Correlation between Phototoxicity and Photoionization Efficiency of Phenothiazine Drugs

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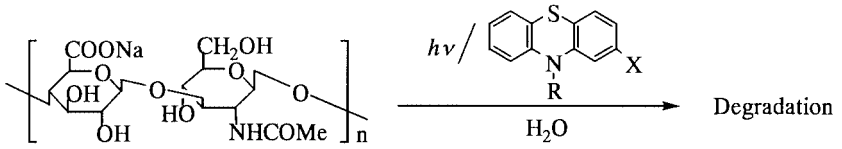
Irradiation of sodium hyaluronate (NaHA) in the presence of phenothiazine derivatives (PTZ) caused degradation of the biopolymer. It was found that measurement of the degradation efficiency was useful for estimation of the phototoxicity of the phenothiazine drugs. The results of laser photolysis suggested that the photoionization of PTZ is a key step in initiating degradation of NaHA.

Chlorpromazine (CPZ) is a major tranquilizer which has a side effect of being highly phototoxic,[1] and the phototoxicity mechanism has aroused considerable interest.[2] One of the present authors, studying ophthalmology, has observed empirically that vitreous liquefaction proceeds rapidly when patients take CPZ. Therefore, we have studied the correlation between this liquefaction and phenothiazine drugs. This paper reports first that PTZ such as promazine (PZ), fluphenazine (FPZ), and thioridazine (TRZ), as well as CPZ, caused the photodegradation of NaHA, which is one of the most important biopolymers existing in vitreous body, skin, joint fluid etc. (see eq 1), whereas no degradation occurred for acetopromazine (APZ). Secondly, it is reported that the degradation efficiency can be closely correlated with the photoionization efficiency of PTZ. On the basis of the effects of oxygen, radical scavengers, and kinetic data, it is suggested that the degradation is probably caused by radical species generated after photoionization.

An aqueous solution containing 4×10^{-5} M (M = mol/dm^3) PTZ and 0.02 wt% NaHA was irradiated under oxygen (O_2) at 20 °C through a 313-nm solution filter using a 400-W high-pressure mercury lamp. The molecular weight of NaHA before and after irradiation (M_0 and M, respectively) was measured as reported previously.[3] As shown in Table 1, the degradation efficiency of NaHA depends on the substituents on the phenothiazine framework, suggesting that the phototoxicity index of PTZ can be determined on the basis of the degradation efficiency. It should be noted that this new test is simpler and more easily reproduced, and also costs less than the mouse and Candida tests currently used to determine the photoxicity index.[4]

In order to understand the degradation mechanism, we



NaHA (1)

PZ: X= H; R= $(CH_2)_3NMe_2$

CPZ: X= Cl; R= $(CH_2)_3NMe_2$

APZ: X= COMe; R= $(CH_2)_3NMe_2$

TRZ: X= SMe; R = $(CH_2)_2$-N(Me)

FPZ: X= CF_3; R= $(CH_2)_3$-N⟨⟩N-$(CH_2)_2OH$

Table 1. Phototoxic index and photophysical characteristics of phenothiazine derivatives

PTZ	NaHA[a]		Pullulan[a]		Mouse[b,c]	Candida[b,d]	E_{OX}/V^e	$\phi_{ion}{}^f$	$d^1O_2/dt^{g,h}$
	O_2	degassed	O_2	degassed					
PZ	1.99	0.59	1.72	0.11	0.06	3.0	0.56	0.24	0.46
TRZ	0.87	0.49	0.93	0.48	0.29	0.6	0.58	0.19	0.83
CPZ	1.0	4.00	1.0	1.53	1.0	1.0	0.60	0.11	1.0
FPZ	0.21	0.01	0.44	0.04	0.17	0.9	0.66	0.07	1.09
APZ	0	0	0.02	0.02	0.12	–[i]	0.63	0	0.03

[a]Relative rate for phenothiazine-sensitized degradation of NaHA and pullulan under oxygen and degassed conditions. [b]Reference 4. [c]Phototoxic index estimated using a mouse test. [d]Phototoxic index estimated using a Candida test. [e]Oxidation potential determined by means of cyclic voltammetry in H_2O at pH = 6.86 vs SCE. [f]Quantum yield for photoionization. [g]Reference 11. [h]Relative rate for the formation of singlet oxygen. [i]Not determined.

