J. Org. Chem. 1986, 51, 672–677

Photodehalogenation and Photodimerization of 2-(4-Halophenyl)benzoxazoles. Dependence of the Mechanism on the Nature of the Halogen Atom

Suzanne Fery-Forgues and Nicole Paillous*

Laboratoire des IMRCP, U.A. au CNRS No. 470, Université Paul Sabatier, 31062 Toulouse Cedex, France

Received May 21, 1985

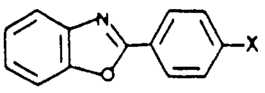
Irradiation of oxygen-free solutions of 2-(4-halophenyl)benzoxazoles at 300 nm led to dimerization or dehalogenation reactions. The fluoro derivative formed only dimer, while the chloro compound underwent both dimerization and dehalogenation. The bromo and iodo compounds did not form dimers but were dehalogenated. Fluorescence studies showed that the intersystem crossing yield decreased from the fluoro to the iodo compound. While dimerization was found to involve a singlet state, the excited state responsible for photodehalogenation of the bromo and iodo compounds was found to be the triplet on the basis of quenching and sensitization experiments. Triplet excited-state lifetimes were estimated. Photodehalogenation of 2-(4-chlorophenyl)benzoxazole occurs via the singlet state, involving an excimer as demonstrated from the influence of concentration on quantum yield. Photodehalogenation of the chloro and bromo compounds was considerably enhanced in the presence of electron donors such as *cis*-piperylene and triethylamine. These dehalogenation reactions are believed to proceed via an excited charge-transfer complex.

Benzoxazole derivatives have numerous therapeutic applications.[1] In particular, benoxaprofen (2-[4-chlorophenyl]-α-methyl-5-benzoxazoleacetic acid, **1**) is a potent antiinflammatory agent. However, its use is limited by undesirable phototoxic effects. These cutaneous side reactions may be attributed to a photoinduced oxidation of skin components involving either a singlet-oxygen[2] mechanism or a free-radical peroxidation. The formation of singlet oxygen has already been detected on irradiation of benoxaprofen.[3] This paper is concerned with the free-radical processes involved in the photochemistry of benoxaprofen model compounds in oxygen-free solutions.

A two-step process has been proposed to explain the phototoxicity of benoxaprofen. Initially, irradiation of an ethanolic solution of benoxaprofen leads to rapid decarboxylation of the drug. The second step is photosensitization of biological membranes by the decarboxylated product producing tissue damage. Since the phototoxicity of benoxaprofen is related to the photochemical reactivity of the decarboxylated compound,[4] we have investigated the photochemical behavior of 2-(4-halophenyl)benzoxazoles **3**–**6** (see Scheme I and Chart I).

In the absence of oxygen, these compounds can undergo a free-radical dehalogenation by cleavage of the carbon–halogen bond or a dimerization reaction as described in a previous paper[5] for 2-phenylbenzoxazole (**2**).

Chart I



X = H, F, Cl, Br, I

2 3 4 5 6

Table I. Effect of Temperature on the Decomposition Rate Constant and on the Half-life of Photodimers 8 and 9 in Cyclohexane Solution

temp, °C	$10^{-5}k_d$, s^{-1}	$t_{1/2}$, h	temp, °C	$10^{-5}k_d$, s^{-1}	$t_{1/2}$, h
Photodimer 8			Photodimer 9		
24.9	1.00	19.25	30.1	2.30	8.37
32.5	2.51	7.67	32.8	3.50	5.50
34.3	3.91	4.92	35.9	5.71	3.37
38.8	5.85	3.29	38	9.59	2.00

Photodimerization. Concentrated oxygen-free solutions of **3**–**6** in cyclohexane were irradiated at 300 nm. Only 2-(4-fluorophenyl)benzoxazole (**3**) and 2-(4-chlorophenyl)benzoxazole (**4**) underwent dimerization. The photodimers **8** and **9** were shown by UV, NMR, and IR to have the same 1,3-diazetidine structure as the dimer **7** of 2-phenylbenzoxazole (see Scheme II). Like **7**, these dimers are stable in the solid state at room temperature, but unstable in solution, easily reverting to the monomer. This quantitative decomposition is accelerated by acids, heat, or UV irradiation. The thermally induced decomposition of **8** and **9** was monitored by UV spectroscopy (Table I) and found to obey a first-order rate law. The activation energy of the thermally induced decomposition and the preexponential Arrhenius factor (Table II) were calculated from the rate constants of reversion determined at various temperatures.

The quantum yield of the photodimerization of the chloro compound **4** was much lower than that of the fluoro derivative **3**, and the activation energy for **4** was correspondingly higher. No photodimers were formed from the bromo and iodo derivatives **5** and **6** under our conditions. This result may be due in part to the low solubility of these compounds ($C \leqslant 10^{-2}$ M) because the yield of dimerization is concentration-dependent.

Photodehalogenation. As the efficiency of dimerization decreased, photodehalogenation became the predominant reaction (see Scheme III). Under irradiation, compounds **2** and **3** gave only the photodimers. Compound **4** underwent both dimerization and photodehalogenation, the quantum yield of the latter being very low ($\simeq 10^{-5}$; Table III). Compounds **5** and **6** exhibit only dehalogenation to 2-phenylbenzoxazole. The quantum yield for

---

(1) (a) Advani, S. B.; Sam, J. *J. Pharm. Sci.* **1968**, *57*, 1693. (b) Kay, J. M.; Smith, P.; Heath, D.; Will, J. A. *Cardiovasc. Res.* **1976**, *10*, 200. (c) Badin, J.; Tinland, B. *Res. Commun. Chem. Pathol. Pharmacol* **1973**, *6*, 1099. (d) Dunwell, D. W.; Evans, D. *J. Med. Chem.* **1977**, *20*, 797.

