant C-\dot{C}H_2$, is in every case at short wavelengths, with λ_{max} inaccessible to measurement due to absorption by the amide group.

The present and previous data[3] show that N-alkylation shifts λ_{max} of α radicals to longer wavelengths.

The transient spectrum arising from attack of OH radicals on an aromatic amide, benzamide, is shown in Figure 8. It differs from all those produced by attack of OH on aliphatic amides in that no peak is apparent below 300 nm. It can be ascribed to substituted cyclohexadienyl radicals resulting from addition of OH to the benzene ring.[9]

Originally,[3] assignment of the spectral features of radicals formed by abstraction of hydrogen from *N*-methyl groups was done by a process of elimination. This assignment has been strengthened in the present work by demonstrating its generality. Further evidence stems from the identification of $CH_3CON(CH_3)CH_2CH_2N(CH_3)COCH_3$ as the only product isolated from the steady irradiation of $CH_3CON(CH_3)_2$ under an atmosphere of N_2O.

Discussion

The values of the molar extinction coefficients (ϵ) presented in Table III were derived on the basis of complete scavenging of the OH radicals, or hydrated electrons, produced in the pulse by the amides present in the solution. For many of the aliphatic amides studied in the present work, however, attack by OH occurs competitively at two or more molecular sites. The fraction of reaction at a given site must be estimated in order to evaluate the concentration of the resulting radical and the corresponding magnitude of ϵ. Conversely, comparison of the relative magnitudes of the resulting values of ϵ can provide a test of the estimations of rates of attack at various sites. These rates are summarized in Table IV.

Table IV. Estimated Rates of Abstraction per Hydrogen Atom

Type of hydrogen atom	Molecular environment	Rate, 10^8 M^{-1} sec^{-1}
N–H	$RCONH_2$	0.5[a]
N–H	RCONHR	0.5–<2.5
α-CH	CH_3CONH_2	0.33[a]
α-CH	$CH_3CONHCH_3$; $CH_3CON(CH_3)_2$	<0.33
α-CH	$CH_3CONHC(CH_3)_3$	0.19[a]
α-CH	$CH_3CH_2CONH_2$	1.6[a]
α-CH	$CH_3CH_2CONHCH_3$	<1.6
α-CH	$(CH_3)_2CHCONH_2$	7.8
α-CH	$(CH_3)_2CHCONHCH_3$	<7.8
β-CH	$CH_3CH_2CONH_2$	1.0
β-CH	$(CH_3)_3CCONH_2$	1.4
N–CH_3	$CH_3CONHCH_3$; $CH_3CON(CH_3)_2$	5.5
N–CH_3	$RCONHCH_3$[b]	3.5
N–CH_3	$(CH_3)_3CCON(CH_3)_2$	4.5
N–$C(CH_3)_3$	$CH_3CONHC(CH_3)_3$	1.0

[a] Determined directly from kinetic and spectroscopic data. [b] R = C_2H_5, $(CH_3)_2CH$, and $(CH_3)_3C$.

Propionamides. Direct characterization of the spectra of $\dot{C}H_2CH_2CONH_2$ and $CH_3\dot{C}HCONH_2$ radicals follows from their formation by reactions 3 and 4, and the data of Figure 1. Figure 1a shows that the same transient spectrum is produced by attack of OH radicals on propionamide at pH 5.3 and 11.8. This result appears to disagree with a recent paper by Chambers, *et al.*,[10] who obtained a transient spectrum, from the reaction of hydrated electrons with aqueous $ClCH_2CH_2CONH_2$ in ethylene-saturated solution at pH 11, with $\lambda_{max} \sim 290$ nm, which was identical with that produced from $CH_2{=}CHCONH_2$ by its reaction with hydrated electrons. These authors explain their data in terms of a set of reactions leading to loss of HCl from a species produced initially by electron addition to β-chloropropionamide. Rapid elimination of HCl from the latter compound itself is, however, to be expected under alkaline conditions; eq 6. In the present work,

$$ClCH_2CH_2CONH_2 + OH^- \longrightarrow CH_2{=}CHCONH_2 + H_2O + Cl^- \quad (6)$$

it was found that at pH 11.0 and room temperature reaction 6 proceeds with $k = 9.5 \times 10^{-5}$ sec^{-1} in 2×10^{-4} *M* aqueous β-chloropropionamide. Acrylamide was identified as the product of reaction 6 by its nmr and uv spectra. Apparently, in the experiments of Chambers, *et al.*,[10] sufficient elimination of HCl took place prior to irradiation that only the intense spectrum of the electron adduct of acrylamide could be observed. In the present work, irradiation of alkaline solutions of β-chloropropionamide was performed sufficiently soon after its dissolution that the amount of elimination of HCl was negligible. The transient spectrum obtained by Chambers, *et al.*,[10] from aqueous

(9) See E. J. Fendler and J. H. Fendler, *Progr. Phys. Org. Chem.*, 7, 260 (1969), for a tabulation of λ_{max} values in HOC_6H_5X radicals.

