Kinetic Studies of Reactions Involving Biradicals and Diamagnetic Zwitterions

William G. Espersen and Robert Kreilick[1]

Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627. *Received December 17, 1969*

Abstract: We have investigated the kinetics of a series of reactions in which diamagnetic zwitterions are in equilibrium with biradicals. The variation in the line width of the nmr peaks from the zwitterions has been used to determine rate constants. A second reaction which interconverted the magnetically nonequivalent ends of the zwitterion was also investigated. Both reactions were studied in a series of solvents over as wide a range of temperatures as possible.

The kinetics of reactions which involve an equilibrium between diamagnetic and paramagnetic molecules may be investigated by monitoring the line width of nmr peaks from the diamagnetic species. The kinetics of electron exchange reactions,[2] hydrogen atom transfer reactions,[3] and radical–radical dimerization reactions[4] have been studied by this technique. Nuclei in the reacting molecules experience a variation of their magnetic environment as the molecules vary between the diamagnetic and paramagnetic states. When the nuclei are in a diamagnetic molecule they experience the external magnetic field and the small local fields which produce chemical shifts. When the nuclei are in a paramagnetic molecule they may also experience the field resulting from the electron–nuclei contact interaction.

The variation in magnetic environment may affect the line width of the nmr peaks from the diamagnetic species. The general equation for the contribution which exchange reactions of this type make to the line width, $(1/T_2)$, is given by[3]

$$\left(\frac{1}{T_2}\right) = \frac{1}{t_D}\left[\frac{\left(\frac{1}{2}at_p\right)^2}{1 + \left(\frac{1}{2}at_p\right)^2}\right] \tag{1}$$

In this equation t_D is the lifetime of the diamagnetic species, t_p is the lifetime of the paramagnetic species, and a is the electron–nuclei coupling constant. In cases in which $(^1/_2at_p)^2$ is greater than 1, the nuclei experience a strong magnetic pulse when they enter the paramagnetic state and the equation for the line broadening reduces to

$$\left(\frac{1}{T_2}\right) = \frac{1}{t_D} \tag{2}$$

In cases in which $(^1/_2at_p)^2 \lesssim 1$, the nuclei experience a weaker magnetic pulse and the nmr lines are broadened less. If the electron–nuclei coupling constants of a given molecule vary over a sufficiently large range, it should be possible to observe both of these limits in a given reaction. If one is able to determine t_D from the broadenings of lines from nuclei which experience a strong magnetic pulse, one can calculate t_p from the broadenings of peaks from nuclei which experience a weaker magnetic pulse.

We have studied a series of reactions in which biradicals are in equilibrium with diamagnetic zwitterions. The general equation for the reactions which have been investigated is shown in Figure 1. The first-order rate equations for the reactions involving the zwitterion and the biradical are given by

$$\begin{gathered}\text{rate}_{\text{forward}} = k_1[\text{zwitterion}] = [\text{zwitterion}]/t_D \\ k_1 = \frac{1}{t_D} \\ \text{rate}_{\text{reverse}} = k_2[\text{biradical}] = [\text{biradical}]/t_p \\ k_2 = \frac{1}{t_p}\end{gathered} \tag{3}$$

In cases in which one can calculate the two lifetimes from nmr line broadenings, it is possible to determine the two rate constants and the equilibrium constant for the reaction.

Process II involves an interchange of the magnetic environment of the two halves of the zwitterions. This reaction interchanges the magnetic environment of the aromatic and quinone ring protons. The lifetime of a given molecule with respect to this reaction (t_I) may be determined from an analysis of the nmr spectra in some cases.[4,5] The rate equation for this reaction is given by

$$\begin{gathered}\text{rate} = \frac{1}{2}k_3[\text{zwitterion}] = \frac{1}{2}[\text{zwitterion}]/t_I \\ k_3 = \frac{1}{t_I}\end{gathered} \tag{4}$$

When k_3 is larger than the separation between the lines from the aromatic and quinone ring protons, one observes a single exchange-narrowed line at a mean position. This line may be broadened by the reaction involving the biradical. In some cases we have been able to observe both types of reactions. At higher temperatures, process II is very fast and the broadening of the lines from the ring protons is due to the zwitterion–biradical interconversion. At low temperatures process I does not contribute appreciably to the line width and process II becomes slow enough to measure.

