[January, 1977] BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 50 (1), 1—5 (1977)

Photoionization of Chlorpromazine Hydrochloride in Binary Mixed Solvent Systems

Teiki Iwaoka and Michio Kondo

Central Research Laboratories, Sankyo Co., Ltd., Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140

(Received November 1, 1975)

Flash photolytic photoionization of chlorpromazine hydrochloride has been investigated in several binary solvent systems, one component being always water. With changing solvent composition, the ionization yield in aerated state shows a convex curve. Opposite roles of oxygen toward photoionization have been found in aqueous and organic solutions: *i.e.* the deaeration causes an efficient ionization in organic solvents, but practically no ionization in water. A change in the reaction mechanism has been suggested in the mixed solvent with water content of about 85 %. It has been found that the photoionization proceeds monomolecularly *via* an excited state, the lifetime of which is far shorter than that of the lowest excited (π-π^*) triplet state.

The interest in the photoionization of chlorpromazine arises from its importance in photodynamic action and photoallergic side effects.[1] It is possible that both hydrophobic and hydrophillic interactions of biological systems influence the photochemical reaction of a substrate (drug) bound into biopolymers or biomembranes. It is considered to be important, for a comparison of a photobiological reaction *in vivo* with a model reaction *in vitro*, that solvent effects of water and organic solvents on the photochemical processes are clarified. We previously investigated the photooxidation of chlorpromazine and established that the formation of the cation radical from photoionization is the initial process in the oxidative formation of the chlorpromazine sulfoxide as a photoproduct.[2] However, the elucidation of the interaction of oxygen with the excited state remained to be investigated. The significant solvent effect found in that photooxidation prompted us to study in detail the photoionization process in binary mixed solvents.

It is the purpose of this paper to show that the characteristic dependence of the photoionization upon the solvent composition is due to the change in the ionization mechanism.

Experimental

Materials. Commercial chlorpromazine hydrochloride was purified by recrystallization from diethyl ether. 2-Chlorophenothiazine (Aldrich Chemical Co.) was chromatographed on a column of silica gel (Kiesel Gel 60, Merck and Co., Inc.), with benzene as the eluent, and was recrystallized twice from this solvent. *N*-Methyl-2-chlorophenothiazine was prepared by adding slowly methyl iodide to a 2-chlorophenothiazine anion, previously prepared from sodium hydride and 2-chlorophenothiazine in dimethyl sulfoxide in a stream of nitrogen. The spectral-grade solvents—dioxane, acetonitrile, and glycerol of Merck and Co., Inc., and G. R.-grade ethanol (Iwai kagaku Co., Ltd.)—were used without further purification. The water was distilled twice in a Pyrex vessel.

Apparatus and Procedure. Flash photolytic experiments were carried out with an Ushio UFP 105 photolysis apparatus, using a combination of UV-D25 and UV-29 or UV-2 only (Toshiba color filters). The intensity of the exciting light was varied by the use of neutral filters or by the interchange of the electric capacitor. Absorption and emission measurements were made with a Hitachi 356 two-wavelength spectrophotometer and a Hitachi MPF-2 spectrofluorimeter. The absolute intensities of the flash light were determined by a ferric oxalate actinometer.

Results

Photoionization in an Aerated Mixture of Water and Organic Solvent. The first absorption band of chlorpromazine (CPZ) has its λ_{max} at 305—310 nm (*e.g.* in ethanol, 308 nm). Flash excitation was confined to this band by the use of coupled glass filters. As has been reported previously,[2] the flash excitation of CPZ in aerated water gave a cation radical ($CPZ^{\dagger}$) as a result of electron ejection, the molecular oxygen probably an electron acceptor. The formation of $CPZ^{\dagger}$ was negligibly small in air-saturated ethanol. However, it is found in this ionization process that a mixture of water and ethanol (1: 1) exceeds the aqueous solution in efficiency by a factor of more than five. Figure 1 shows the ionization yield ($CPZ^{\dagger}$ yield) for several solvent pairs: ethanol–water, dioxane–water, acetonitrile–water, and glycerol–water. The spectrum of $CPZ^{\dagger}$ is not influenced in its shape or peak position by the solvents used.