(10) K. W. Chambers, E. Collinson, and F. S. Dainton, *Trans. Faraday Soc.*, 66, 142 (1970).

α-chloropropionamide at pH 11 is in agreement with that reported here.

Attack of OH on $CH_3CH_2CONHCH_3$ involves reactions 7–10. The spectrum shown in Figure 2 is qualitatively that expected for a radical produced by reaction 7, but the relatively high intensity of the two

$$CH_3CH_2CONHCH_3 + OH \rightarrow \begin{cases} CH_3CH_2CONH\dot{C}H_2 + H_2O & (7) \\ CH_3\dot{C}HCONHCH_3 + H_2O & (8) \\ \dot{C}H_2CH_2CONHCH_3 + H_2O & (9) \\ CH_3CH_2CO\dot{N}CH_3 + H_2O & (10) \end{cases}$$

absorption bands characteristics of such radicals would be expected to dominate over absorption due to lesser or comparable amounts of the other products. Thus the fraction $k_7/\Sigma_7^{10}k_i$ must be evaluated in order to estimate ϵ_{350} and ϵ_{242} for the product of reaction 7. Furthermore, corrections must be made for any absorption in the same region by other radicals.

The value of k_9 can be estimated by assuming that the rate of abstraction of β-hydrogen *per β-methyl group* is approximately independent of the number of such groups and of substitution on amide nitrogen and, similarly, that the rate of abstraction from nitrogen in $RCONH_2$, eq 11, depends but little on the nature of R.

$$RCONH_2 + OH \longrightarrow RCO\dot{N}H + H_2O \quad (11)$$

Since 50% of the total specific rate of attack of OH on acetamide is due to abstraction from nitrogen,[3] the specific rate of reaction 11 (see Table I) can be taken as $\sim 1.0 \times 10^8\ M^{-1}\ sec^{-1}$, leaving $1.3 \times 10^9\ M^{-1}\ sec^{-1}$ as the rate of abstraction of β-hydrogen from $(CH_3)_3CCONH_2$. The resulting value per methyl group of $k(OH + \beta\text{-}CH_3) = 4.3 \times 10^8$ is not greatly different from the value, 2.9×10^8, derived from spectral and rate data for $CH_3CH_2CONH_2$. Their average, *i.e.*, $3.6 \times 10^8\ M^{-1}\ sec^{-1}$, is taken as the specific rate of attack of OH per β-methyl, except for derivatives of pivalamide. An upper limit to the value of k_8 can be estimated from the specific rate of abstraction of α-hydrogen from propionamide which is available from spectral and rate data, $3.2 \times 10^8\ M^{-1}\ sec^{-1}$, by assuming that alkyl substituents on nitrogen do not increase the rate of abstraction of α-hydrogen atoms. Evidence presented below suggests that they probably inhibit α abstraction. The lower limit of k_8 can be taken as negligible compared to k_9, *i.e.*, $k_8 < 10^8\ M^{-1}\ sec^{-1}$.

The value of k_{10} may possibly be greater than the value per hydrogen atom of abstraction of amido hydrogen from acetamide. An upper limit can be estimated by analogy to the effect of one β-methyl group on the rate of abstraction of α-hydrogen. Thus $k_{10} \sim 0.5\text{–}2.5 \times 10^8$, and it follows that $k_7 \sim 0.5\text{–}1.0 \times 10^9\ M^{-1}\ sec^{-1}$. Maximum corrections for absorption at 350 nm by $CH_3\dot{C}HCONHCH_3$ and at 242 nm by both $\dot{C}H_2CH_2CONHCH_3$ and $CH_3CH_2CO\dot{N}CH_3$ can be estimated from available spectroscopic and rate data to be no more than about 6% of total absorbance.

