

Research Article

Photoreactivity of LY277359 Maleate, a 5-HT₃ (5-HT₃) Receptor Antagonist, in Solution

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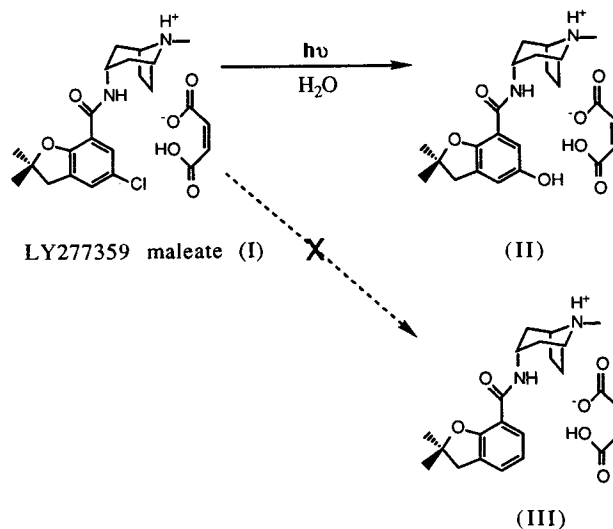
Compound LY277359 maleate undergoes a photoinduced solvolysis reaction in water to generate the corresponding hydroxylated product and release chloride. Attempts to stabilize a parenteral formulation of the compound led to an investigation of possible reaction mechanisms. The data are consistent with 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-HT₃ 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 photosubstitution 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.



Scheme 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 (I). 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), \approx 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 $30 \pm 1^\circ\text{C}$ 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_4 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 *mM* 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* $(\text{NH}_4)_2\text{SO}_4$, 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 λ_{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 λ_{max} . This and the magnitude of the molar absorptivity, $4800 \text{ cm}^{-1} \text{ M}^{-1}$ 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_{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_{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_{obs} values was seen in the presence of increasing amounts of acetonitrile in water. Irradi-

Table I. Absorbance and Reactivity Data for the Compounds Investigated

Compound	λ_{\max} (nm)	k_{obs}^a	Structure
IV	310 ^b	0.00446	
	322 ^c	0.00692	
V	282	No reaction	
VI	280	No reaction	
VII	308	No reaction	
VIII ^d	300	0.000958	
IX	290	No reaction	
X	301	No reaction	

^a Observed rate constant in min^{-1} from 0.043 mM solutions at 10 cm. $k_{\text{obs}} = 0.00708 \text{ min}^{-1}$ for compound I.

^b Ionized carbonyl.

^c Protonated carbonyl.

^d Maleate salt used.

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_{obs} was observed.

When excess chloride was added, the reaction was slowed; k_{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,

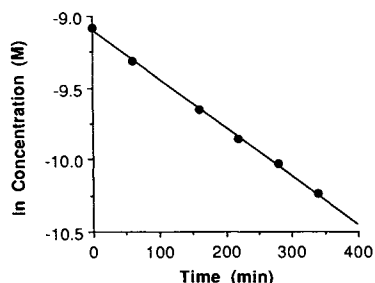


Fig. 1. Representative data showing the first-order disappearance of compound I over time.

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 hydroxyl-carbonyl 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)	k_{obs} ($\text{min}^{-1} \times 10^3$)
H ₂ O (27.8 M)/CH ₃ OH	0.110	2.4
H ₂ O (control)	"	4.1
H ₂ O (41.7 M)/CH ₃ CN	"	3.6
H ₂ O (27.8 M)/CH ₃ CN	0.110	2.4
H ₂ O (13.1 M)/CH ₃ CN	"	0.79
CH ₃ CN	"	No reaction
CH ₃ OH	0.043	"
(CH ₃) ₂ OH	"	"
(CH ₃) ₃ 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 ₂ O, pH 3.0 ^a	0.043	4.7
pH 4.4 ^a	"	4.6
pH 11.0 ^a	"	5.0

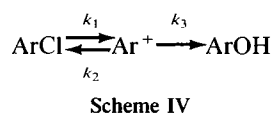
^a The starting pH of 4.4 was adjusted to pH 3.0 with 0.1 N HCl and to pH 11 with 1.0 N NaOH.