(2) Ito, T. *Photochem. Photobiol.* **1978**, *28*, 493.

(3) (a) Reska, K.; Chignell, C. F. *Photochem. Photobiol.* **1983**, *38*, 281. (b) Navaratnam, S.; Hugues, S. L.; Parsons, B.; Phillips, G. O. *Photochem. Photobiol.* **1985**, *41*, 375.

(4) Kochevar, I. E.; Hoover, K. W.; Gawienowski, M. *J. Invest. Dermatol.* **1984**, *82*, 214.

(5) Roussilhe, J.; Fargin, E.; Despax, B.; Lopez, A.; Paillous, N. *J. Org. Chem.* **1983**, *48*, 3736.

0022-3263/86/1951-0672$01.50/0

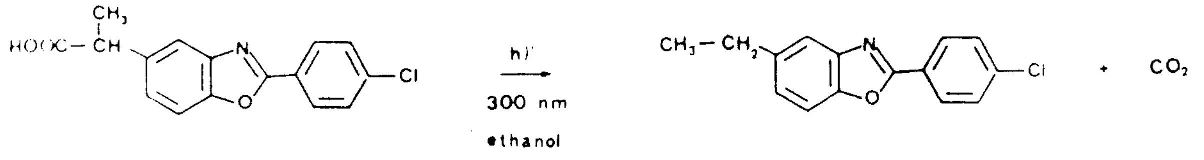
Table II. Quantum Yield of Dimerization, Activation Energy, and Arrhenius Preexponential Factor of Reversion

compd	[C], M	Φ_{dim}	$E^{\ddagger}$, kJ mol^{-1}	A
2	1×10^{-1}	8×10^{-2}	90	2.6×10^{10}
3	1×10^{-1}	$2 \times 10^{-2} \pm 0.75 \times 10^{-2}$	104.5	1.8×10^{13}
4	5×10^{-2}	$1.42 \times 10^{-3} \pm 0.53 \times 10^{-3}$	154.6	1.1×10^{22}

Table III. Quantum Yield of Dehalogenation in Methanol and Cyclohexane

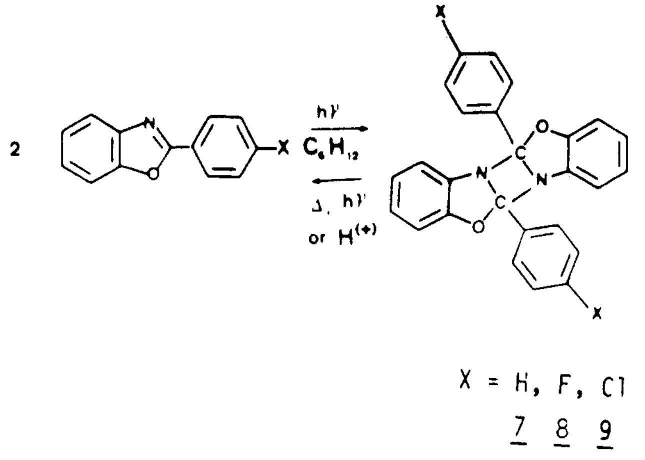
	methanol		cyclohexane	
compd	[C], M	Φ	[C], M	Φ
4	1.7×10^{-2}	$3.98 \times 10^{-5} \pm 0.8 \times 10^{-5}$	2.8×10^{-2}	$2.7 \times 10^{-5} \pm 0.5 \times 10^{-5}$
5	8.8×10^{-3}	$1.87 \times 10^{-3} \pm 0.4 \times 10^{-3}$	7.5×10^{-3}	$7.5 \times 10^{-4} \pm 0.3 \times 10^{-4}$
6	2×10^{-3}	0.17 ± 0.05	3.8×10^{-3}	0.14 ± 0.03

Scheme I

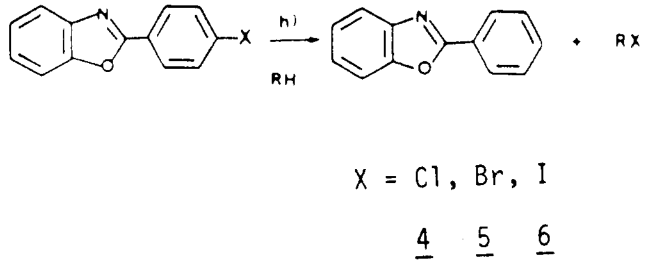


1

Scheme II



Scheme III



dehalogenation, which is zero for the fluorinated compound, increased markedly from the chloro to the iodo derivative (Table III). It was slightly higher in methanol than in cyclohexane.

Spectroscopic Study. The UV and fluorescence spectra of cyclohexane solutions of **1**–**6** were recorded, and the fluorescence quantum yields were measured at an excitation wavelength of 299 nm. The quantum yield of fluorescence was rather high for **2**, and decreased dramatically as the substituent changed from fluorine to iodine (Table IV). This result may be explained by an enhancement of intersystem crossing due to an intramolecular heavy atom effect. We have also pointed out that the fluorescence quantum yield of benoxaprofen was slightly higher than that of its chloro analogues.