---

[1] Alfred P. Sloan Foundation Fellow.

[2] E. DeBoer and C. MacLean, *J. Chem. Phys.*, **44**, 1334 (1966).

[3] R. W. Kreilick and S. I. Weissman, *J. Amer. Chem. Soc.*, **88**, 2645 (1966).

[4] D. J. Williams and R. W. Kreilick, *ibid.*, **90**, 2775 (1968).

[5] A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *ibid.*, **88**, 3185 (1966).

Table I. Analytical Data, Melting Points, and Yields of the Phenols

	Analytical					
	Theoretical		Found			
Phenol	% C	% H	% C	% H	Mp, °C	% yield
1	77.04	9.70	77.12	9.77	206	74
2	77.75	10.08	77.76	10.21	227	33
3	79.35	8.94	79.37	9.00	219	50
4	74.50	9.38	74.80	9.06	227	64
5	74.81	9.52	74.92	9.62	190	64

Table II. Chemical Shifts of the Various Zwitterions[a]

Compound	Solvent	Temp, °C	Ring	t-Butyl	R
1	$CDCl_3$	−8	6.75	1.31	2.66
2	Acetone-d_6	−76	7.13, 6.72	1.32	1.46
3	CS_2	−60	6.84, 6.41	1.23, 0.96	7.58[b]
4	CS_2	−32	6.65	1.23	4.03
5	CS_2	−91	6.88, 6.47	1.23	4.46,[c] 1.23[d]

[a] The shifts are in ppm from TMS. [b] Center of a group of lines. [c] Center of quartet. [d] Triplet overlapped with t-butyl signal.

Table III. Optical Spectra of the Various Zwitterions

	Compound				
	1	2	3	4	5
λ^a	662	666	679	634	636
ϵ^b	8.6×10^3	2.2×10^4	1.8×10^4	1.8×10^4	8.6×10^3
λ	452	459	445	459	458
ϵ	4.5×10^3	3.2×10^3	5.6×10^3	6.1×10^3	3.3×10^3
λ	364	382	302	293	278
ϵ	3.0×10^3	6.4×10^3	1.0×10^4	1.1×10^4	1.1×10^4
λ	322	317			
ϵ	9.0×10^3	7.4×10^3			
λ		279			
ϵ		8.4×10^3			

[a] The wavelengths are in mμ. [b] The extinction coefficients are in M^{-1} cm^{-1}.

Experimental Section

(1) Compounds. The zwitterions were prepared by oxidation of the appropriate phenols. The phenols were synthesized by the reaction of bis-2,6-di-t-butyl-4-hydroxyphenylamine with the appropriate acid chloride. This amine was prepared by catalytic reduction (Pd–charcoal in $CHCl_3$) of tetra-t-butylindophenol.[6] The amine was easily air oxidized back to the indophenol and care had to be taken to exclude air from the reaction mixture after the reduction was completed. A tenfold excess of the acid chloride was added directly to the reaction mixture at the end of the reduction and the mixture was refluxed under N_2 for 5 hr. The mixtures were normally red owing to the presence of small amounts of the indophenol. The phenolic precursor of compound 1 was purified by elution through a column of neutral alumina with ether and recrystallization from a mixture of isooctane and benzene. The other phenols were purified by recrystallization from isooctane–benzene mixtures. Yields, melting points, and analytical data for the phenols are given in Table I.

The zwitterions were made by oxidizing ethereal solutions of the phenols with lead dioxide. The reaction times were from 15 to 30 min. The solutions were filtered and evaporated to yield green solids. All of the zwitterions except compound 1 were relatively stable and could be kept as solids at 0° for several weeks without significant decomposition. Solutions of compound 1 decomposed in about 24 hr, while the solid showed significant decomposition in about 1 week. All of the compounds were unstable in solutions exposed to the air and attempts at recrystallization led to decomposition.

The structural assignment of the oxidation product was based on nmr and spectral data. At low temperature (*ca.* −70°) the nmr spectra showed separate lines from the aromatic and quinone ring protons. The t-butyl lines were also split into doublets in some cases. The high-field peak in the aromatic region of the spectra was broadened further at lower temperature but we were unable to resolve it into another doublet in the accessible temperature range. The broadening of this peak indicates that two of the protons on one of the rings may be magnetically nonequivalent. An alternative structure to the zwitterions might involve a structure with an aziridine ring. This structure was ruled out by the nmr data and the high colors of these compounds. Nmr and optical spectral data are given in Tables II and III.