(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



for $[\text{Ar}^+]$, then the loss of ArCl can be described by Eq. (3):

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

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

$$k_{\text{obs}} = \frac{k_1 k_3}{k_2 + k_3} \quad (4)$$

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 (0–0.2 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):

$$\frac{1}{k_{\text{obs}}} = \frac{k'_2[\text{Cl}^-]}{k_1 k_3} + \frac{1}{k_1} \quad (5)$$

This equation shows a linear relationship between $1/k_{\text{obs}}$ and $[\text{Cl}^-]$. 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 ($k_2 = k'_2[\text{Cl}^-]$) 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 $k_{\text{obs}} = k_1$.

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 worst-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 $k_{\text{obs}} = k_1$ and the observed rate is independent of the amount of chloride present or being produced.

To evaluate the k_3 component ($k_3 = k'_3[\text{H}_2\text{O}]$), 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_{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_{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_{obs} values with increasing intensity. Attempts to linearize the data by plotting k_{obs} against the reciprocal of the concentration (26) were unsuccessful, indicating changes in the quantum yield, Φ , 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 Φ and/or intensity is the potential for the product, II, to absorb light competitively (inner-filter

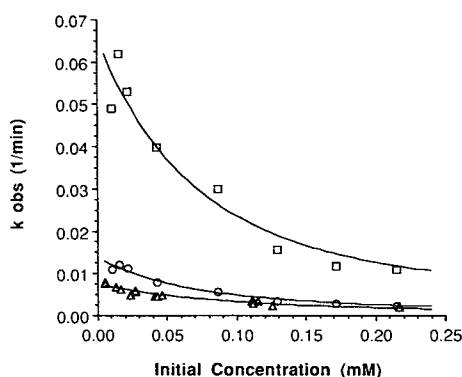


Fig. 3. Plot of k_{obs} versus the initial molar concentration of I for reaction vessels at different distances from the light source. Each point represents results from one reaction vessel. The overlaid lines are a fit of Eq. (9) to the data. (\square) 5 cm; (\circ) 10 cm; and (\triangle) 15 cm.

effect) (27). Since a UV scan of compound II shows it to have an absorbance spectrum almost identical to that of compound I, competitive light absorption by the product was highly probable.

In a light irradiation experiment, the inner filter effect can be described as the absorption of incident radiation by a species other than the intended primary absorber (28). In this experiment, the secondary absorber proves to be the product, II, of the reaction. Zimmerman *et al.* (29) were the first to consider the case where the reactant and product have similar spectral characteristics. The concept was later expanded by Bunce (30) to cover the general case where the product and reactant are different spectrally. For our studies we use a form intended for irradiation studies at an isosbestic point (30).

$$\ln \frac{C_0}{C_f} = \frac{\Phi_r I_0 (1 - e^{-2.303 \text{ Abs}})}{C_0} \quad (6)$$

In Eq. (6), C_0 and C_f are initial and final concentrations of reactant respectively, Φ_r is the quantum yield for reactant disappearance, and I_0 is the accumulated photon dose. The term $(1 - e^{-2.303 \text{ Abs}})$ is a correction factor for the amount of light actually absorbed. Differentiation with respect to time gives Eq. (7), where I is now an intensity term, i.e., photon dose per unit time.

$$-\frac{dC}{dt} = \frac{\Phi_r I (1 - e^{-2.303 \text{ Abs}})}{C_0} C \quad (7)$$

Although this equation describes reactions run using monochromatic light, we assume for demonstrative purposes that it will hold for the summation of wavelengths initiating our reaction. This is a reasonable assumption since the reactant and product have almost identical UV absorption spectra.