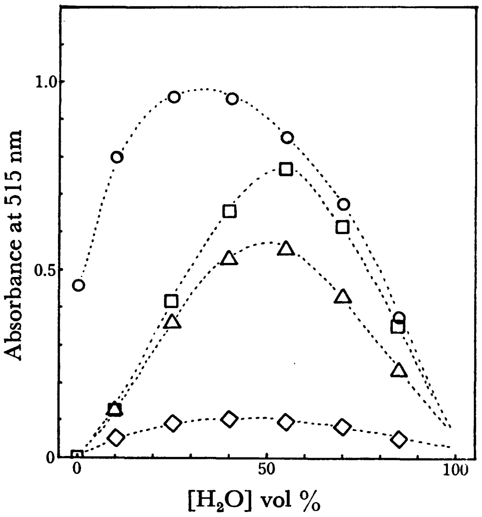

Fig. 1. $CPZ^{\dagger}$ yields (absorbance at 515 nm) in the aerated mixed solvents. $[CPZ]=2.0\times10^{-4}$ M. □: Ethanol–water. ○: Glycerol–water. △: Dioxane–water. ◇: Acetonitrile–water.

Transients in the Deaerated State. The transient spectra obtained in the deaerated ethanol upon flash excitation are shown in Fig. 2. The transient absorption at 465 nm can safely be assigned to the (π-π^*) triplet

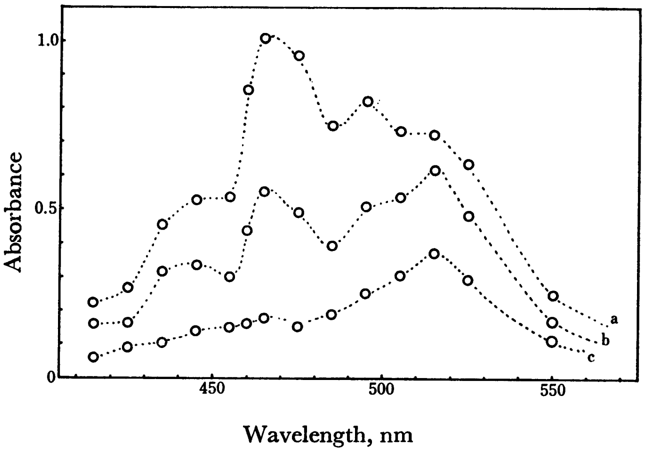

Fig. 2. Transient absorption spectra obtained by the flash photolysis of the degassed ethanol solution of CPZ. [CPZ]$=2.0\times10^{-4}$ M. a: 0 μs (immediately after flash), b: 25 μs, c: 175 μs.

state (^{3}CPZ),[2] while that at 515 nm is in fair agreement with the spectrum of CPZ$^+$. These two transients decay at different rates, and at 175 μs after the flash the absorption is practically all due to CPZ$^+$. When the technique of argon gas bubbling was applied instead of degassing *in vacuo*, no appreciable change was observed in the transient species. The lifetime of ^{3}CPZ in this case is, however, short (k_d(Ar): 5.8×10^4 s^{-1}, k_d (degassed): 2.6×10^4 s^{-1}), perhaps because of a quenching by residual oxygen in the solution.

The flash photolysis of CPZ in dioxane, glycerol, and acetonitrile gave ^{3}CPZ and CPZ$^+$ similarly, but in an aqueous solution no transients were observed.

Dependence of the Photoionization Yield on the Solvent Composition. The absorption increase of CPZ$^+$ at 515 nm is coincident with the time profile of a flash, as is the case for the (π-π^*) triplet state and the maximum value of the absorbance is used for the comparison of the relative ionization yields. The dependences of the yield of photoionization upon the solvent composition of the above solvent pairs are shown in Figs. 3—5, which illustrate a characteristic effect of the oxygen concentration on the ionization. The decay rates of the resultant CPZ$^+$ are summarized in Tables 1—2, which confirm that the decay feature of CPZ$^+$ is determined by the solvent composition, not by the oxygen concentration. The effects of the light intensity of the exciting flash were examined in anhydrous ethanol, ethanol, and ethanol–water (1: 1) *in vacuo*. The yields of CPZ$^+$ and that of ^{3}CPZ were directly proportional to the flashing light intensity.

