#### Research Article

## Photoreactivity of LY277359 Maleate, a 5-Hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) Receptor Antagonist, in Solution

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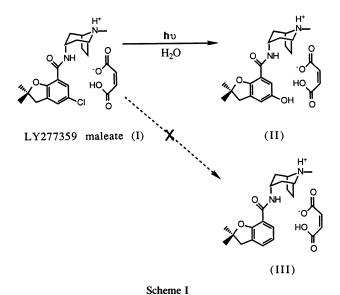
Compound LY277359 maleate undergoes a photoinduced solvolysis reaction in water to generate the corresponding hydroxylated product and release chloride. Attempts to stabilize a parenteral formulation of the compound led to an investigation of possible reaction mechanisms. The data are consistent with a mechanism involving homolytic cleavage of the aryl-chloride bond followed by electron transfer to give an aryl cation intermediate. The cation thus formed reacts with surrounding nucleophiles to give the substituted product. A kinetic expression for reaction rate was derived from the mechanism, and various components of the rate constant were evaluated experimentally. The reaction is slowed with the addition of chloride, presumably via a common ion effect (enhanced retroreaction). In the absence of added chloride, the reaction can be described kinetically by an initiation term. An inner filter effect is also observed, where increasing amounts of the hydroxylated product slow the reaction. Experimental data for observed rate constants as a function of starting concentration and light intensity are fit with good correlation to an equation describing the filter effect. Additional studies evaluated the effects of various structural features of the parent compound on the rate of the reaction in glass containers. It was determined that reactivity was dependent on two features: (1) the ortho positioning of the carboxyl and ether groups, which shifted an absorption band above the container cutoff; and (2) the para orientation of the chloro group to the ether, which is para activating in the photoexcited state.

KEY WORDS: photosubstitution; aryl cation; inner filter; kinetics; common ion effect.

#### INTRODUCTION

Preformulation studies on LY277359 maleate (I), a potent and selective 5-HT<sub>3</sub> receptor antagonist, were complicated when we discovered that aqueous solutions were unstable in the presence of light. The use of amber vials slowed the reaction but did not impart sufficient stability for formulation. Analysis of the reaction mixture by high-performance liquid chromatography (HPLC)/mass spectrometry and nuclear magnetic resonance (NMR) indicated that the only product formed was the substituted product (II) (Scheme I). The complete absence of the corresponding reduction product (III) was interesting, and this fact along with the need for a stable parenteral formulation of compound I led us into further studies to explore the nature of this reaction.

In the study reported here, we examine the impact of chemical structure and reaction conditions on the photosub-stitution reaction and investigate possible reaction mechanisms. The overall goal was to understand the reaction better so that appropriate measures could be undertaken to stabilize a parenteral formulation of compound I.



#### MATERIALS AND METHODS

#### Materials

Compounds I (endo-5-chloro-2,3-dihydro-2,2-dimethyl-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-7-ben-



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zofurancarboxamide (Z)-2-butendioate), II, IV, and VIII–X were used as received from Lilly Research Laboratories (1). Compounds V–VII, XI, and XII were obtained from Aldrich. HPLC-grade acetonitrile was used and all other chemicals were reagent grade. All solutions and buffers were prepared using water for injection, and all glassware used for drug solutions was silanized to prevent drug adsorption. Twenty-milliliter scintillation vials (Kimble), ≈280-nm cutoff, were used as reaction vessels in the light stability studies.

#### **UV Absorption Spectra**

A Beckman DU-70 spectrophotometer was used for UV absorption spectra using a 1-cm-path length cell and 60-nm/min scan speed. Solutions were scanned from 500 to 190 nm. The solvent of interest was used for calibration and background correction.