Table IV. UV and Fluorescence λ_{max} and Quantum Yields of Halogenated Derivatives in Cyclohexane

compd	UV λ_{max}, nm	EM λ_{max}, nm	Φ_{em}
1	308.5	343	0.75 ± 0.05
2	299	333	0.76 ± 0.04
3	299	332	0.64 ± 0.04
4	305	340	0.57 ± 0.03
5	306	342	0.16 ± 0.03
6	309.5	344	<0.05

Mechanism. As has been shown previously for 2-phenylbenzoxazole,[5] photodimerization occurs through a singlet excited state, probably involving the formation of an excimer. However, a mechanism for the photochemical

$$\begin{gathered} \mathrm{Bz} \xrightarrow{h\nu} \mathrm{Bz}^1 \\ \mathrm{Bz}^1 + \mathrm{Bz} \rightarrow (\mathrm{Bz}\text{–}\mathrm{Bz})^* \\ (\mathrm{Bz}\text{–}\mathrm{Bz})^* \rightarrow \text{dimer} \end{gathered} \tag{1}$$

dehalogenation of 2-(4-halophenyl)benzoxazoles has not been proposed. The photolysis of aryl halides in solution has been studied extensively since about 1960. It appears that these reactions can proceed by a wide range of mechanisms,[6] which depend on both the nature of the halogen and the aromatic compound. Simple energy considerations indicate that aryl halides can undergo homolysis if the energy of the excited state is close to the necessary bond-dissociation energy. Numerous investigators have concluded that triplet state homolysis of the Ar–X bond is the preferred pathway when the triplet energy of the halo compound is sufficiently high. This condition is always fulfilled in the photolysis of iodoaromatic compounds,[7] and the triplet mechanism is still possible for the majority of bromo derivatives.[8] For aryl chlorides, reductive dechlorination can proceed by variety of mechanisms. Homolytic cleavage of the C–Cl bond may derive from a triplet[9-12] or a singlet[11,13-15] excited state,

---

(6) Grimshaw, J.; De Silva, A. P. *Chem. Rev.* **1981**, 181.

(7) (a) McD. Blair, J.; Bryce-Smith, D.; Pengilly, B. W. *J. Chem. Soc.* **1959**, 3174. (b) Wolf, W.; Kharash, N. *J. Org. Chem.* **1965**, *30*, 2493.

(8) (a) Matsuura, T.; Omura, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 944. (b) Pinhey, J. T.; Rigby, R. D. G. *Tetrahedron Lett.* **1969**, *16*, 1267.

(9) Tissot, A.; Boule, P.; Lemaire, J. *Chemosphere* **1984**, *13*, 381.

(10) Bunce, N. J.; Bergsma, J. P.; Bergsma, M. D.; De Graaf, W.; Kumar, Y.; Ravana, L. *J. Org. Chem.* **1980**, *45*, 3708.

(11) Ruzo, L. O.; Zabik, M. J.; Schuetz, R. D. *J. Am. Chem. Soc.* **1974**, *12*, 3809.

(12) Bunce, N. J.; De Schutter, C. T.; Toone, E. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 859.

(13) Nishiwaki, T.; Shinoda, T.; Anda, K.; Hida, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3565.

Table V. Influence of Quenchers on the Quantum Yield of Dehalogenation of 2-(4-Iodophenyl)benzoxazole

[6], 10^3M	[Q], 10^3M	Φ_0/Φ	[6], 10^3M	[Q], 10^3M	Φ_0/Φ
	cis-Piperylene			Naphthalene	
1.56	12.3	1.63	1.25	8	1.99
1.56	6.12	1.39	1.25	6	1.77
3.08	3.21	1.25	1.25	4	1.43
3.08	2.14	1.20	1.25	2	1.27
1.56	1.23	1.16			
1.56	0.61	1.03			

sometimes involving an excimer as an intermediate.[10,16,17] The reaction may also be initiated by electron transfer,[18-20] possibly accompanied by protonation[21,22] of the excited aryl chloride. On the basis of literature data,[23] the bond energies D (C–X) can be estimated to be

$$D(\mathrm{Ph{-}I}) = 255\ \mathrm{kJ\ mol^{-1}}$$

$$D(\mathrm{Ph{-}Br}) = 305\ \mathrm{kJ\ mol^{-1}}$$

$$D(\mathrm{Ph{-}Cl}) = 365\ \mathrm{kJ\ mol^{-1}}$$

Substitution by halogen changes the excited-state energies of the parent aromatic system very little. Accordingly, the triplet state energy of halogenated aromatic derivatives must be close to 267.5 kJ mol^{-1}, which is an accepted value for the triplet energy of 2-phenylbenzoxazole.[24] From fluorescence studies we estimate the singlet energy to be around 370.7 kJ mol^{-1}. These considerations suggest that the mechanism of photodehalogenation may not always be a simple triplet state homolysis.

We attempted to establish the mechanism of photodehalogenation by photosensitization or quenching experiments using benzophenone (E_T = 289 kJ mol^{-1}), naphthalene (E_T = 255.5 kJ mol^{-1}), and *cis*-piperylene (E_T = 247 kJ mol^{-1}) as additives. The photodehalogenation of the iodo compound **6** is quenched by naphthalene in methanol and by *cis*-piperylene in cyclohexane. On the other hand, this reaction is strongly sensitized by benzophenone (Table V). These results indicate that photodehalogenation of the iodo derivative involves the triplet excited state as suggested from energetic considerations.