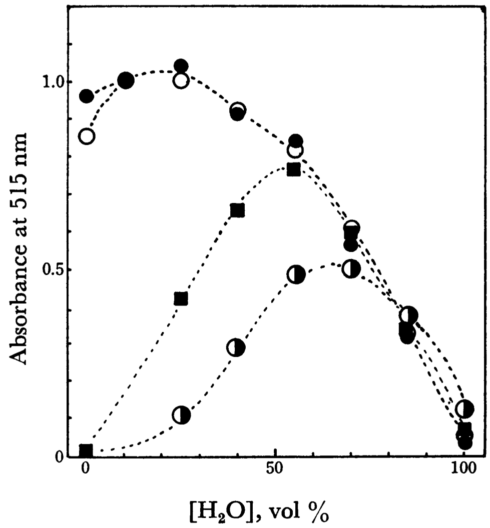

Fig. 3. CPZ$^+$ yields(absorbance at 515 nm) in the degassed (●), argon bubbled (○), air saturated (■), and oxygen bubbled (◑) mixed solvents of ethanol and water. [CPZ]$=2.0\times10^{-4}$ M.

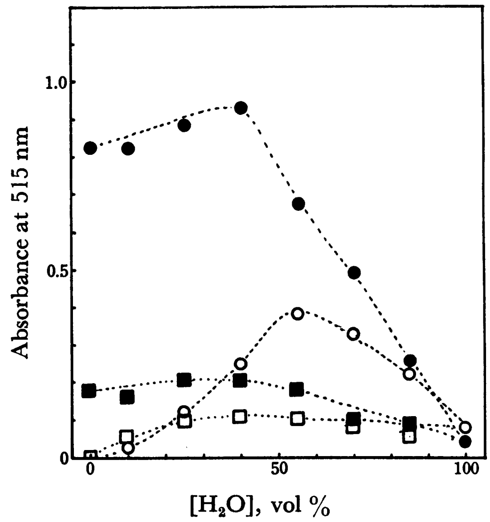

Fig. 4. CPZ$^+$ yields(absorbance at 515 nm) in dioxane–water and acetonitrile–water. Dioxane–water, ●; argon bubbled, ○; oxygen bubbled. Acetonitrile–water, ■; argon bubbled, □; air saturated. [CPZ]$=2.0\times10^{-4}$ M.

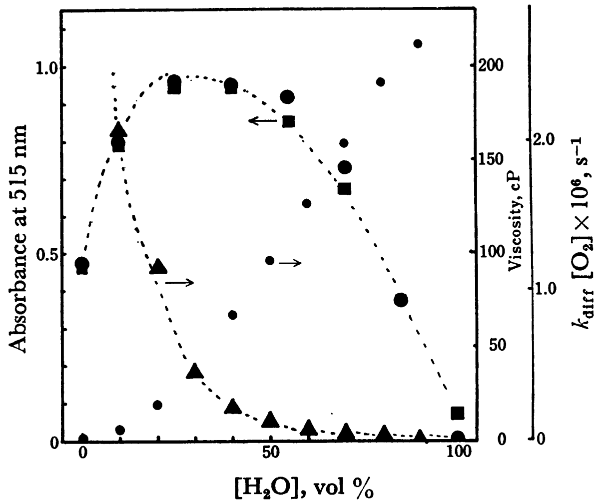

Fig. 5. CPZ$^+$ yields(absorbance at 514 nm) in glycerol–water. ●: Argon bubbled. ■: Air saturated. Viscosities (▲) and quenching rate by oxygen, k_{diff} [O$_2$] (●) are also shown.