#### Kinetic Studies

A clear, incandescent, 100-W bulb (General Electric) was used as the light source and a light chamber was constructed to fix the distance the reaction vessels were placed from the bulb. The temperature in the chamber was controlled at 30 ± 1°C by air circulation. Solutions were prepared by weighing the compound of interest into volumetric flasks, solubilizing with the desired solvent, and decanting 20 ml into the vessels. For studies with added halogens, KI, KBr, KCl, and NaCl were weighed directly into the vessels and solubilized with a 0.042 mM solution of compound I to make the solutions 0.154 M in halogen. Once prepared, all solutions were stored in the dark until needed. The studies were conducted by placing the capped vessels in the light chamber at a measured distance from the source and taking 0.5-ml aliquots over time. Reversed-phase HPLC was used to assay the aliquots for compound concentration and monitor the appearance of reaction products. Reactions were followed for 6 hr. Unless otherwise noted, all reactions were conducted with the vessels placed 10 cm from the light source.

Rate-concentration dependency studies were performed by varying the initial concentration of compound I.

The effect of chloride ion was studied by monitoring the kinetics of the reaction in solutions that were 0.017, 0.077, 0.154, and 0.308 M in chloride and 0.1 mM in compound I. Ionic strength effects were evaluated in a similar manner by using NaClO<sub>4</sub> in various concentrations up to 0.2 M.

Reactions run in water/acetonitrile solutions were prepared by solubilizing compound I in a known amount of water and bringing to volume with acetonitrile. The solutions evaluated were 55.6, 41.7, 27.8, and 13.9 *M* in water and 0.1 m*M* in compound I.

Varying light intensity was accomplished by placing the reaction vessels 5, 10, or 15 cm from the filament of the bulb.

The effect of compound II on the reaction kinetics of I was studied by mixing aqueous solutions (of known concentrations) of I and II prior to light irradiation. Effects of other light absorbing organic species were studied by dissolving compound I in aqueous 1.1 mM solutions of p-aminobenzoic acid (XI) or p-nitrophenol (XII) before initiating the reaction. Control reactions were included in each study.

#### **HPLC Analysis**

LY277359 maleate and its photoreaction products were separated isocratically on a DuPont Zorbax TMS column (4.6 mm  $\times$  25 cm) at ambient temperature. The mobile phase was acetonitrile:0.125 M (NH $_4$ ) $_2$ SO $_4$ , pH 4.0 (28:72), delivered at a 1.5-ml/min flow rate with a Spectra-Physics Model 8810 pump. Injections were made using a Bio-Rad autosampler (Model AS-48) with a 20-µl fixed loop operated at 4°C. The sample chamber of the autosampler was covered with aluminum foil to protect the samples from light. Effluent was monitored on an Applied Biosystems Spectraflow UV absorbance detector (Model 783A) at a wavelength of 235 nm with peak areas being determined on a Hewlett-Packard 3396A integrator. Concentrations were calculated from external standard curves generated from aqueous drug solutions prepared in silanized glassware.

#### **RESULTS**

#### **UV** Absorbance

The UV absorption spectra of compound I in water shows a secondary absorption band at 318 nm. The nature of this band was evaluated by comparing the UV absorbance spectrum in polar and nonpolar solvents. The direction of shift in the  $\lambda_{\rm max}$  on changing solvents can be used as an indication of  $n-\pi^*$  versus  $\pi-\pi^*$  transitions (2,3). Upon changing the solvent from n-hexane to water, a 12-nm red shift was observed in the  $\lambda_{\rm max}$ . This and the magnitude of the molar absorptivity,  $4800~{\rm cm}^{-1}~M^{-1}$  at 318 nm, are indicative of a  $\pi-\pi^*$  (B-band) transition. The wavelength of maximal absorption for this band in water is given in Table I for the series of structurally related compounds evaluated in the present work.

No appreciable change in molar absorptivity was noted when the solvent was changed to methanol, ethanol, *n*-propanol, or acetonitrile.

#### **Reaction Kinetics**

Representative data from light stability studies are shown in Fig. 1. The data demonstrate apparent first-order behavior as would be expected for a photochemical process in dilute solution. A least-squares regression analysis of the data gives the solid line, the slope of which is used to calculate an observed rate constant  $(k_{\rm obs})$  value. These values are compared as the reaction conditions are varied.