Isobutyramides. Application of the same analysis to $(CH_3)_2CHCONH_2$ leads to $k_{13} \sim 7 \times 10^8$ and $k_{12} \sim 8 \times 10^8\ M^{-1}\ sec^{-1}$. Attack on *N*-methylbutyramide can

$$(CH_3)_2CHCONH_2 + OH \rightarrow \begin{cases} (CH_3)_2\dot{C}CONH_2 + H_2O & (12) \\ CH_3(\dot{C}H_2)CHCONH_2 + H_2O & (13) \end{cases}$$

take place at four structurally distinct positions, as shown in eq 14–17. Estimation of rates of attack at the

$$(CH_3)_2CHCONHCH_3 + OH \rightarrow \begin{cases} (CH_3)_2CHCONH\dot{C}H_2 + H_2O & (14) \\ (CH_3)_2\dot{C}CONHCH_3 + H_2O & (15) \\ \dot{C}H_2(CH_3)CHCONHCH_3 + H_2O & (16) \\ (CH_3)_2CHCO\dot{N}CH_3 + H_2O & (17) \end{cases}$$

various positions by the procedures employed for $CH_3CH_2CONHCH_3$ leads to the values $k_{15} < 8 \times 10^8$, $k_{16} \sim 7 \times 10^8$, $k_{17} \sim 0.5\text{–}2.5 \times 10^8$, and $k_{14} \sim 0.2\text{–}1.1 \times 10^9\ M^{-1}\ sec^{-1}$. Correction for absorption by $(CH_3)_2CHCO\dot{N}CH_3$ at 235 nm is negligible and for absorption by $\dot{C}H_2(CH_3)CHCONHCH_3$ can be estimated from the data of Figure 3. Uncertainty as to the correct value of k_{17} and lack of information as to ϵ_{350} of $(CH_3)_2\dot{C}CONHCH_3$ hinders correction for absorption at 350 nm by the α radical. However, its maximum contribution can be no more than about 10% of the observed absorption.

Pivalamides. Assignment of relative rates of attack at the two different sites of $(CH_3)_3CCONH_2$ is made above. Absorption by $(CH_3)_3CCO\dot{N}H$ at 240 nm can be neglected in assigning ϵ_{240} to $\dot{C}H_2(CH_3)_2CCONH_2$. The wavelength of the absorption maximum is below the experimentally accessible region, however.

Three reactions are expected with $(CH_3)_3CCONHCH_3$, as represented in eq 18–20. Their specific rates,

$$(CH_3)_3CCONHCH_3 + OH \rightarrow \begin{cases} (CH_3)_3CCONH\dot{C}H_2 + H_2O & (18) \\ \dot{C}H_2(CH_3)_2CCONHCH_3 + H_2O & (19) \\ (CH_3)_3CCO\dot{N}CH_3 + H_2O & (20) \end{cases}$$

estimated as above, are $k_{19} \sim 1.3 \times 10^9$, $k_{20} \sim 0.5\text{–}2.5 \times 10^8$, and $k_{18} \sim 0.8\text{–}1.0 \times 10^9\ M^{-1}\ sec^{-1}$. The usual analysis gives, for *N,N*-dimethylpivalamide, $k_{21} \sim 2.7 \times 10^9\ M^{-1}\ sec^{-1}$.

$$(CH_3)_3CCON(CH_3)_2 + OH \longrightarrow (CH_3)_3CCONCH_2(CH_3) + H_2O \quad (21)$$

The radicals produced by attack of OH at each of the three sites of $(CH_3)_3CCONHC(CH_3)_3$ are expected to absorb at short wavelengths with λ_{max} for each below the experimentally accessible region. Presumably, most of the observed absorption is due to abstraction of hydrogen from methyl groups.

Acetamides. Hydroxyl radical is expected to attack *N-tert*-butylacetamide at three sites, as shown in eq 22–24. Combination of the spectral data of Figure 6

$$CH_3CONHC(CH_3)_3 + OH \rightarrow \begin{cases} CH_3CONHCCH_2(CH_3)_2 + H_2O & (22) \\ \dot{C}H_2CONHC(CH_3)_3 + H_2O & (23) \\ CH_3CO\dot{N}C(CH_3)_3 + H_2O & (24) \end{cases}$$

and rate data of Table I gives $k_{23} \sim 6.0 \times 10^7\ M^{-1}\ sec^{-1}$. Actually, ~7% of the OH radicals appear to react *via* reaction 23. The usual assumptions concerning k_{24} give $k_{22} \sim 0.8\text{–}1.0 \times 10^9\ M^{-1}\ sec^{-1}$. It is noteworthy that substitution of amido hydrogen by the *tert*-butyl group reduces the rate of attack at the α position to about one-half of its value in acetamide. The attack of hydroxyl on *tert*-butyl bound to nitrogen

appears to be somewhat slower (60–75%) than its attack on *tert*-butyl bound to carbonyl.