Reaction of ^{3}CPZ with Water. The triplet-triplet absorption in organic solvents *in vacuo* decreased drastically upon the addition of water and was not observed at a concentration of 10% v/v in water. A linear relation-

TABLE 1. DECAY CONSTANTS OF CHLORPROMAZINE CATION RADICAL ($CPZ^{\dagger}$) IN THE MIXED SOLVENT OF ETHANOL AND WATER

λ_{obsd}: 515 nm. [CPZ]$=2.0\times 10^{-4}$ M. k_1, $k_2/\varepsilon d$: first and second order rate constants in unit of s^{-1}.
ε: molecular extinction coefficient. d: optical path length (10 cm).

H_2O vol %	Degassed		Ar-bubbled		Air-saturated		O_2-bubbled	
	$k_2/\varepsilon d$	k_1	$k_2/\varepsilon d$	k_1	$k_2/\varepsilon d$	k_1	$k_2/\varepsilon d$	k_1
100	—	$\approx 10^3$	—	$\approx 10^3$	—	$\approx 6\times 10^3$	—	$\approx 5\times 10^3$
85	—	7.7×10^3	—	5.8×10^3	—	5.5×10^3	—	5.5×10^3
70	1.8×10^4	3.2×10^3	1.4×10^4	3.4×10^3	$\approx 3\times 10^4$	4.6×10^3	$\approx 4\times 10^4$	5.4×10^3
55	1.1×10^4	7.9×10^2	1.1×10^4	2.8×10^2	9×10^3	4.7×10^3	9.2×10^3	5.3×10^3
40	1.5×10^4	$\approx 4\times 10^2$	1.8×10^4	$\approx 2\times 10^2$	8.6×10^3	2.2×10^3	8.6×10^3	1.6×10^3
25	2.2×10^4	$\approx 2\times 10^2$	3.5×10^4	$\approx 1\times 10^2$	9.2×10^3	—	4.1×10^4	—
10	3.0×10^4	$\approx 7\times 10^2$	2.3×10^4	$\approx 4\times 10$	—	—	—	—
0	3.6×10^4	—	3.0×10^4	—	—	—	—	—

TABLE 2. SECOND ORDER DECAY RATE ($k_2/\varepsilon d$, s^{-1}) OF $CPZ^{\dagger}$ IN GLYCEROL–WATER

[CPZ]$=2.0\times 10^{-4}$M. λ_{obsd}: 515 nm.

H_2O vol %	$k_2/\varepsilon d$ (Ar)	$k_2/\varepsilon d$ (Air)
85	$\approx 10^4$	$\approx 10^4$
70	1.2×10^4	1.0×10^4
55	3.5×10^3	4.0×10^3
40	1.5×10^3	2.1×10^3
25	4.6×10^2	1.1×10^3
10	2.7×10^2	3.2×10^2
0	$\approx 10^1$	2.0×10^2

TABLE 3. VALUES OF Φ_f, Φ_p, AND Φ_i

Φ_f	Φ_p	Φ_i[a]
0.003	0.4—0.6	0.27(10.0) 0.37(25.0)
EtOH, 25 °C	EPA, 77 K	0.31(40.0) 0.24(55.0)

a) The concentration of water in vol % is shown in parentheses.

ship of Φ (^3CPZ)$^{-1}$ against [H_2O] was obtained. The yields and lifetimes of $CPZ^{\dagger}$, however, do not show such a sharp decrease upon the addition of water.

Quantum Yields of Fluorescence, Phosphorescence and Photoionization. A rough estimation of the quantum yields of the fluorescence (Φ_f), phosphorescence (Φ_p), and photoionization (Φ_i) of CPZ was carried out (Table 3). The quantum yield of photoionization was estimated in aerated glycerol using the reported value of the molecular extinction coefficient of $CPZ^{\dagger}$.[3] The procedure is as follows. The exciting light absorbed by CPZ is given by:

$$I_{abs} = \int I_{ex}(\lambda) I_f(\lambda)\,(1-e^{-\alpha(\lambda)cd})\,10^3\,d\lambda \qquad (1)$$

where $I_{ex}(\lambda)$, $I_f(\lambda)$, $\alpha(\lambda)$, c, and d are the light intensity of an exciting flash, the transmittance of the filter system, the absorption coefficient, the molar concentration of CPZ, and the optical path length respectively. The quantum yield (Φ_i) is estimated by:

$$\Phi_i = A_{CPZ^{\dagger}}/(I_{abs}\,\varepsilon d) \qquad (2)$$

The quantum yields of fluorescence and phosphorescence were determined by comparing the emission from CPZ with that of quinine sulfate[4] and that of triphenylene in EPA[5] respectively. It is obvious from Table 3 that the value of ($\Phi_f+\Phi_p+\Phi_i$) does not exceed one.