The effect of solvent polarity on the occurrence and rate of the substitution reaction is demonstrated rather dramatically in Table II. Due to possible variations in the reaction conditions, (lamp aging, different initial concentrations, etc.), a control reaction was run for each set of experiments. When the polarity of the medium was reduced by using a mixture of methanol in water, the  $k_{\rm obs}$  value was reduced by half. Two additional peaks appeared on the chromatograms from that study but were not isolated and identified. Their relative position on the chromatogram suggests the possibilities of a methoxy substitution and/or the reduction product.

A similar reduction in  $k_{\rm obs}$  values was seen in the presence of increasing amounts of acetonitrile in water. Irradi-



| Compound          | λ <sub>max</sub> (nm) | $k_{\mathrm{obs}}^{}a}$ | Structure     |
|-------------------|-----------------------|-------------------------|---------------|
| IV                | 310 <sup>b</sup>      | 0.00446                 | O OH          |
|                   | $322^c$               | 0.00692                 | <b>Q</b> OH a |
| v                 | 282                   | No reaction             |               |
| VI                | 280                   | No reaction             | но Сона       |
| VII               | 308                   | No reaction             | HD.           |
| $\mathrm{VIII}^d$ | 300                   | 0.000958                | YOUNH         |
| IX                | 290                   | No reaction             | ÇÇQ a         |
| X                 | 301                   | No reaction             |               |

Table I. Absorbance and Reactivity Data for the Compounds Investigated

ating solutions of compound I in pure nonaqueous solvents of differing polarity gave no reaction.

Also included in Table II are the results of reactions run in water of varying pH. No significant change in  $k_{\rm obs}$  was observed.

When excess chloride was added, the reaction was slowed;  $k_{\rm obs}$  showed a dependency on the reciprocal of the chloride concentration. This correlation is illustrated in Fig. 2. However, when halogen ions other than chloride were added, the rate of reaction was faster than when an equimolar amount of chloride was added (Table II), and additional products were generated. Although these products were not identified, the chromatographic results are in agreement with the proposal that iodide and bromide compete with chloride and water for substitution, generating the corresponding 5-bromo and 5-iodo compounds.

#### Structural Effects

Structural effects on the rate of the solvolysis reaction of compound I are given in Table I. The reactivity of compound IV indicates no involvement by the amide-linked tropane ring in the reaction, but elimination of the carbonyl,

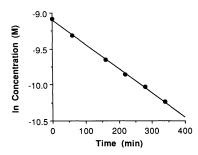


Fig. 1. Representative data showing the first-order disappearance of compound I over time.

compound IX, or moving the chloro group to the four position, compound X, destroys reactivity. Likewise, removal of the 2,3-dihydrofuran ring, compound V, eliminates reactivity. Compounds VI and VII, assessing the importance of an oxygen attached para to the halogen and possibly hydroxylcarbonyl interactions, respectively were also nonreactive. However, some reactivity was observed with compound VIII, which is the opened-ring version of compound I.

#### **DISCUSSION**

Aromatic photosubstitution reactions have been under

Table II. Effects of Solvent, Added Halogens, and pH on the Observed Rate Constant

| Solvent  | [Compound I] (mM) | $(\min^{-1} \times 10^3)$ |
|--|-------------------|---------------------------|
| H <sub>2</sub> O (27.8 <i>M</i> )/CH <sub>3</sub> OH | 0.110             | 2.4                       |
| H <sub>2</sub> O (control)                           | <i>II</i>         | 4.1                       |
| H <sub>2</sub> O (41.7 M)/CH <sub>3</sub> CN         | "                 | 3.6                       |
| H <sub>2</sub> O (27.8 M)/CH <sub>3</sub> CN         | 0.110             | 2.4                       |
| H <sub>2</sub> O (13.1 M)/CH <sub>3</sub> CN         | "                 | 0.79                      |
| CH₃CN  | "                 | No reaction               |
| CH₃OH  | 0.043             | "                         |
| (CH <sub>3</sub> ) <sub>2</sub> OH                   | "                 | "                         |
| (CH <sub>3</sub> ) <sub>3</sub> OH                   | "                 | "                         |
| NaCl (0.154 M)                                       | 0.043             | 3.9                       |
| KCl (0.154 M)  | "                 | 4.0                       |
| KBr (0.154 M)  | "                 | 9.6                       |
| KI (0.154 M)   | 0.043             | 5.9                       |
| $H_2O$ , pH $3.0^a$                                  | 0.043             | 4.7                       |
| pH 4.4 <sup>a</sup>                                  | n .               | 4.6                       |
| pH 11.0 <sup>a</sup>                                 | "                 | 5.0                       |