(2) Instruments. The nmr spectra were taken on a Jeolco 4H-100 nmr spectrometer. Esr samples were investigated with a Jeolco 3BSX esr spectrometer. The samples for esr experiments were oxidized with lead dioxide in a sealed degassed apparatus. The solvent for the esr samples was CCl_4. Optical spectra were taken on a Cary 11 spectrophotometer with spectral grade cyclohexane as the solvent.

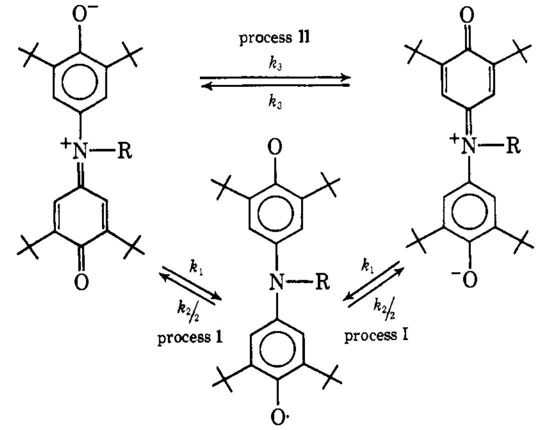

Figure 1. Reactions investigated: compound 1, R = CH_3CO; compound 2, R = t-C_4H_9CO; compound 3, R = C_6H_5CO; compound 4, R = CH_3OCO; compound 5, R = C_2H_5OCO.

(3) Calculation of t_1. The equations of Gutowsky and Holm[7] for exchange between two nonequivalent diamagnetic sites were used to calculate theoretical spectra with different t_1's. The natural line width terms were included in these calculations. Experimental measurements were only made in the region in which the doublet had collapsed into a single broadened line. A theoretical plot of t_1 *vs.* the width of this peak was made. The experimental line width of the peak from the ring protons was then used to determine t_1 from this plot.

The broadening of the high-field line in the aromatic region at lower temperatures indicated that we might be dealing with three magnetically nonequivalent sites. We were unable to resolve this broadened peak into a doublet at the lowest accessible temperature. Spectra for a triangular and linear three-site exchange were calculated using the general theory of Gutowsky, McCall, and Slichter.[8] These calculations indicated that when the chemical shift between the two high-field lines is small, one can use the two-site equations without producing a large error in the values of t_1. The calculations for both the two- and three-site situations were carried out

---

[6] G. Coppinger, *Tetrahedron*, 18, 61 (1962).

[7] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 25, 1228 (1956).

[8] H. S. Gutowsky, D. W. McCall, and C. P. Slichter, *ibid.*, 21, 279 (1953).

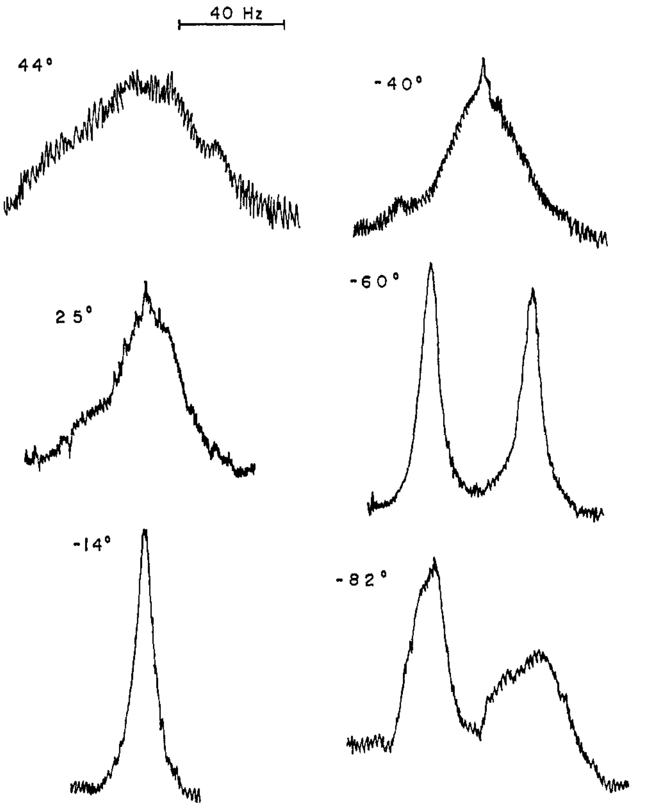

Figure 2. Nmr lines from the ring protons of compound 3 in CS$_2$.

on an IBM 360/65 computer, and the spectra were plotted with a Calcomp digital plotter.