Discussion

A comparison of the results in the presence of oxygen with the deaerated ones (Figs. 3 and 4) shows that oxygen inhibits the ionization at concentration smaller than 60% v/v of water. The differences in the yields of $CPZ^{\dagger}$ between the air-saturated and oxygen-bubbled solutions imply that the intermediate state responsible for the ionization is of a very short lifetime. An estimation of the lifetime of such an intermediate state is possible from the ratio of the ionization yield ($\Phi_i(O_2)/\Phi_i(\text{air})$), assuming a diffusional quenching by oxygen. Several tens of nanoseconds were obtained for dioxane–water, and *ca.* 200 nanoseconds for the ethanol–water system. Thus, the increase in the ionization efficiency with the increase in the water content in the aerated state (Fig. 1) may be

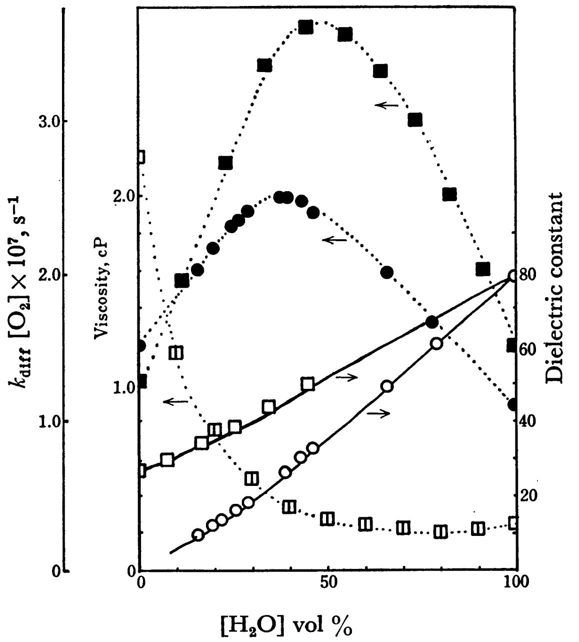

Fig. 6. Dependences of dielectric constant, viscosity and diffusional quenching rate by oxygen (k_{diff} [O_2]) on the composition of the mixed solvents.[8] Dielectric constant, □; ethanol–water, ○; dioxane–water. Viscosity, ■; ethanol–water, ●; dioxane–water. Quenching rate, ◫; ethanol–water.

attributed to the decrease in the quenching rate caused by the changes in the viscosity and oxygen concentration shown in Fig. 6.[6] It is quite reasonable that the difference in the ionization yield between air-saturated and argon-bubbled glycerol is quite small, since any diffusional quenching of the intermediate state with oxygen should be entirely suppressed. It may be said further that the efficiency of the photoionization in question is independent of the polarities and the hydrogen bonding abilities of the solvent employed.

An oxygen-catalyzed photoionization of a low yield prevails in the aqueous and nearly aqueous solutions. Either an electron transfer from the excited singlet state of CPZ to oxygen or a dissociation from the excited state of a charge-transfer complex ($CPZ^{\delta+}O_2^{\delta-}$) into CPZ^+ and O_2^- is possible for such an ionization.[7] The complexation of CPZ with oxygen in water on the basis of polarographic studies has been reported by Martin *et al.*[8] Autophotoionization from the excited state of such a change-transfer complex as $(CPZ^{\delta+}O_2^{\delta-})^*$ can be expected to occur in polar solvents, and it is natural that this photoionization process becomes dominant with an increase in the water content.