Comparing Eq. (7) to Eqs. (3) and (4) gives Eq. (8), where the observed rate constant is seen to be a function of the initial concentration of compound I used and the absorbance of the solution.

$$k_{\text{obs}} = \frac{\Phi_r I (1 - e^{-2.303 \text{ Abs}})}{C_0} \quad (8)$$

It should be noted at this time that the I term contains

factors of geometry, etc., which are unique to the apparatus being used. It should therefore be replaced with the more general term n as suggested by Moore (26). By making this substitution and one for the Beer's law expression for absorbance into the equation, a working form is generated.

$$k_{\text{obs}} = \frac{\Phi_r n (1 - e^{-2.303 \epsilon b C_0})}{C_0} \quad (9)$$

The data from Fig. 3 were fit to Eq. (9) with the nonlinear regression function provided in the SAS software, while floating the quantities $(\Phi_r n)$ and (ϵb) . Initial estimates were obtained from a Taylor's series expansion of Eq. (9) which gave a final result linear in concentration describing the limiting slope at low C_0 values. The results of the SAS regression are given in Table III and are used to generate the solid lines in Fig. 3.

The good fit of Eq. (9) to our experimental data indicates that the changes in k_{obs} with concentration can be explained in terms of an inner-filter effect. This is further substantiated in Table IV, where the addition of compound II and other organic species, compounds XI and XII, known to absorb light in the same wavelength range, are seen to slow the reaction.

Structure-Reactivity Relationships

Spectroscopic analysis of the compounds in Table I provides some rationale for the observed reactivity. All of the compounds show a $\pi-\pi^*$ band peaking in the wavelength range of 280–325 nm. Compounds V and VI, having functional groups either meta or para to the chloro substituent, show an absorption band peaking around 280 nm. This wavelength is below our reaction vessel cutoff and these compounds would not be expected to show reactivity. The compounds which have a carbonyl and an ether or hydroxyl oxygen in an ortho configuration show a red shift in this peak (VII, 308 nm; VIII, 300 nm), presumably due to hydrogen bonding. These absorption bands are barely in the spectrum transmitted by the vessel and reactivity would still be questionable. The fact that VIII (lower λ_{max}) has some reactivity and VII does not implies that factors other than vessel cutoff are involved. One possibility is the need for the alkoxy-group activation of the para position (31,32) not just the ortho/para direction (33) as has been postulated for hydroxy groups. The lack of reactivity with X ($\lambda_{\text{max}} = 301$ nm), where the chloro is in the 4 position, further suggests that para activation is of considerable importance.

Constraining the ether oxygen into a ring further shifts the λ_{max} as illustrated by compounds I (320 nm) and IV (322) (protonated carbonyl) and gives full reactivity. However, allowing a charge on the carbonyl or removing it (IX),

Table III. Parameters Generated from SAS Regression Analysis

Distance from light source (cm)	$\Phi_r n \times 10^6$	$\epsilon b \times 10^{-4}$
5	2.55	1.13
10	0.509	1.18
15	0.362	0.89

Table IV. Effect of Adding UV Absorbing Species on the Observed Rate of the Substitution Reaction

Species added	[Compound I] (mM)	[Species] (mM)	Distance from light source (cm)	k_{obs} ($\text{min}^{-1} \times 10^3$)
II	0.11	0.11	10	2.84
II	"	0.0733	"	2.78
II	"	0.0367	"	4.12
Control	0.11	—	10	4.68
XI	0.017	1.12	22	2.20
XII	"	1.06	"	0.351
Control	"	—	"	5.30

even with the oxygen tied into the furan ring, reduces or eliminates reactivity in our system as the λ_{max} is shifted back toward the vessel cutoff.