Results and Discussion

The two types of reactions affected the nmr spectra of the zwitterions in different temperature regions. Spectra showing the temperature dependence of the signals from the ring protons of compound 3 are shown in Figure 2. At room temperature the signal from the ring protons appeared as a single broadened line. In some cases this line was broadened enough to be lost in the base line. As the temperature was lowered this line sharpened to a width of less than 10 Hz and then broadened again and in some cases split into a doublet. The broadening at higher temperatures can be accounted for by the zwitterion–biradical interconversion. At low temperatures, this reaction becomes slow and the spectra are affected by process II.

The line from the ring *t*-butyl protons was slightly broadened in the higher temperature spectra. This line broadened as the temperature was lowered, and in one case it split into a doublet. The signals from the methyl and *t*-butyl substituents of compounds 1 and 2 were broadened more than the line from the ring *t*-butyl protons but less than the line from the ring protons. These signals sharpened as the temperature was lowered and did not broaden again in the low-temperature region. A plot showing the temperature dependence of the width of the various peaks from compound 1 is shown in Figure 3.

The slight broadening of the ring *t*-butyl peaks at higher temperatures indicates that these protons experience a weak magnetic pulse $[(\frac{1}{2}at_p)^2 < 1]$. The methyl and *t*-butyl substituents of compounds 1 and 2 experience a stronger pulse $[(\frac{1}{2}at_p)^2 \sim 1]$, and the lines from these protons are broadened more than the ring *t*-butyl peaks but less than the lines from the ring protons. The relative broadenings of the signals from the three types of protons can be explained by differences in the electron–nuclei coupling constants of these nuclei. The coupling to aromatic protons in phenoxy radicals is normally 1–2 G, while the *t*-butyl couplings are generally 0.06–0.07 G. One predicts that the signal from the ring protons will be governed by the strong pulse limit, while the line from the ring *t*-butyl protons will be broadened less than 1 Hz when the lifetime of the biradical is of the order of 5×10^{-7} sec.

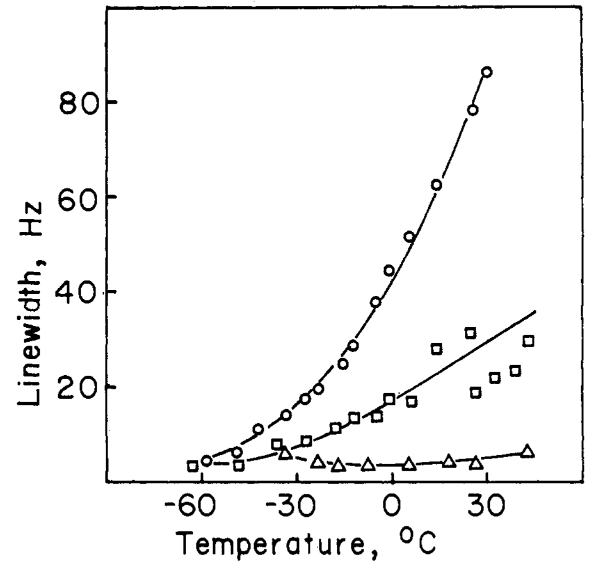

Figure 3. Plot of the nmr line width *vs.* temperature for compound 1 in CDCl$_3$: Δ = *t*-butyl peak, □ = methyl peak, ○ = ring peak.