<sup>&</sup>lt;sup>a</sup> The starting pH of 4.4 was adjusted to pH 3.0 with 0.1 N HCl and to pH 11 with 1.0 N NaOH.



<sup>&</sup>lt;sup>a</sup> Observed rate constant in min<sup>-1</sup> from 0.043 mM solutions at 10 cm.  $k_{\rm obs} = 0.00708 \, {\rm min}^{-1}$  for compound I.

<sup>&</sup>lt;sup>b</sup> Ionized carbonyl.

<sup>&</sup>lt;sup>c</sup> Protonated carbonyl.

d Maleate salt used.

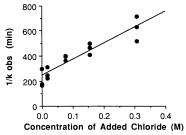


Fig. 2. Plot of  $1/k_{\rm obs}$  versus the molar concentration of added chloride. Each point represents data from one reaction vessel.

investigation since the observation in the mid-1950s that UV irradiation of nitrophenyl phosphates gave a substitution product, the corresponding nitrophenol (4). The seemingly nucleophilic photosubstitution reaction generated considerable interest because the meta isomer showed the most efficient and clean reaction. This is in contrast to ground-state orientation rules for thermal reactions. By the late 1960s it was recognized that nucleophilic aromatic photosubstitution is a fairly general reaction (5,6). It can occur with a variety of cyclic, polycyclic, and heterocyclic aromatic systems, various solvents, and a whole range of leaving groups and reacting nucleophiles. As investigations continue, there is an increasing number of proposed mechanisms for the reactions, most of them dependent on the reaction conditions.

#### **Mechanistic Studies**

In general, irradiation of aryl halides produces products of nucleophilic substitution [Eq. (1)], reductive dehalogenation [Eq. (2)], and inter- and intramolecular arylation (7).

$$ArX \xrightarrow{h\nu} ArY + X^{-} \tag{1}$$

$$ArX \xrightarrow{h\nu} ArH + SX \tag{2}$$

Four general classes of mechanisms have been identified for photostimulated aromatic substitution reactions (8) [Eq. (1)]. The classification is based on the type of intermediate formed and uses an abbreviated notation for unimolecular (1), nucleophilic (N), substitution (S), via radicals (R). When radical anions or cations are formed, the reaction is termed  $S_{R^-N}1$  or  $S_{R^+N}1$ , respectively. If a primary photodissociation into an aromatic cation occurs the mechanism is denoted  $S_N1$  (AR\*) and the classification of  $S_N2$  (AR\*) is used for reactions involving the formation of  $\sigma$  complexes.

Reductive dehalogenation, Eq. (2), provides yet another mechanism to be considered and usually involves homolytic cleavage of the aryl-halogen bond. The aryl radical intermediate thus formed can abstract a hydrogen atom from appropriate hydrogen donor solvents to give the reduced product (9). The absence of a reduction product in the current reaction does not necessarily eliminate the possibility of an aryl radical as the reactive intermediate but does suggest that alternative pathways are more probable.

The effect of solvent polarity on the rate of reaction is consistent with the appearance of a polar or charged intermediate in the rate-determining step. Possible charged species are the aryl cation, the radical anion, radical cation, and the  $\sigma$  complex. Of these, radical anions are probably not involved as they are known to be quenched very efficiently by oxygen (10), and the reaction proceeded quite well in our studies even though we made no attempt to deoxygenate the solutions. Although not totally eliminated, radical cations are unlikely because of the enhanced reactivity in the presence of potassium iodide. Iodide reduces cation radicals very well and, in fact, is sometimes used for the iodometric assay of cation-radical salts (11). If the intermediate is a radical cation, the presence of iodide should decrease the rate.

