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Photochemistry of 2,6-Dichlorodiphenylamine and 1-Chlorocarbazole, the Photoactive Chromophores of Diclofenac, Meclofenamic Acid and Their Major Photoproducts

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ABSTRACT

Diclofenac and meclofenamic acid are two structurally related nonsteroidal anti-inflammatory drugs with some photosensitizing potential. Their photochemistry involves cyclization to monohalogenated carbazoles. In principle, photocyclization could occur by photodehalogenation, followed by intramolecular radical addition, or by 6π electrocyclization and subsequent dehydrohalogenation of the intermediate dihydrocarbazoles. Previously, it has been assumed that the reaction follows the first pathway and that the key species associated with phototoxicity are the resulting aryl radicals. In the present work, we have performed photophysical and photochemical studies on 2,6-dichlorodiphenylamine (1a). **This is a suitable model compound because since it contains the active chromophore present in diclofenac and meclofenamic acid, and its photoreactivity should be relevant to the understanding of the photobiological properties of both drugs. Our results clearly show that the first photochemical reaction is a very rapid 6π-electrocyclization, and hence no radicals are formed at this stage. Instead, cleavage of the carbon–halogen bond occurs in the 1-chlorocarbazole photoproduct** 2a. **The reduced lifetime of the** 2a **triplet (as compared with the unsubstituted carbazole) and the observed reaction quenching by oxygen are in agreement with the reaction occurring from the excited triplet state. Overall, the above results suggest that the potential phototoxicity of diclofenac and meclofenamic acid is due to a photobiologically active photoproduct that is able to generate radicals upon photolysis, rather than to the parent drug.**

INTRODUCTION

Studies on the photodegradation of drugs are relevant to the drug development process, because the photolysis products may have biological effects different from those of the parent compounds. This may explain, at least partially, the phototoxicity mechanism. Reports on cutaneous photosensitivity disorders provoked by new pharmaceuticals appear with increasing frequency. The nonsteroidal anti-inflammatory drugs (NSAID)† are implicated more often than other drugs, probably because they are used to a large extent (1). This group contains a variety of compounds with quite different chromophoric groups (2–4).

Diclofenac (2-[2,6-dichloroanilino]phenylacetic acid, **I**) is a potent NSAID therapeutically used in inflammatory and painful diseases of rheumatic and nonrheumatic origin (5). It is widely used, but it appears to possess some photosensitizing potential (6–9). Diclofenac is related to meclofenamic acid (*N*-[2,6-dichloro-*m*-tolyl]anthranilic acid, **II**), also used as an anti-inflammatory agent, that was reported to be unstable when irradiated by UV light (10) (Chart 1).

The propionic acid-derived NSAID benoxaprofen (11), ibuprofen (12), naproxen (13), ketoprofen (14), suprofen and tiaprofenic acid (15) undergo photodecarboxylation. In comparison, the photoproducts from **I** and **II** retain the carboxylic group (10, 16); this is also the case for carprofen (17). The photochemistry reported for both compounds **I** and **II** involves cyclization to the corresponding monohalogenated carbazoles **III**, **IV** and **V** (Chart 1). However, the detailed mechanistic pathways and the nature of the reactive excited states and/or transient intermediates remain to be established.

In principle, photocyclization could occur by two alternative pathways (Scheme 1): (a) photodehalogenation, as it has been reported for related aryl halides (18,19), followed by intramolecular radical addition or (b) 6π electrocyclization, similar to the well-established behavior of diarylamines (20–25) and subsequent dehydrohalogenation of the intermediate dihydrocarbazole. Previously, it has been assumed (16) that the reaction follows the first pathway and that the key species associated with phototoxicity are the resulting aryl radicals.

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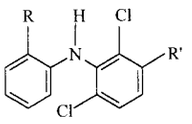
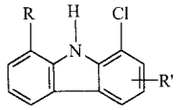
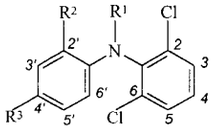
†*Abbreviations:* GC, gas chromatography; ISC, intersystem crossing; MS, mass spectrometry; NSAID, nonsteroidal anti-inflammatory drug; PMT, photomultiplier tube.



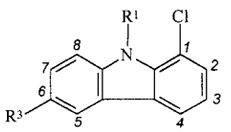
I : R = CH_2CO_2H, R' = H
II : R = CO_2H, R' = CH_3



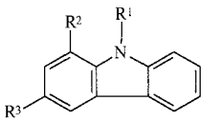
III : R = CH_2CO_2H, R' = H
IV : R = CO_2H, R' = 4-CH_3
V : R = CO_2H, R' = 2-CH_3



1a : $R^1 = R^2 = R^3 = H$
1b : $R^1 = COCH_3$, $R^2 = R^3 = H$
1c : $R^1 = R^2 = H$, $R^3 = COCH_3$
1d : $R^1 = R^3 = H$, $R^2 = COCH_3$



2a : $R^1 = R^3 = H$
2b : $R^1 = COCH_3$, $R^3 = H$
2c : $R^1 = H$, $R^3 = COCH_3$



3a : $R^1 = R^2 = R^3 = H$
3b : $R^1 = COCH_3$, $R^2 = R^3 = H$
3c : $R^1 = R^2 = H$, $R^3 = COCH_3$
3d : $R^1 = R^3 = H$, $R^2 = COCH_3$
3e : $R^1 = R^2 = H$, $R^3 = Cl$

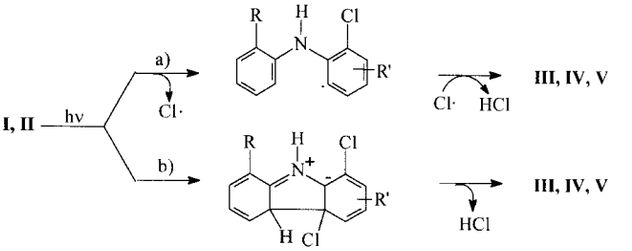
Chart 1. Structures of diclofenac (**I**), meclofenamic acid (**II**), their photoproducts (**III–V**) and the model compounds (**1a–d**, **2a–c** and **3a–e**).