The signal from the *t*-butyl protons of compound 1 was broadened enough at higher temperatures that we were able to use the line width of this signal to calculate t_p and k_2 (Table IV). We assumed a value of 0.065 G for the *t*-butyl coupling constants in this calculation. The value obtained for t_p was combined with the

Table IV. Kinetic and Thermodynamic Data for Process I at 240°K

Compd	Solvent	k, sec^{-1}	$\Delta G^\ddagger$	$\Delta S^\ddagger$	$\Delta H^\ddagger$
1	CDCl$_3$	4.3×10^1	11.8[b]	−31[b]	4.2[b]
	CDCl$_3$[a]	1.3×10^6	6.9	−23	1.5
2	CDCl$_3$	0.025×10^1	14.3	−24	8.5
	CS$_2$	0.18×10^1	13.3	−40	3.7
	Acetone-d_6	0.04×10^1	14.1	−25	7.9
3	CDCl$_3$	1.5×10^1	12.3	−32	4.5
	CS$_2$	0.7×10^1	12.7	−30	5.4
	Acetone-d_6	1.2×10^1	12.4	−37	3.7
4	CDCl$_3$	2.0×10^1	12.2	−30	5.1
	CS$_2$	2.3×10^1	12.1	−31	4.7
	Acetone-d_6	1.2×10^1	12.4	−29	5.5
5	CDCl$_3$	1.3×10^1	12.4	−29	5.4
	CS$_2$	1.5×10^1	12.3	−32	4.6
	Acetone-d_6	0.6×10^1	12.8	−22	7.6

[a] For the reverse reaction. [b] Free energies and enthalpies are in kcal/mol. The estimated error is ±0.5 kcal/mol. Entropies are in entropy units. The estimated error is ±2 eu.

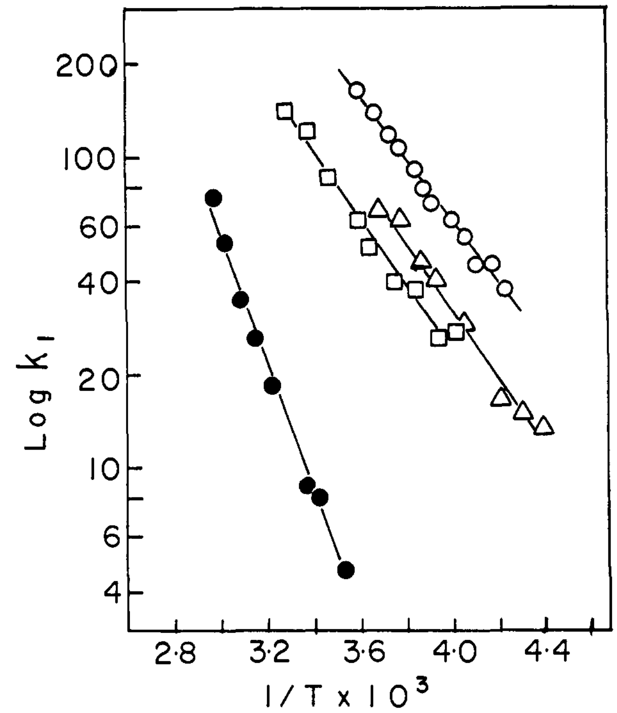

Figure 4. Plot of log k_1 *vs.* the reciprocal of temperature for experiments conducted with $CDCl_3$ as the solvent: ○ = compound 1, ● = compound 2, □ = compound 3, Δ = compound 4.

broadening of the signal from the methyl protons to obtain an estimation of the methyl proton coupling constant ($a_{CH_3} = 0.16$ G).

Esr spectra from the monoradicals of the various phenols were obtained by partial oxidation of the samples. These spectra were poorly resolved and we were unable to obtain accurate coupling constants. Estimates of the coupling constants from the two *meta* ring protons and the nitrogen could be obtained in some cases. The values of these coupling constants are given in Table V.

Table V. Hyperfine Coupling Constants (G) of the Monoradicals as Measured by Esr Spectroscopy

	Compound			
	2	3	4	5
Aromatic (2 H)	1.2	1.4	1.1	1.2
Nitrogen	1.2		0.7	0.7
t-Butyl				0.06

When the samples were oxidized further we observed the spectrum of the tetra-*t*-butylindophenoxy radical.[6] Apparently this radical is one of the decomposition products of the zwitterion. We were unable to observe the spectrum of the biradical from any of the compounds which were investigated. An estimation of the concentration of the biradical can be obtained from the lifetimes which were determined from the nmr experiments. The equilibrium constant calculated from the lifetimes is about 10^{-4} at 25°. With this equilibrium constant, the maximum concentration of the biradical which could have been present in our samples would have been of the order of 10^{-5} *M*. The signal from the impurity radical would mask the signal from the biradical at this concentration.