A  $\sigma$  complex intermediate has been proposed as a possible intermediate in the photosubstitution of halophenols and haloanisoles (12), but the solvent system used was dioxane/water (95:5). The greater nucleophilicity of dioxane relative to water would greatly enhance its ability to interact in an  $S_N$ 2-type reaction. The kinetics of  $S_N$ 2 reactions with one reactant in excess are usually apparent first order as is seen for the present reaction. However, when the kinetic expression for the dependence of the reaction on added chloride is derived from Scheme II using a steady-state assumption for the concentrations of the intermediates, the observed rate constant is independent of chloride concentration (see Appendix). The kinetics of the present reaction do

$$ArCl + OH^{-} \longrightarrow ArOH + Cl^{-} \longrightarrow + Cl^{-} \longrightarrow (ArCl \cdots Cl)^{-}$$
Scheme II

show dependence on added chloride concentration. A linear relationship is seen between chloride concentration and  $1/k_{\rm obs}$  (Fig. 2). This kinetic disagreement in the presence of added chloride, the expectation that  $S_{\rm N}2$  (AR\*) processes occur predominantly in less polar media (13), and the independence of reaction rate on pH argues against an  $S_{\rm N}2$  (AR\*)-type reaction.

The above evidence leads us to a mechanism involving an aryl cation intermediate,  $S_N 1$  (AR\*). This mechanistic scheme, proposed by Kropp *et al.* (14–17), involves initial homolytic cleavage of the carbon halogen bond followed by electron transfer within the resulting radical pair to generate an ion pair (Scheme III). The aryl cation can then interact, in

ArCl
$$\longrightarrow$$
Ar' + Cl' electron transfer  $H_2O$  ArOH +  $H^+$ 

Scheme III

our solvolysis reaction, with water to give the hydroxysubstituted product, compound II, or with chloride ion to regenerate compound I. The applicability of the mechanism has been expanded to cover a variety of alkyl halide photoreactions (18,19). Perhaps even more germane to the present work is the use of the mechanism to explain photosolvolysis reactions in water (20,21). As explained by Moore and Pagni



(21), the absence of the reduction product is due to the inability of the radical intermediates to abstract a hydrogen atom efficiently from water. Therefore the two radicals either recombine or undergo electron transfer to give the ions. The large dielectric constant of water will facilitate the electron transfer and favor the formation of ionic species.

The aryl cation formed is highly reactive and will react rather indiscriminately with surrounding nucleophiles (usually water). The ability of added nucleophiles to react with the cation is dependent upon the stability of the cation and the concentration of the nucleophile. For the highly reactive and unstable phenyl cation, nucleophile concentrations must approach that of the solvent for reaction to occur (22). The reactivity of compound I shows a modest inverse dependence on added chloride as a competing nucleophile (see below), the dependency agreeing kinetically with Scheme III. This is not unexpected as the cation formed, relative to the phenyl cation, should be somewhat stabilized by the ether oxygen. On changing the pH from 3 to 11, no effect on reaction rate was observed, further supporting a reactive cationic intermediate. In spite of the nucleophilicity of OH, its concentration at pH 11 cannot compete with the availability of water. There are several examples in the literature of photohydrolyses that are independent of hydroxide ion concentration over a large pH range (23).

#### Kinetic Description

The proposed mechanism illustrated in Scheme III can be described by Scheme IV if it is assumed that the electron transfer occurs very fast and the concentrations of water and chloride are invariant. If a steady-state assumption is made

$$ArCl \xrightarrow{k_1} Ar^+ \xrightarrow{k_3} ArOH$$

for [Ar<sup>+</sup>], then the loss of ArCl can be described by Eq. (3):

$$-\frac{d[ArCl]}{dt} = \frac{k_1 k_3}{k_2 + k_3} [ArCl]$$
 (3)

and the relationship between the rate constants from Scheme IV and  $k_{\rm obs}$  is

$$k_{\text{obs}} = \frac{k_1 k_3}{k_2 + k_3} \tag{4}$$

In comparing Scheme IV to Scheme III, it is seen that photochemical initiation, containing terms for intensity and quantum efficiency, is incorporated into  $k_1$ . A chloride concentration term is included in  $k_2$  and can be described as  $k_2 = k'_2[\text{Cl}^-]$ , and  $k_3$  incorporates a water concentration term,  $k_3 = k'_3[\text{H}_2\text{O}]$ . No ionic strength effect was observed over the range evaluated  $(0\text{--}0.2\ M)$ .

