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INTERMEDIATE STATE IN THE PHOTOIONIZATION OF CHLORPROMAZINE IN ETHANOL

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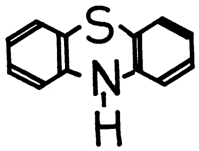
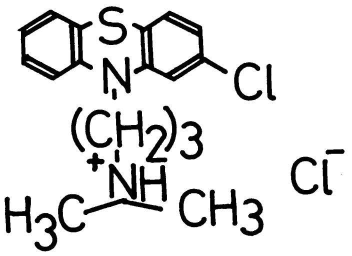
The excited state responsible for the photoionization of chlorpromazine was investigated in ethanol. Triplet-triplet energy transfer experiment excluded the participation of the lowest $(\pi-\pi^*)$triplet state in the ionization process. Fluorescence was not influenced by the addition of several quenchers which retarded the photoionization. The higher triplet state of different electronic configuration from the lowest $(\pi-\pi^*)$triplet state is suggested to be the reactive state for the ionization.

Many reports on the photoionization of phenothiazine1) and its derivatives (tranquilizers) are found in the literature. The nature of the excited state responsible for such an ionization, however, has not been determined experimentally. The phototoxicity and photoallergic side effect of chlorpromazine in the patients treated with high dosage have been attributed to the formation of a radical produced by the photoionization.2) We have obtained the first strong evidence from


(Phenothiazine)


(Chlorpromazine)

a flash($\lambda_{exc} \gtrsim$ 300 nm)photolytic experiment that chlorpromazine hydrochloride photoionizes(cation radical formation) through the higher triplet state, neither through the (π-π^*)triplet nor the singlet excited state.

The absorption intensities of the (π-π^*)triplet state$^{3)}$ and the cation radical of chlorpromazine increased simultaneously after flashing and then decreased with different decay rates. Computer simulation of the accumulation curves under the assumption of independent formations of these transients was successful, using the observed values of specific decay constants and the time profile of a flashing light.$^{4)}$

The excited state involved in the photoionization was examined by using the technique of triplet-triplet energy transfer in ethanol. The (π-π^*)triplet state$^{5)}$ was quenched completely without any effect on the yield of photoionization by the addition of biacetyl of 3 x 10^{-3} M(^{3}E, triplet energy: 20.0 Kcm^{-1}).$^{6)}$ Both trans-1,3,5-hexatriene(^{3}E: 16.45 Kcm^{-1})$^{6)}$ and oxygen quench efficiently the (π-π^*)triplet state and cause the decrease of the yield of the cation radical.$^{7)}$ Trans-1,3-pentadiene which has the triplet energy(^{3}E: 20.7 Kcm^{-1})$^{6)}$ higher than that of chlorpromazine had no effect upon the lifetime of the (π-π^*)triplet state, but it exerted appreciable quenching effects on the yields of photoionization and (π-π^*)triplet state. Additional evidence for the indifference of the (π-π^*)triplet state to the ionization comes from following findings. First, in the mixed solvents of ethanol-water (from 0 to 20% v/v), the yield of the cation radical was almost constant but the triplet-triplet absorption was extremely diminished. Secondly, the yield of the cation radical was proportional to the flash light intensity$^{8)}$ in ethanol, absolute ethanol, and also ethanol-water (1:1).

The fluorescence of chlorpromazine is not quenched by oxygen in all the solvents listed in Table I, while the ionization suffers drastic quenching.$^{7,9)}$ Addition of 1,3-pentadiene, even at a concentration of 0.1 M, hardly had any effect on the fluorescence intensity. From these observations, the fluorescent state is also eliminated as the candidate for the excited state of the photoionization process.

Table I. Effects of Oxygen(Air) on the Fluorescence and Photoionization Yield of Chlorpromazine at Room Temperature (20°C)

Solvent	Dielectric constant	Viscosity	Fluorescence[a)] Air	Fluorescence[a)] Deaerated	Photoionization[b)] Air	Photoionization[b)] Deaerated
Methyl cyclohexane	2.02	0.73	107	124	0	0
p-Dioxane	2.21	1.26	98	101	0	0.42
2-Propanol	19.9	2.86	99	100	0	0.43
Ethanol	24.6	1.19	95	100	0	0.46
Ethylene glycol	37.7	19.9	105	106	0.40	0.53
Glycerol	42.5	1412	107	108	0.17	0.21
Water	78.4	1.00	29	29	0.03	0.01

a) Relative intensity. The fluorescence intensity in the degassed ethanol was normalized to 100(λ_{exc}: 320 nm, λ_{obs}: 450 nm). Estimated error: ± 5%. b) Initial change of the absorption of the cation radical at 515 nm.

The lifetime of the excited state involved in the ionization process was estimated less than 10^{-6} sec from the quenching experiment by oxygen and hexatriene. It may be considered in Table I that the quenching is neglected in ethylene glycol, and the lifetime of the excited state is ca 10^{-7} sec. The lifetime of the (π-π^*)triplet state, however, was 3 x 10^{-4} sec from our experiments. Since the yields of the (π-π^*)triplet state in ethanol as a function of the oxygen concentration calculated under the assumption that oxygen quenches only the (π-π^*)triplet exceeds the experimental value, the precursor[10)] of the (π-π^*)triplet must be quenched by oxygen. A semi-ionized state or a geminate ion pair may be possible as the intermediate for these processes(ionization and (π-π^*)triplet formation), however, quenching by dienes suggests this intermediate of triplet character.

References and notes

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4) Such a treatment was necessary because the duration of a flash, and the lifetimes of these transients were not different so much.

5) The triplet energy level of chlorpromazine is estimated to be 20.6 Kcm^{-1} from the peak position in the phosphorescence spectrum.

6) S. L. Murov, "Handbook of Photochemistry", Marcel Dekker Inc., New York, 1970 p 3.

7) It should be noticed that the lifetime of the cation radical is not influenced by oxygen in our time scale of flash photolysis. Therefore the decrease of the cation radical should be attributed to a quenching of its precursor.

8) Biphotonic ionization through (π-π^*)triplet state occurs frequently: R. Lescaux and J. Jousset-Dubien, "Organic Molecular Photophysics", Vol. I, J. B. Birks. Ed. John Wiley Sons. New York, 1973 p 472.

9) If a singlet excited state is reactive, the following equation should be applied. Φ_f(deaerated)/Φ_f(air) = Φ_i(deaerated)/Φ_i(air), where Φ_f and Φ_i are the quantum yields of fluorescence and photoionization.

10) Intersystem crossing from singlet excited state(π-π^*) would occur much faster to (n-π^*)triplet than to (π-π^*)triplet state, therefore the (n-π^*)triplet state is probably the precursor of the (π-π^*)triplet state in this case; M. A. El-Sayed, J. Chem. Phys., 38, 2834 (1963).

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