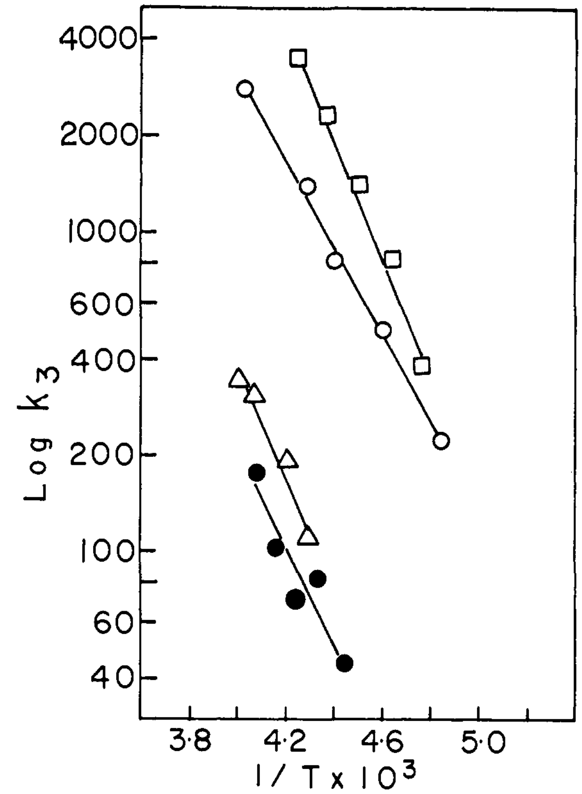

Figure 5. Plot of log k_3 *vs.* the reciprocal of temperature: ○ = compound 2 in acetone-d_6, ● = compound 3 in $CDCl_3$, Δ = compound 3 in CS_2, □ = compound 5 in acetone-d_6.

The rate constant for the reaction in which the zwitterion goes to the biradical was determined from the broadening of the nmr line of the ring proton in each case. The line broadening which results from this first-order reaction should be independent of the concentration of the zwitterion. The zwitterions were not soluble enough to study the reactions over an extended concentration range. We examined samples with a concentration difference of a factor of 2–3 in $CDCl_3$. Within experimental error, the rate constants determined from these samples were identical. The reaction was also examined in carbon disulfide and acetone-d_6. A plot of the log of the rate constants *vs.* the reciprocal of temperature is shown in Figure 4. The rate constants and thermodynamic parameters for this reaction are listed in Table IV.

We were able to measure the rate constant for the reverse reaction in the case of compound 1. The temperature dependence of this reaction was followed by monitoring the broadening of the lines from the methyl and ring protons. The rate constant and thermodynamic parameters for this reaction are listed in Table IV. There may be some error in the value of the rate constant, as we used an estimated value for the coupling constant of the *t*-butyl proton. The broadening of the signals from the *t*-butyl protons was too small for accurate measurements in the cases of the other zwitterions.

The rate constant for process II could only be measured in cases in which the signal from the ring protons split into a well-resolved doublet. In the other cases we were unable to determine the chemical shifts of the two peaks. A plot of the log of k_3 *vs.* the reciprocal of temperature is shown in Figure 5. These plots were extrapolated to 240°K to obtain a comparison of the rate data for the two reactions. The rate constants and thermodynamic parameters for process II are listed in Table VI.

Table VI. Kinetic and Thermodynamic Data for Process II at 240°*K*

Compd	Solvent	k, sec^{-1}	$\Delta G^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$
2	Acetone-d_6	1.8×10^3	10.0[a]	−18[a]	5.7[a]
3	$CDCl_3$	0.15×10^3	11.2	−12	8.3
	CS_2	0.19×10^3	11.1	−17	7.1
5	CS_2	4.7×10^3	9.6	−4	8.6
	Acetone-d_6	5.2×10^3	9.5	−7	8.0

[a] Free energies and enthalpies are in kcal/mol. The estimated error is ±1.0 kcal/mol. Entropies are in entropy units. The estimated error is ±4 eu.