The influence of quencher concentration of the quantum yield of the reaction was measured in both systems. Plotting the relative value Φ_0/Φ against the concentration of quencher [Q] gives a value for the Stern–Volmer quenching constant

$$k_q\tau = 124.5 \pm 10.8\ \mathrm{M^{-1}}\ (\text{naphthalene})$$

$$k_q\tau = 46.8 \pm 6\ \mathrm{M^{-1}}\ (\textit{cis}\text{-piperylene})$$

where Φ_0 and Φ are respectively the quantum yields of 2-phenylbenzoxazole formation in the absence and in the presence of quencher and τ is the lifetime of the excited triplet state. Assuming that quenching is diffusion-controlled, the triplet lifetime was calculated as $k_q = 12 \times 10^9$ M^{-1} s^{-1}, $\tau = 10.3 \times 10^{-9}$ s (naphthalene in methanol), and $k_q = 6.8 \times 10^9$ M^{-1} s^{-1}, and $\tau = 6.8 \times 10^{-9}$ s (*cis*-piperylene in cyclohexane). These lifetimes seem somewhat short for a triplet state, but they are of the same order as the triplet lifetimes of halobenzenes and polychlorinated biphenyls determined from quenching experiments.[9,21]

Table VI. Relative Variations of the Photodehalogenation Yield of 5 and 6 in Water–Methanol Mixtures at 30 °C

vol of water × 100/[vol of (water + MeOH)]	kin visc η, cSt	Φ_{rel}	vol of water × 100/[vol of (water + MeOH)]	kin visc η, cSt	Φ_{rel}
Compound 5			Compound 6		
0	0.659	1.00	0	0.659	1.00
2.5	0.725	0.97	10	0.933	0.69
5	0.812	0.76	20	1.160	0.56
7.5	0.880	0.74	30	1.331	0.49
10	0.933	0.66			

Table VII. Relative Variations of the Photodehalogenation Yield of 5 and 6 in Glycol–Methanol Mixtures at 30 °C

vol of glycol × 100/[vol of (glycol + MeOH)]	kin visc η, cSt	Φ_{rel} compd 5	Φ_{rel} compd 6
0	0.659	1.00	1.00
5	0.740	0.78	0.69
10	0.839	0.73	0.57
15	0.948	0.71	0.54

Table VIII. Influence of Naphthalene on the Quantum Yield of Photodehalogenation of 2-(4-Bromophenyl)benzoxazole

[Q], 10^3 M	Φ_0/Φ
10	1.36
8	1.27
6	1.19
4	1.16
2	1.10

We have pointed out that the quantum yield of dehalogenation is slightly greater in methanol than in cyclohexane. It is also decreased by adding water to the methanol (Table VI). These effects cannot be explained by the involvement of an ionic process because the increase in the polarity of the solution with the proportion of water in methanol would enhance the reaction efficiency, which is not the case. The effect of water in decreasing the quantum yield of dehalogenation may be due to an increase of viscosity, which changes from 0.659 to 1.331 cSt (at 30 °C) when the proportion of water in methanol varies from 0 to 30%. For a homolytic mechanism an increase in solution viscosity could increase the probability of recombination of radicals in the solvent cage. A similar effect was observed when the water in methanol was replaced by glycol (Table VII), supporting this assumption.

The following mechanism is proposed for the photodehalogenation of the iodo compound **6**.

$$\begin{gathered}
\mathrm{BzX} \xrightarrow{h\nu} \mathrm{BzX^1} \\
\mathrm{BzX^1} \xrightarrow{k_{st}} \mathrm{BzX^3} \\
\mathrm{BzX^3} \xrightarrow{k_{r^3}} (\mathrm{Bz\cdot} + \mathrm{X\cdot}) \\
\mathrm{Bz\cdot} + \mathrm{RH} \xrightarrow{k_p} \mathrm{BzH} + \mathrm{R\cdot} \\
\mathrm{BzX^3} \xrightarrow{k_{d^3}} \mathrm{BzX}
\end{gathered} \tag{2}$$

---

(14) Robinson, G. E.; Vernon, J. M. *J. Chem. Soc., Chem. Commun.* **1969**, 977.

(15) Robinson, G. E.; Vernon, J. M. *J. Chem. Soc. C* **1971**, 3363.

(16) Soumillon, J. P.; De Wolf, B. *J. Chem. Soc., Chem. Commun.* **1981**, 436.

(17) Kojima, M.; Sakuragi, H.; Tokumaru, K. *Chem. Lett.* **1981**, 1539.

(18) Bunce, N. J.; Pilon, P.; Ruzo, L. O.; Sturch; O. J. *J. Org. Chem.* **1976**, *41*, 3023.

(19) Ruzo, L. O.; Bunce, N. J.; Safe, S. *Can. J. Chem.* **1975**, *53*, 688.

(20) Ohashi, M.; Tsujimoto, K.; Seki, K. *J. Chem. Soc., Chem. Commun.* **1973**, 384.

(21) Smothers, W, K.; Schanze, K. S.; Saltiel, J. *J. Am. Chem. Soc.* **1979**, *101*, 1895.

(22) Bunce, N. J.; Kumar, Y.; Ravanal, L. *J. Org. Chem.* **1979**, *44*, 2612.

(23) Benson, S. "The Foundations of Chemical Kinetics"; McGraw-Hill: New York, *1960*; p 670.

(24) Olszowski, A.; Romanowski, H.; Ruziewicz, Z. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1973**, *21*, 381.

Table IX. Influence of Temperature on the Relative Quantum Yield of Photodehalogenation of 2-(4-Bromophenyl)benzoxazole in Methanol

T, °C	Φ_{rel}
50	1.00
30	0.84
7	0.47

The possibility of recombination is not considered because of the spin restriction against recombination of triplet radical pairs.

The photodehalogenation of the bromo compound **5** is sensitized by benzophenone and quenched by naphthalene (Table VIII), suggesting involvement of a triplet state. The corresponding Stern–Volmer slope (31.8 ± 3.5 M^{-1}) allowed us to calculate the value of the excited triplet lifetime in methanol ($\tau = 2.6 \times 10^{-9}$ s), which is slightly shorter than the triplet lifetime of the iodo derivative. The effect of solvent is similar to that reported for the iodo compound. Again, the viscosity dependence is consistent with a free-radical mechanism (Tables VI, VII). Considering that the carbon–bromine bond energy is 37.5 kJ mol^{-1} higher than the triplet energy, homolysis of the Ar–Br bond via the triplet state might be endothermic. A large temperature effect on the quantum yield of the reaction was observed (Table IX), but it could also be explained by a decrease in viscosity.