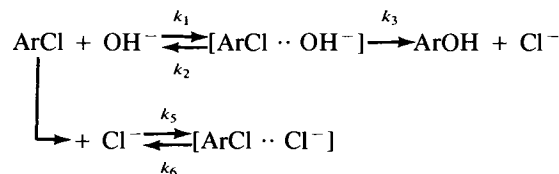
In conclusion, the photoinduced solvolysis reaction of compound I probably involves homolytic cleavage of the aryl-chloride bond followed by electron transfer to give an aryl cation intermediate. This highly reactive species then reacts almost indiscriminately with surrounding nucleophiles to give the corresponding substitution product; in water this is the hydroxylated species. Greatest reactivity is seen when the parent molecule contains a substituent oriented para to the chloro group which is para activating in the photoexcited state and, of course, an absorption band appearing at wavelengths above the vessel cutoff. For the series of compounds investigated, this occurs with an ether-linked oxygen para to the chloro group (preferably constrained into a furan ring) and an uncharged carbonyl attached ortho to the ether.

The reaction is slowed with the addition of sodium chloride attributed to a common ion effect (enhanced retroreaction) (34,35). In the absence of added chloride, the reaction can be described kinetically by an initiation term. An inner-filter effect is seen with this reaction where the appearance of II slows the reaction by absorbing a portion of the incident radiation. The addition of II, or other species known to absorb light in the wavelength range of 370–280 nm, slows the reaction via the same mechanism. Unfortunately, the use of this technique to formulate stable parenteral formulations of I is complicated by the requirements that excipients need to be nontoxic and pharmacologically inactive and to contain a chromophore absorbing in the necessary wavelength range. They must also not act as a nucleophile capable of entering into the substitution pathway. To date, these requirements have precluded the use of most excipients to stabilize the formulation.

However, by using a combination of techniques, a stable parenteral formulation of I has been achieved. Combining the use of amber vials, added chloride, and the concentration effect has granted stability unachievable by any single method.

APPENDIX

The effect of chloride on the rate of loss of ArCl can be determined from Scheme II* by writing the differential equations for each of the species involved. If the steady-state assumption is used for the concentration of the dichloro intermediate (i.e., $d[\text{ArCl} \cdot \text{Cl}^-]/dt = 0$), it appears that the chloride dependence should drop out. Proof of that state-



Scheme II*

ment is as follows. The differential equation describing the loss of ArCl with time is

$$\begin{aligned}
 \frac{d[\text{ArCl}]}{dt} = & -k_1[\text{OH}^-][\text{ArCl}] + k_2[\text{ArCl} \cdot \text{OH}^-] \\
 & - k_5[\text{Cl}^-][\text{ArCl}] + k_6[\text{ArCl} \cdot \text{Cl}^-] \quad (10)
 \end{aligned}$$

likewise,

$$\frac{d[\text{ArCl} \cdot \text{Cl}^-]}{dt} = k_5[\text{Cl}^-][\text{ArCl}] - k_6[\text{ArCl} \cdot \text{Cl}^-] \quad (11)$$

and

$$\frac{d[\text{ArCl} \cdot \text{OH}^-]}{dt} = k_1[\text{OH}^-][\text{ArCl}] - (k_2 + k_3)[\text{ArCl} \cdot \text{OH}^-] \quad (12)$$

Invoking the steady-state assumption for $[\text{ArCl} \cdot \text{Cl}^-]$ and $[\text{ArCl} \cdot \text{OH}^-]$ and rearranging gives

$$[\text{ArCl} \cdot \text{Cl}^-] = \frac{k_5[\text{Cl}^-][\text{ArCl}]}{k_6} \quad (13)$$

and

$$[\text{ArCl} \cdot \text{OH}^-] = \frac{k_1[\text{OH}^-][\text{ArCl}]}{(k_2 + k_3)} \quad (14)$$

Substituting Eqs. (13) and (14) into Eq. (10) and rearranging gives

$$\frac{d[\text{ArCl}]}{dt} = \left[-k_1[\text{OH}^-] + \frac{k_1 k_2 [\text{OH}^-]}{k_2 + k_3} \right] [\text{ArCl}] \quad (15)$$

and it is seen that the dependence on $[\text{Cl}^-]$ is eliminated.

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