Process II is a type of valence tautomerism. The aromatic ring must be twisted with respect to the plane of the quinone ring in order for the ring protons to be magnetically nonequivalent. The interchange of the two halves of the molecule can proceed when the aromatic ring rotates so that the molecule is in a planar conformation. The rate constant which we have measured probably represents the rate of rotation of this ring. The reaction which interconverts the zwitterion and the biradical requires a change in the hybridization of the nitrogen atom. This reaction was slower than the valence tautomerism reaction in each case. The smaller values for k_1 appear to be mainly due to the larger negative entropies for this reaction. The relative values of the entropies probably reflect the geometric requirements of the two reactions.

The values of the k_1's depended on both the steric bulk of the R group and the solvent. Molecules with bulkier R groups had smaller rate constants in each case. The variation in the rate constants with solvent was different for each of the compounds. Both the activation enthalpy and the activation entropy varied when the solvent was changed. Apparently each of the compounds interacts with the solvent in a slightly different manner and the rate data do not show a systematic solvent dependence.

Acknowledgment. This work was supported in part by National Science Foundation Grant No. GP-9339.

Sites of Attack of Hydroxyl Radicals on Amides in Aqueous Solution

E. Hayon, T. Ibata,[1] N. N. Lichtin,[1] and M. Simic[2]

Contribution from the Pioneering Research Laboratory,
U. S. Army Natick Laboratory, Natick, Massachusetts 01760,
and the Department of Chemistry, Boston University,
Boston, Massachusetts 02215. *Received January 19, 1970*

Abstract: The reactivity and sites of attack of hydroxyl radicals on simple amides in aqueous solution were studied. The following amides were examined: formamide (F), N-methylformamide (NMF), N,N-dimethylformamide (DMF), acetamide (A), N-methylacetamide (NMA), and N,N-dimethylacetamide (DMA). The rate constants for reaction of OH radical with NMF, DMF, NMA, and DMA fall in the range $(1.0–3.5) \times 10^9\ M^{-1}\ sec^{-1}$, but the reactivity with F and A is significantly lower. The absorption spectra in the wavelength range 225–600 nm and the specific rates of decay of the transient species produced by the reaction of OH radicals with amides were determined and their structures assigned. With F and A, OH radicals attack at both sites on the molecule to give $HCO\dot{N}H$, $\dot{C}ONH_2$, $CH_3CO\dot{N}H$, and $\dot{C}H_2CONH_2$ radicals. With the N-methylated amides, abstraction by OH radicals takes place mainly from the N-methyl group, *e.g.*, $OH + CH_3CON(CH_3)_2 \rightarrow CH_3CON(\dot{C}H_2)(CH_3) + H_2O$. The implications of these results with respect to the radiolysis of peptides are discussed.

A number of investigations have been carried out on the optical absorption and nmr spectral properties of simple amides and peptides in solution (see, *e.g.*, ref 3–5 and references cited therein), containing one or two peptide groups, but very little work appears to have been done on the free radical chemistry of the amide group. Such information is clearly of great interest in the study of the photochemistry and radiation chemistry of peptides in solution.

This paper deals with the reactivity and site of attack of hydroxyl radicals on simple amides in aqueous solution. The technique of pulse radiolysis and kinetic absorption spectrophotometry has been used as a convenient method for generating OH radicals and for observing and identifying the transient species produced. The intermediates produced in the radiolysis of neat liquid amides have been examined and are described[6] separately.

---

(1) Chemistry Department, Boston University. Support of their efforts by Grants No. R01 RH 00394 and R01 EC 00092 of the Environmental Control Administration of the U. S. Public Health Service is gratefully acknowledged by T. Ibata and N. N. Lichtin.

(2) National Academy of Science–National Research Council Research Associate at the U. S. Army Natick Laboratory.

(3) E. B. Nielsen and J. A. Schellman, *J. Phys. Chem.*, 71, 2297 (1967).

(4) R. C. Neuman, Jr., W. R. Woolfenden, and V. Jonas, *ibid.*, 73, 3177 (1969).

(5) M. Rabinowitz and A. Pines, *J. Amer. Chem. Soc.*, 91, 1585 (1969).

(6) N. Hayashi, E. Hayon, T. Ibata, N. N. Lichtin, and A. Matsumoto, submitted for publication.