When we attempted to determine the triplet lifetime of **5** using *cis*-piperylene, an unexpected effect was observed: the addition of quencher increased the rate of photodehalogenation. The change of Φ_r^{-1} vs. $[\mathrm{Q}]^{-1}$ was linear and the slope was 1.45 ± 0.10 M. Similar abnormal behavior has been reported for halonaphthalenes.[11] The increase in reaction rate cannot be explained by energy transfer, since the triplet energy of *cis*-piperylene is considerably lower than that of 2-phenylbenzoxazole. It seems that *cis*-piperylene acts as an electron donor to the excited bromobenzoxazole. The intermediate might be an excited charge transfer complex, favoring heterolytic cleavage of the C–Br bond. It has recently been shown that 2-phenylbenzoxazole participates in the photoinduced reactions with electron donors such as azide ions.[25] On the other hand, examples of photodehalogenation assisted by dienes have been reported.[19] Smothers, Schanze, and Saltiel[21] studied the photodechlorination of 9,10-dichloroanthracenes promoted by 2,4-hexadiene. The involvement of an electron-transfer process has also been postulated by Bunce and Gallagher[26] for aryl chlorides.

In the absence of an electron donor, the photodehalogenation of the bromo derivative **5** appears to follow the triplet mechanism (2). In the presence of diene, the reaction may involve electron transfer via the singlet or the triplet state.

$$\begin{aligned} \mathrm{BzX}^* + \mathrm{D} &\xrightarrow{k_{\mathrm{D}}} (\mathrm{BzX}^- ...\mathrm{D}^+)^* \\ (\mathrm{BzX}^- ...\mathrm{D}^+)^* &\xrightarrow{k_{\mathrm{rD}}} \mathrm{Bz}\cdot + \mathrm{X}^- + \mathrm{D}^+ \\ (\mathrm{BzX}^- ...\mathrm{D}^+)^* &\xrightarrow{k_{\mathrm{dD}}} \mathrm{BzX} + \mathrm{D} \end{aligned} \tag{3}$$

The photodehalogenation of the iodo compound **6**, which proceeds by a triplet reaction, was not enhanced by *cis*-piperylene. It is possible that enhancement by the diene operates only on a singlet excited state.

Table X. Influence of Concentration on the Relative Quantum Yield of Photodehalogenation of 4 and 6

[C], 10^{3}M	Φ_{rel}	[C], 10^{3}M	Φ_{rel}
Compound 4		Compound 6	
17.2	1.00	4.8	1.00
2.4	0.11	3.8	0.99
1.1	0.06	2.7	0.92
0.55	0.03	1.4	0.89

In the irradiation of 2-(4-chlorophenyl)benzoxazole, no effect of solvent upon the quantum yield of photodechlorination was observed when varying the concentration of water in methanol from 0 to 20%. The reaction appeared to be independent of polarity, which is in agreement with a nonionic mechanism. The absence of quenching on addition of naphthalene suggests the involvement of a singlet excited state in the photodehalogenation, as expected from energy considerations; the energy of the excited triplet state is not sufficient to induce the homolytic fission of the C–Cl bond. The energy difference would make the reaction unreasonably endothermic, even if vibrational contributions are included.

Nevertheless, further experimental evidence for the involvement of the excited singlet state was sought. An attempt at sensitization by benzophenone led to photodechlorination despite the fact that the energy of the triplet excited state of benzophenone is too low to sensitize the singlet excited state of benzoxazole. However, the formation of side reaction products indicated that the reaction took a different course, probably due to an electron transfer process. A similar mechanism involving the excited singlet state has been postulated for the photolysis of chlorobenzene[14,15] and of chloronaphthalene[10] whose energy is very close to that of 2-phenylbenzoxazole. In contrast to the small effect of concentration on the photodehalogenation of the iodo derivative **6**, the quantum yield of photodehalogenation of the chloro compound **4** was considerably enhanced at higher concentrations (Table X), suggesting the involvement of an excimer.

$$\begin{aligned} \mathrm{BzX} + \mathrm{BzX}^1 &\xrightarrow{k_{\mathrm{e}}} (\mathrm{BzX})_2{}^* \\ (\mathrm{BzX})_2{}^* &\xrightarrow{k_{\mathrm{de}}} 2\ \mathrm{BzX} \\ (\mathrm{BzX})_2{}^* &\xrightarrow{k_{\mathrm{re}}} \mathrm{BzX} + \mathrm{Bz}\cdot + \mathrm{X}\cdot \end{aligned} \tag{4}$$

As occurred with the bromo compound, irradiation of 2-(4-chlorophenyl)benzoxazole in the presence of *cis*-piperylene led to enhanced photolability. This reaction can likewise be attributed to electron transfer from diene to the chloro compound. Several photoadducts of *cis*-piperylene to **4** were identified by mass spectroscopy. Based on measurement of the disappearance of **4** the slope of a plot of Φ^{-1} vs. $[\mathrm{pip}]^{-1}$ is $35.65 \times 10^{-2} \pm 3 \times 10^{-2}$ M (Figure 1).

In order to avoid side reactions and to help support the hypothesis of a charge-transfer process, experiments were undertaken with triethylamine as electron donor.[27] Triethylamine did in fact promote photodehalogenation[18,28] of **4** in methanol. The quantum yield of the reaction was increased by a factor of 1100 by adding 2×10^{-2} M TEA. A plot of Φ^{-1} vs. $[\mathrm{TEA}]^{-1}$ gave a slope of 3.70 ± 0.18 (Figure 1). This value is somewhat lower than that obtained in the *cis*-piperylene experiments. However, since no side products were formed with TEA, the slope obtained gives a direct measure of the effect of the electron donor on the rate of dehalogenation.