measured the transient absorption spectra of PTZ using 308-nm laser photolysis under argon, which, except in the case of APZ, resulted in hydrated electron (e_{aq}^-) together with the parent cation radical ($PTZ^{\bullet+}$) and triplet. García et al. have proposed that the photoionization occurs through biphotonic excitation for CPZ and PZ,[5] and Chignell et al. have reported that a wavelength shorter than 280 nm is essential for the ionization.[6] But, the absorbance due to $PTZ^{\bullet+}$ observed in our experiment varied linearly with laser intensity (I_L < 10 mJ $pulse^{-1}cm^{-2}$), supporting the hypothesis advanced by Navaratnam et al. in favor of a monophotonic ionization mechanism.[7] The quantum yields for the photoionization of PTZ used in the present study were determined using the procedure reported already by Saito et al.[8] As can be seen in Table 1 and Figure 1, there is no doubt that the photoionization efficiency is closely correlated with the degradation efficiency of NaHA sensitized by PTZ, as well as with the oxidation potentials of PTZ, except in the case of APZ. Therefore, monophotonic ionization of PTZ must be the most important process initiating the degradation. When the laser photolysis was carried out under oxygen, e_{aq}^- could not be observed, probably due to the formation of superoxide anion radical [$O_2^{\bullet-}$, eq 2; $k(e_{aq}^- + O_2) = (1.2 \pm 0.3) \times 10^{10}\ M^{-1}s^{-1}$].[7]

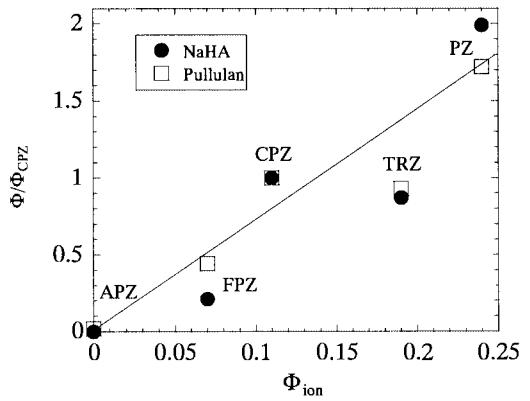
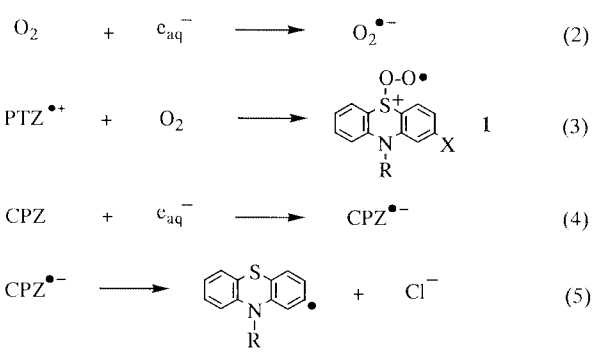


Figure 1. Plot of the relative degradation efficiency (Φ/Φ_{CPZ}) of NaHA and pullulan on irradiation with phenothiazines under oxygen vs their photoionization efficiency (Φ_{ion}) determined by means of laser photolysis.

The PTZ-sensitized degradation of NaHA was suppressed under degassed conditions, as shown in Table 1; therefore, O_2 must play an important role in the degradation process. Because superoxide dismutase had no effect on degradation efficiency in the concentration of 5–100 units/cm^3, it seems likely that $PTZ^{\bullet+}$ react with O_2 to produce peroxyl cation radicals **1** (eq 3),[9] which at this stage seems to be the active species causing degradation



through hydrogen abstraction, as in the case of hydroxyl radical generated using titanium dioxide as a photocatalyst.[3]

If homolytic bond cleavage on the C2 carbon for CPZ and TRZ (C–Cl and C–SCH_3, respectively) occurred, the phenothiazine radical (PZ•), Cl•, and •SCH_3 etc would be generated,[6] and these would also decompose NaHA through hydrogen abstraction. However, the bond dissociation energy for C–Cl is known to be extremely large (for example, 405 kJ/mol for chlorobenzene); accordingly, the reaction of e_{aq}^- with CPZ in the absence of O_2 probably produces the anion radical ($CPZ^{\bullet-}$), which readily generates PZ•, releasing Cl^- (eqs 4 and 5), as suggested by Epling et al.[10] It seems likely that the generated PZ• reacts more readily with NaHA than **1**; therefore, in the case of CPZ the degradation of NaHA would proceed more efficiently under degassed conditions.

On the basis of the relative rates for the formation of singlet oxygen ($^1O_2$) determined by Saucin and Van de Vorst, as cited in Table 1,[11] it can be stated that FPZ, CPZ, and TRZ generate the activated oxygen more efficiently than PZ. However, $^1O_2$ is not a reactive species for NaHA;[3] therefore, the reaction producing $^1O_2$ is an energy consuming process for the excited PTZ.

It is significant that radical scavengers such as glutathion, tyrosine, and *t*-butyl alcohol suppressed the degradation of NaHA. This result clearly indicates that radical species, which are generated after the photoionization of PTZ and abstract hydrogen atoms, participate in the degradation processes.

Photoinduced electron transfer (PET) decomposition of NaHA, as found in the case of methylene blue and methyl viologen,[3] was not involved in the PTZ-sensitized reactions. This is demonstrated by the fact that polysaccharides such as pullulan and methyl cellulose, which do not degrade through PET reaction, were also fragmented, as can be seen in Table 1 and Figure 1.

Further studies are now in progress in which the method outlined here is being used to determine the phototoxicity and decomposition mechanism for other PTZ.

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