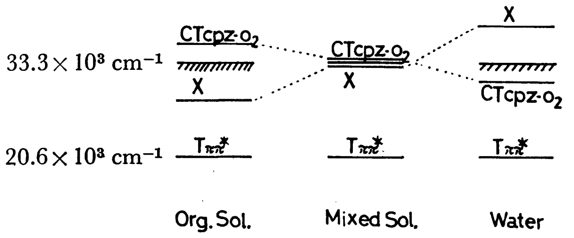

Fig. 7. Assumed changes with solvent in the disposition of energy levels of CPZ. $T_{\pi-\pi^*}$: Lowest (π-π^*) triplet state. X: Intermediate state responsible for the ionization. CT_{CPZ-O_2}: Excited state of charge transfer complex of CPZ with oxygen. Blue edge of the exciting light (///) is also shown.

The ionization in the deaerated state poses a problem regarding the solvent effect on the ionization; that is, why does the ionization efficiency shows a steep drop at a H_2O concentration of more than 50—60% v/v. A possible explanation is that the intermediate species for the photoionization is labilized and becomes short in its lifetime upon the addition of water. The energy level diagram shown in Fig. 7 is likely to elucidate our experimental results. When the employed solvent is alcohol, the transient state (X) serves as a reactive one within the available photon energy, and oxygen acts as an inhibitor of the ionization. The excited state of a charge-transfer complex ($CPZ^{\delta+}O_2^{\delta-}$) is expected to be located far above the excitation energy. In an aqueous solution, however, X possibly disposes at a higher energy, and practically no ionization is observed in the absence of oxygen. The low solubility of 2-chlorophenothiazine in water (10^{-7} M, practically insoluble) predicts that the solvation of the aromatic moiety by an organic solvent dominates over an equimolar ratio in the mixed solvent employed. Thus, it may be considered that ionization retains its high yield until a water content of about 60%.

The fluorescence of CPZ shows a large Stokes shift in both organic and aqueous solutions; this suggests an increase in the coplanarity of the two benzene rings in the fluorescent state. Both 2-chlorophenothiazine and *N*-methyl-2-chlorophenothiazine show the same locations as those of CPZ and a similar degree of Stokes shift in their fluorescence spectra. This excludes the possibility that the emission of CPZ originates from its intramolecular exciplex state. The biphotonic pathway for the ionization is definitely excluded by the findings of the proportionalities of the CPZ^+ yield with the flash intensities. Oxygen does not affected the fluorescence intensity.

The oxidation potentials of phenothiazine derivatives have been estimated from electrochemical anodic oxidation: phenothiazine (PTH, 306 mV *vs.* NCE), 2-chlorophenothiazine (354 mV), and CPZ (473 mV). These values were discussed by Malieu and Pullman[9] in terms of the "H (*R*)-intra" and "H (*R*)-extra" configurations of PTH. The degree of conjugation of the benzene rings was proposed to be dependent upon these configurations. Fulton and Lyons[10] gave the ionization potentials of several phenothiazine tranquilizers from their charge-transfer bands, 6.96 eV for PTH and 7.38 eV for CPZ. The formation of the cation radical observed in the deaerated solutions, however, shows that the photoionization occurs at about 4.1 eV, corresponding to the blue edge in an exciting flash light. Preliminary experiments on the photoionization of *N*-methylphenothiazine and *N*-methyl-2-chlorophenothiazine reveal that the photoionization proceeds more efficiently by chlorine substitution on the phenothiazine ring at 2 position. Hence, it seems that the ease of oxidation in the excited state is not necessarily parallel to that in the ground state, and that a conformation of the excited state different from that of the ground state may be a factor responsible for that.

The photoionization of *N*-methyl-2-chlorophenothiazine was examined with respect to the solvent depend-