---

(25) Reska, K.; Hall, R. D.; Chignell, C. F. *Photochem. Photobiol.* **1984**, *40*, 707.

(26) Bunce, N. J.; Gallacher, J. *J. Org. Chem.* **1982**, *47*, 1955.

(27) Dalton, J. C.; Snyder, J. J. *J. Am. Chem. Soc.* **1975**, *97*, 5192.

(28) Bunce, N. J. *J. Org. Chem.* **1982**, *47*, 1948.

Table XI. Conditions of Irradiation of 2-(4-Halophenyl)benzoxazoles in the Presence of Quenchers

compd	[C], 10^3M	[Q], M	t, min	compd	[C], 10^3M	[Q], M	t, min
		Piperylene				Naphthalene	
4	2.5	2.5×10^{-2} to 4.1×10^{-3}	20	4	2.5	2.5×10^{-3}	14640
5	7.5	6.4×10^{-2} to 6.4×10^{-3}	60	5	7.5	1×10^{-2} to 2×10^{-3}	140
6	1.5–3	1.2×10^{-2} to 6.1×10^{-4}	3	6	1.2	8×10^{-3} to 2×10^{-3}	2

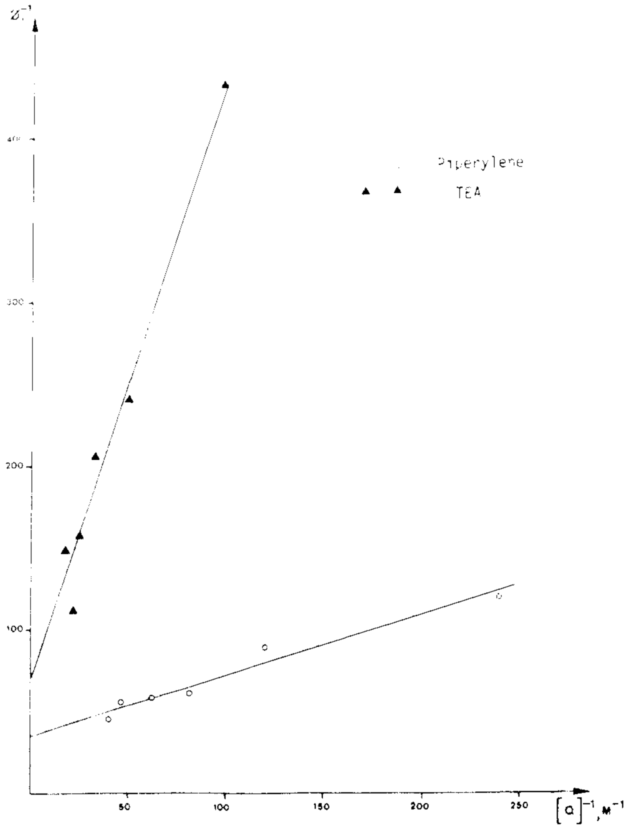


Figure 1. Variation of the reciprocal of the photodechlorination quantum yield vs. the reciprocal of concentration of the electron donor.

An analogous mechanism is likely to occur with benzophenone. This point is important since *cis*-piperylene and benzophenone are commonly used in determining the nature of the excited states. In particular, the accuracy of triplet lifetimes estimated using *cis*-piperylene as a quencher must be assessed carefully since an electron transfer process can disrupt the normal quenching effect in such reactions. From these results it appears that 2-(4-chlorophenyl)benzoxazole which was our initial subject of investigations is usually quite unreactive under irradiation. However, the presence of an electron donor provides its dehalogenation with a dramatic efficiency. Therefore, we can postulate that such an assisted photodechlorination may occur with benoxaprofen in tissues and the formation of free radicals would be partially responsible for of the observed phototoxicity.

Experimental Section

General. Elemental analyses were performed at the CNRS Central Microanalysis Laboratory, Vernaison. ^{1}H NMR spectra were measured in C_6D_6 (isotopic purity ≥99.9%) on a Bruker WM 250 MHz spectrometer. Chemical shifts are reported in parts per million with internal Me_4Si as a reference. Infrared spectra were obtained on KBr pellets with a Perkin-Elmer model 683 spectrophotometer. UV spectra were determined with a Beckman 5260 UV–visible spectrophotometer coupled with an HP 85 computer. Fluorescence spectra were recorded on a thermostated Aminco SFP 500 (corrected spectra) spectrofluorometer coupled with an HP 85 computer. Gas chromatography analyses were performed with an Intersmat model IGC 120 FL gas chromatograph equipped with a flame-ionization detector. The column (1.8 m × 2 mm) consisted of 1% OV1 on 100–120 mesh chromosorb WAW. The column was operated from 120 to 220 °C, 15°/min, with nitrogen as the carrier gas. Injector and detector were maintained at 240 °C. Peak integrals were measured with an HP model 3390 A electronic integrator. Gas chromatography in conjunction with mass spectrometry (GC/MS) was run on a NERMAC R 110 instrument at 180 °C with 70 eV. Spectra were recorded on an integrator PDP8 Dec.

Starting Materials. 2-Phenylbenzoxazole halides were prepared and purified as reported previously.[5] They were recrystallized from methanol and sublimed under vacuum (10^{-2} torr). Cyclohexane and methanol (Merck, Spectroquality) were used without further purification in fluorescence and irradiation experiments.