The various components of the overall rate constant were evaluated experimentally by altering the reaction conditions and examining the resulting observed rate constants. By monitoring the reaction in the presence of added chloride ion, alterations in  $k_2$  were imposed. Transforming Eq. (4) by

substituting the chloride terms for  $k_2$  and rewriting in the reciprocal form gives Eq. (5):

$$\frac{1}{k_{\text{obs}}} = \frac{k'_{2}[\text{Cl}^{-}]}{k_{1}k_{3}} + \frac{1}{k_{1}}$$
 (5)

This equation shows a linear relationship between  $1/k_{\rm obs}$  and [Cl<sup>-</sup>]. The inverse of the y intercept is equal to  $k_1$ , and this value along with the slope can be used to solve for the ratio of  $k_3$  to  $k'_2$ . This plot, given in Fig. 2, shows good linearity over the chloride range studied (r=0.93). Regression analysis gives a value of 0.00407 for  $k_1$  and a relationship of  $k'_2=5.22~k_3$ . Thus at chloride concentrations around 0.2 M, the  $k_2~(k_2=k'_2[{\rm Cl}^-])$  and  $k_3$  terms are approximately equal and at chloride concentrations of 0.02 M or less, the  $k_3$  term dominates and Eq. (4) reduces to  $k_{\rm obs}=k_1$ .

In the strictest sense, Eq. (3) is not valid at zero added chloride since the chloride concentration changes as the reaction progresses. However, as a worse-case scenario, if the reaction is followed to completion in the absence of added chloride, the maximum amount of chloride ion produced in our studies would be equal to the initial concentration of compound I (approximately 0.1 mM). This chloride concentration is easily within the range discussed above where  $k_{\rm obs} = k_1$  and the observed rate is independent of the amount of chloride present or being produced.

To evaluate the  $k_3$  component  $(k_3 = k'_3[H_2O])$ , the water concentration was varied by using a mixed solvent system with decreasing amounts of water in acetonitrile. The results are given in Table II and indicate that  $k_{\rm obs}$  decreases as water concentration decreases. In retrospect, this study should not have given us any information since zero added chloride causes the  $k_3$  term to drop out and therefore our model is insensitive to this effect. In addition, since the aryl cation that is formed during the reaction is quite reactive, the nucleophilicity of acetonitrile may allow the formation of the nitrilium ion, as has been seen for anthracene (24). It seems reasonable that the decrease in reaction rate that we are seeing is due to the decreased polarity of the solvent which decreases the ability of the electron transfer to occur and the ionized species to form (17,18,25). Thus under these conditions, the assumptions made in deriving Scheme IV fail.

Evaluation of the  $k_1$  term, containing intensity and quantum yield, using the  $k_{\rm obs}$  relationship [Eq. (4)], began with a determination of the rate constants for the reaction as light intensity was varied. These results are given in Fig. 3 for a range of starting concentrations. As the initial concentration of compound I increases,  $k_{obs}$  decreases in a nonlinear fashion. Varying the light intensity by changing the distance the reaction vessel is placed from the light source gives similar concentration effects but causes the curve to shift to higher  $k_{\rm obs}$  values with increasing intensity. Attempts to linearize the data by plotting  $k_{\rm obs}$  against the reciprocal of the concentration (26) were unsuccessful, indicating changes in the quantum yield,  $\Phi$ , and/or the intensity with concentration. Since the reaction was conducted at concentrations of compound I where not all of the incident light was absorbed, alterations in the intensity term are expected, and can be corrected by using Beer's law. Among the many other causes for variations in  $\Phi$  and/or intensity is the potential for the product, II, to absorb light competitively (inner-filter



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