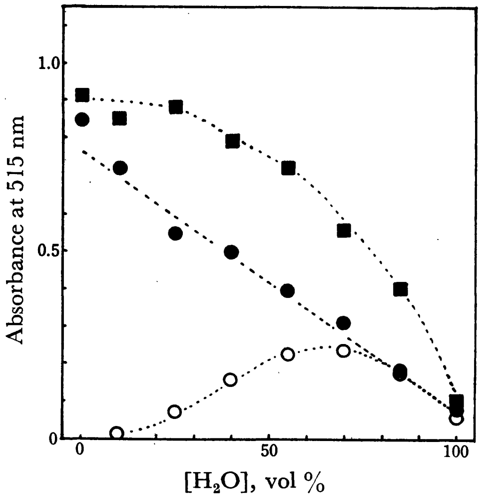

Fig. 8. Ionization yields in dioxane–50% v/v aqueous acetic acid. Comparison of CPZ with *N*-methyl-2-chlorophenothiazine. *N*-Methyl-2-chlorophenothiazine, ●; argon bubbled, ○; air saturated. CPZ, ■; argon bubbled.

ence of ionization in a dioxane–50% v/v aqueous acetic acid solution (Fig. 8). The transients observed and their dynamic behaviors were the same as those of CPZ. Even though the electronic system of this compound was the same as that of CPZ, the ionization shows a linear relationship between the CPZ^{+} yield and the solvent composition. It is probable that the side-chain amine causes some modification of the ionization yield, as a result of the proximity of tetravalent nitrogen[11] to the aromatic ring. The most suitable orientation for the ionization of the side-chain amine to the aromatic ring could be realized over a range of mixed solvents appropriately composed.

A further investigation of the reaction of CPZ with water was warranted, since no transients were found from ^3CPZ and since an internal quenching of ^3CPZ by the side-chain amine is possible. A similar quenching of the acetone triplet by alkylamine has been reported.[12] Neither the addition of 3-chloro-*N*,*N*-dimethylpropylamine at 6.7×10^{-1} M nor that of triethylamine (10^{-1} M) to an ethanol solution of CPZ caused any quenching of ^3CPZ. The absorption spectra after the prolonged UV irradiation of CPZ in a deaerated aqueous solution indicated only the decomposition of CPZ. These results made it probable that the (π-π^*) triplet of CPZ reacts with water in some degradative mode.

Our tentative scheme for the photoionization of CPZ explains well the characteristic solvent dependence and quenching effect by oxygen, however, the lifetimes obtained suggest that the intermediate state in question is not the excited state, but some transient species of a very short lifetime. Either a half-ionized state or a geminate ion pair may be possible for such a transient. Further investigations from this point of view are now in progress.

References

1) H. Ippen, *Proc. 3rd Intrn. Congr. Dermatol.*, **1961**, 509; H. Ippen, *Proc. 12th Intrn. Congr. Dermatol.*, **1962**, 1073; F. W. Grant, *Adv. Biochem. Psychopharmacol.*, **9**, 539 (1974).

2) T. Iwaoka and M. Kondo, *Bull. Chem. Soc. Jpn.*, **47**, 980 (1974).

3) D. C. Boag and G. C. Cotzias, *Proc. Natl. Acad. Sci. U.S.A.*, **48**, 643 (1962).

4) W. H. Melhuish, *J. Phys. Chem.*, **64**, 762 (1960).

5) R. E. Kellogg and R. G. Bennet, *J. Chem. Phys.*, **41**, 3042 (1964).

6) J. E. Lind, Jr. and R. M. Fuoss, *J. Phys. Chem.*, **65**, 999 (1961); R. W. Kunze and R. M. Fuoss, *J. Phys. Chem.*, **67**, 911 (1963); G. D. Parfitt and A. L. Smith, *Trans. Farad. Soc.*, **61**, 2736 (1965).

7) S. Nagakura, "Excited States," Vol. 2, ed by E. C. Lim, Academic Press, New York (1975), p. 369.

8) H. F. Martin, S. Price, and B. J. Gudzinowicz, *Archiv. Biochem. Biophys.*, **103**, 196 (1963).

9) J. P. Malrieu and B. Pullman, *Theor. Chim. Acta*, **2**, 293 (1964).

10) A. Fulton and L. E. Lyons, *Aust. J. Chem.*, **21**, 873 (1967).

11) The structure of the protonated form, $-NH^+(CH_3)_2$, in the side chain of CPZ was ascertained by NMR measurement.

12) R. W. Yip, R. O. Loutfy, Y. L. Chow, and L. K. Magdzinski, *Can. J. Chem.*, **50**, 3426 (1972).