Fluorescence Studies. Fluorescence emission spectra were recorded at 25 °C with an excitation wavelength of 299 nm. They were corrected in terms of quanta. Dilute solutions (10^{-7} M) of 2-phenylbenzoxazole halides in cyclohexane were degassed by bubbling 5 min with argon. The fluorescence quantum yields were determined relatively with quinine sulphate as a standard[29] ($\Phi_s = 0.50$) as described in a previous paper.[30]

Photochemical Procedures. Irradiations were performed in a Rayonnet RPR 100 reactor equipped with 16 mercury lamps having a maximum output at 300 or 350 nm. The chamber temperature was approximately 30 °C. Equal illumination of samples being photolysed simultaneously was assured by use of a "merry-go-round" apparatus. Light intensities were monitored with benzophenone/benzhydrol actinometry. Because of the high molar extinction coefficients of 2-phenylbenzoxazole halides the solutions absorbed all of the UV light whatever their concentration. Aliquots (4 mL) of the benzoxazole solutions were transferred to clean dry Pyrex tubes (diameter 14 mm). They were degassed by four freeze-pump-thaw cycles and sealed under vacuum (2×10^{-5} torr). For calculation of quantum yields, conversions were limited to ≤ 10% to minimize light absorption and reactions of photoproducts.

Dimerization. During photolysis of concentrated (0.1 M for **3** and 0.05 M for **4**) solutions of 2-(4-halophenyl)benzoxazoles in cyclohexane, a precipitate was formed. At the end of the irradiation, the tubes were opened. The precipitate was isolated by filtration, washed with cyclohexane, and dried under vacuum. The chemical yield of **8** after 8 h of irradiation reached 41% and that of **9** after 50 h of irradiation was 37%.

8. Anal. Calcd for $C_{26}H_{16}N_2O_2F_2$: C, 73.23; H, 3.78; N, 6.37. Found: C, 73.39; H, 3.95; N, 6.37. ^{1}H NMR (16 scans, C_6D_6): δ 7.83 (dd, J = 8.5, 5 Hz, 2 × 2 H, H_{ortho}), 6.85 (dd, J = 8, 1 Hz, 2 × 1 H, H_4), 6.71 (t, J = 8.5 Hz, 2 × 2 H, H_{meta}), 6.69 (td, J = 8, 1 Hz, 2 × 1 H, H_5), 6.51 (dd, J = 8, 1.5 Hz, 2 × 1 H, H_7), 6.43 (td, J = 8, 1.5 Hz, 2 × 1 H, H_6). The IR spectrum did not exhibit the peaks shown by **3** at 1622 cm^{-1} (C=N) and 1562 cm^{-1} (N=C—O).

9. Anal. Calcd for $C_{26}H_{16}N_2O_2Cl_2$: C, 67.97; H, 3.51; N, 6.09; O, 6.96. Found: C, 68.11; H, 3.49; N, 5.88; O, 7.49. ^{1}H NMR (16 scans, C_6D_6): δ 8.06–7.10 (dd, J = 8.5 Hz, 2 × 2 H, H_{meta}), 7.75–7.02 (dd, J = 8.5 Hz, 2 × 2 H, H_{ortho}), 6.84 (dd, J = 8, 1 Hz, 2 × 1 H, H_4), 6.67 (td, J = 8, 1.4 Hz, 2 × 1 H, H_5), 6.49 (dd, J = 7.2, 1.4 Hz, 2 × 1 H, H_7), 6.39 (td, J = 8, 1 Hz, 2 × 1 H, H_6). In comparison with the IR spectrum of **4** a disappearance of the bands at 1619 cm^{-1} (C=N) and 1579 cm^{-1} (N=CO) was observed.

Decomposition Measurements. The dimer **8** or **9** (5 mg) was dissolved in 2 mL of cyclohexane, and the decomposition kinetics

---

[29] Reiser, A.; Leyshon, L. J.; Saunders, D.; Mijovic, M. V.; Bright, A.; Bogie, J. *J. Am. Chem. Soc.* **1972**, *94*, 2414.

[30] Roussilhe, J.; Paillous, N. *J. Chim. Phys. Phys.-Chim. Biol.* **1983**, *80*, 595.

were recorded at different temperatures by UV measurements at 299 nm every 10 min. The program used to determine the decomposition rate constant was VA 04A (optimization of the parameter by minimization). The kinetics were also recorded by ^{1}H NMR (16 scans, C_6D_6).

Dehalogenation Measurements. Dilute (10^{-2} to 2.5×10^{-3} M) solutions of 4, 5, and 6 were irradiated for 320 h, 140 min, and 2 min, respectively. At regular time intervals, the tubes were opened, and the solution was evaporated at room temperature and redissolved in chloroform (0.1 mL). Quantitative measurements were made by gas chromatography, using acenaphthene (0.1 mL, 7.4×10^{-3}M) in chloroform as internal standard.

Quenching Experiments. *cis*-Piperylene (Fluka) and naphthalene (Merck) were used without purification. *cis*-Piperylene was diluted with cyclohexane and naphthalene was used in methanolic solution. Irradiations were performed at 300 nm. The relative concentrations of the quencher and the substrate were selected such that the quencher absorbed no more than 1% of the incident light. Solutions (2 mL) of 2-(4-halophenyl)-benzoxazole were added to solutions (2 mL) containing the quenchers and then deoxygenated by bubbling with argon. Irradiation times depended on both the compound and the quencher (see Table XI).

Dehalogenation yields were measured by VPC as described above. For the reaction of 4 with *cis*-piperylene, analysis by GC/MS of the mixture indicated the formation of a photoadduct (m/e $M^+ = 297, 282, 229$). Other products were detected corresponding to m/e $M^+ = 297, 260$, and 256, m/e $M^+ = 399, 297$, and 282, and m/e $M^+ = 282$ and 206, indicating that *cis*-piperylene is bonded to the carbon of the C=N double bond.