The attack of OH upon $CH_3CON(CH_3)C(CH_3)_3$ is expected to proceed *via* reaction 25, in addition to

$$CH_3CON(CH_3)C(CH_3)_3 + OH \longrightarrow CH_3CON(\dot{C}H_2)C(CH_3)_3 + H_2O \quad (25)$$

reactions analogous to eq 22 and 23. Although the specific rate of attack of OH on this substrate was not determined, the kinetics available for $CH_3CONHC(CH_3)_3$, and the extensive evidence that the specific rate of attack on an $N-CH_3$ group is about 1×10^9 M^{-1} sec^{-1}, leads to the estimate that $\geq 50\%$ of the attack of OH on $CH_3CON(CH_3)C(CH_3)_3$ is *via* reaction 25, while most of the balance is *via* the analog of reaction 22.

The principal expected mode of attack of OH upon *N*,*N*-diethylacetamide is represented by eq 26. However, a significant contribution from reaction 27 is possible.[11]

$$CH_3CON(C_2H_5)_2 + OH \longrightarrow \begin{cases} CH_3CON\dot{C}HCH_3(C_2H_5) + H_2O & (26) \\ CH_3CON(CH_2\dot{C}H_2)(C_2H_5) + H_2O & (27) \end{cases}$$

Benzamide. Attack of OH on benzamide is expected to produce a mixture of 2-, 3-, and 4-hydroxy-1-carboxamidocyclohexadienyl radicals. Their spectra are not resolved in Figure 8. Treatment of the data as if only one radical were formed provides the data entered in Table III.

Rate Constants for Attack at Various Sites. Comparison of values of ϵ_{max} and recombination rate constants for radicals produced by abstraction of hydrogen from *N*-methyl groups determined in the present or previous[3] work, or estimated in this work, indicates that greatest consistency is obtained if estimated values are based on the upper limits of estimated rates of these abstraction reactions. The value of ϵ_{max} for the various $-CON\dot{C}H_2$ radicals selected in this way fall in the range 7000–9000 M^{-1} cm^{-1} for the short-wavelength peak and 1600–2600 M^{-1} cm^{-1} for the long-wavelength peak.

Table IV summarizes rate constants for abstraction of H atoms from various sites obtained either directly or by the methods of estimation indicated above. Although measured rate constants are only one or two orders of magnitude less than diffusion-controlled rates, systematic differences in reactivity are apparent. Thus hydrogen in an α-methyl group is less reactive than in a β-methyl group. β-Methyl groups enhance the reactivity of α-hydrogen. *N*-Alkyl groups reduce the reactivity of α-hydrogen. The hydrogen atoms of $N-CH_3$ groups are more reactive than those of any other methyl group examined.

Similar effects of alkyl substituents at sites of abstraction of hydrogen from carbon by hydroxyl radicals were deduced previously[12] from data based on steady radiolysis of alcohols, ethers, carboxylate ions, and polyhydroxy compounds in aqueous solution. Similar rate enhancement by alkyl substituents has also been observed in the much slower abstraction reactions *in the gas phase* of peroxy[13] and methyl[14] radicals, as well as in the fast reactions of Cl atoms.[15,16] The rate of abstraction by gaseous Cl atoms of hydrogen bonded to carbon atoms adjacent to the carbonyl groups of esters and acid chlorides is reduced,[15] much as was found in the present work for attack of OH radicals at the α position of amides.

Apparently solvation does not play a dominant role in determining the reactivity of different sites toward abstraction by hydroxyl radicals in aqueous solution. Enhancement of reactivity by alkyl substituents can be correlated with reduction in C–H bond energies and the associated lowering of the energy of the transition states. A similar explanation may be appropriate for the enhanced reactivity of methyl groups bound to amide nitrogen. Reduced reactivity of the position α to carbonyl groups toward abstraction by OH or Cl radicals presumably is caused by increased dipole–dipole repulsion in the transition states. Reduction in reactivity α to the carbonyl group by alkyl substitution on amide nitrogen can be accounted for on steric grounds.

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