Sensitization by TEA. TEA (Prolabo) was used without further purification. Methanolic solutions of 4 (2 mL, 5.2×10^{-3} M) were added to solutions of TEA (2 mL, 3×10^{-2} to 1.5×10^{-1} M). The tubes were degassed and irradiated at 300 nm for 206 min. The analytical procedure was as described above.

Sensitization by Benzophenone. Benzophenone (Prolabo) was used without purification. Aliquots (4 mL) of a cyclohexane solution of 2-(4-halophenyl)benzoxazole (2 mL, 5×10^{-3} M) and benzophenone (2 mL, 2×10^{-2} M) in Pyrex tubes were deoxygenated as described. The tubes were irradiated at 350 nm on a "merry-go-round" sample holder immersed in an acetone bath to avoid irradiation at 300 nm. Irradiation times were 234 h for 4, 145 min for 5, and 2 min for 6. The analytical procedure was as described above.

Viscosity Measurements. Kinematic viscosity was measured at 30 °C on a semiautomatic Schott-Geräte viscosimeter, model AVS/N.

Registry No. 1, 51234-28-7; 2, 833-50-1; 3, 397-54-6; 4, 1141-35-1; 5, 3164-13-4; 6, 33116-00-6; 8, 99966-75-3; 9, 99966-74-2; *cis*-piperylene, 1574-41-0; naphthalene, 91-20-3; triethylamine, 121-44-8.

Conformational Analysis. 46. Conformational Equilibria in 3-Hydroxy-, 3-Methoxy-, and 3-Acetoxythianes, Their Sulfoxides and Sulfones, and Some Corresponding 3-Methyl Homologues

Ernesto Brunet and Ernest L. Eliel*

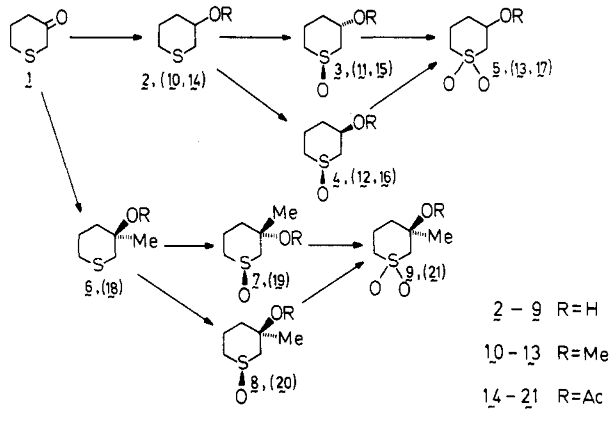
W. R. Kenan, Jr. Laboratories, Department of Chemistry 045A, University of North Carolina, Chapel Hill, North Carolina 27514

Received July 22, 1985

Conformational equilibria have been measured, by low-temperature carbon-13 and proton NMR spectroscopy, for 3-hydroxythiane, its two epimeric sulfoxides, and the corresponding sulfone and their methyl ethers and acetates, as well as the corresponding derivatives of 3-methyl-3-hydroxythiane and their acetates. Of particular note are large solvent and concentration effects on the conformational free energies, $\Delta G^\circ_{a \rightleftharpoons e}$, especially in cases where intramolecular and intermolecular hydrogen bonding are competitive. Thus, in 3-hydroxythiane, ΔG° rises from −1.20 kcal/mol in 4 M CD_2Cl_2 to −0.22 kcal/mol in 0.0011 M CD_2Cl_2; for the corresponding cis sulfoxide the rise is from <−1.3 kcal/mol in 0.3 M CD_3OD to −1.0 kcal/mol in 2.8 M CD_2Cl_2 to >+1.3 kcal/mol in 0.0023 M CD_2Cl_2 and in the sulfone it is from <−1.3 kcal/mol in 0.3 M CD_3COCD_3 to −0.9 kcal/mol in 0.3 M CD_2Cl_2 to −0.16 kcal/mol in 0.002 M CD_2Cl_2.

In previous publications[1] we have reported on conformational equilibria in compounds of type $MeS^*CHR^1CHR^2OR^3$ where $S^* = S$, SO, or SO_2, R^1 and R^2 = alkyl or aryl, and R^3 = H, Me, or Ac. The technique used was proton NMR spectroscopy, specifically the evaluation of vicinal coupling constants by means of the Altona equation.[2] These studies gave valuable information as to the nature of the interactions between the heteroatomic functions; however, the results were quantitatively somewhat uncertain, especially in the sulfoxide and sulfone cases where the electronegativity values of the SO and SO_2 functions, required in the equation,[2] are not well-known.[1d] We have therefore now studied, and here report, conformational equilibria in the cyclic analogues shown in

Scheme I



---

[1] (a) Alcudia, F.; Brunet, E.; García Ruano, J. L.; Rodriguez, J. H.; Sánchez, F. *J. Chem. Res. Synop.* **1982**, 284; *J. Chem. Res. Miniprint* **1982**, 2826. (b) Brunet, E.; Garcia Ruano, J. L.; Hoyos, M. A.; Rodriguez, J. H.; Prados, P.; Alcudia, F. *Org. Magn. Reson.* **1983**, *21*, 643. (c) Brunet, E.; García Ruano, J. L.; Martinez, M. C.; Rodriguez, J. H.; Alcudia, F. *Tetrahedron* **1984**, *40*, 2023. (d) Brunet, E.; García Ruano, J. L.; Rodriguez, J. H.; Alcudia, F. *Tetrahedron* **1984**, *40*, 4433.

[2] Haasnot, C. A.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

0022-3263/86/1951-0677$01.50/0 © 1986 American Chemical Society