In this connection, the present work deals with the mechanistic aspects of the photodegradation process of **I** and **II** and their implication in phototoxic activity. For this purpose, we have used **1a** as a model compound, because it contains the 2,6-dichlorodiphenylamine substructure that is present in both drugs and appears to be the active chromophore. The results point to a predominance of 6π electrocyclization (pathway b) and to the role of chlorocarbazoles in the phototoxicity mechanism.

MATERIALS AND METHODS

Chemicals. Carbazole (**3a**), 2,6-dichloroaniline and bromobenzene were purchased from Aldrich (Steinheim, Germany). Acetophenone was from Carlo Erba (Milano, Italy). Copper metal, zinc metal (both powdered), glacial acetic acid, potassium carbonate and potassium hydroxide were from Panreac (Barcelona, Spain). Acetic anhydride was from Probus (Barcelona, Spain). Sulfuryl chloride and perchloric acid were provided by Merck (Darmstadt, Germany). Methanol and acetic acid (HPLC grade) were from SDS (Peypin, France). All other chemicals were of reagent grade.

1-Chlorocarbazole (**2a**) and 3-chlorocarbazole (**3e**) were prepared as previously described (17), using gas chromatography (GC) to follow the reaction.



Scheme 1. Possible mechanistic pathways for the photocyclization of **I** and **II**.

N-acetylcarbazole (**3b**) was prepared from carbazole in 95% yield by treatment with acetic anhydride containing 30% perchloric acid, under stirring, during 15 min at room temperature (26).

2,6-Dichlorodiphenylamine (**1a**) was synthesized from 2,6-dichloroacetanilide as described (5). 2,6-Dichloroacetanilide was prepared by treatment of 2,6-dichloroaniline with acetic anhydride, glacial acetic acid and zinc dust for 30 min at reflux temperature and subsequent hydrolysis of the reaction mixture with cold water. It was recrystallized from 2% aqueous ethanol with a yield of 50%. 2,6-Dichlorodiphenylacetamide (**1b**) was obtained as **1a** but without hydrolyzing at the last step. All the products were characterized by ^{1}H-NMR, mass spectrometry (MS) and IR.

Steady-state photolysis. Photodegradation of **1a, 1b, 2a** and **3e** (0.001 *M*) was followed in methanolic solution. Irradiations were performed in two different ways: (a) with quartz- (for **1b**) or pyrex-filtered light from an OSRAM-HLQ 125 W medium-pressure Hg lamp located inside an immersion well photoreactor (Applied Photophysics model 3230), in 10 mL test tubes, both under aerobic and anaerobic atmospheres or (b) with a Lo255 Oriel xenon lamp, in a 3 mL quartz cell, using a Melles Griot (03FCG127; WG 345) long pass colored glass filter for triplet-sensitized reactions.

The kinetics of these photoreactions were monitored by reverse-phase HPLC, using a Hitachi apparatus equipped with a spherisorb column (ODS-2, 10 μm packing), an L-6250 intelligent pump and an L-400 fixed-wavelength UV detector (254 nm) and methanol/water 70/30 as mobile phase. In addition, HPLC-MS analyses were done with a Waters Integrity System that consisted of a Waters 996 photodiode array detector, a thermobeam mass detector and a Waters 2690 separation module.

For measurement of photodehalogenation quantum yields, 2 mL of 0.001 *M* methanolic solutions of **2a**, **3e** and carprofen (as reference) were placed in quartz cells of 10 mm pathlength and bubbled with nitrogen. Irradiation was performed with 10 ns laser pulses from the Nd-YAG laser system at λ = 266 nm. Irradiation time was adjusted to have less than 10% conversion. Actinometry was performed by using the ferric oxalate actinometer (27). The reaction was monitored by means of the HPLC system described before, using the same methodology. The uncertainty on the quantum yields is estimated ±15%.

Isolation and identification of the photoproducts. Isolation of the photoproducts was achieved on a Tracer HPLC instrument with a Lichrosorb column (RP-18, 7 μm packing), using methanol/water 70/30 as mobile phase. Also, column and preparative layer chromatography were used in order to purify the products.

As stated above, products **1a** and **1b** were prepared according to reported procedures (5); their characterization was done by determining their spectral properties. Compound **1a**: ^{1}H-NMR ($CDCl_3$) δ 7.38 (d, *J* = 8 Hz, 2H, $H_{3,5}$), 7.24 (dd, *J* = 8 and 7 Hz, 2H, $H_{3',5'}$), 7.05 (t, *J* = 8 Hz, 1H, H_4), 6.93 (tt, *J* = 8 and 1 Hz, 1H, $H_{4'}$), 6.72 (dd, *J* = 8 and 1 Hz, 2H, $H_{2',6'}$), 5.83 (s, 1H, NH); MS, *m/z* 241 (M^+ + 4, 5), 239 (M^+ + 2, 20), 237 (M^+, 40), 204 (5), 202 (15), 167 (100). Compound **1b**: ^{1}H-NMR ($CDCl_3$) δ 7.48 (d, *J* = 8 Hz, 2H, $H_{3,5}$), 7.41–7.18 (m, 6H, $H_{4,2',6'}$), 2.21 (s, 3H, CH_3); MS, *m/z* 283 (M^+ + 4, 3), 281 (M^+ + 2, 15), 279 (M^+, 20), 237 (80), 202 (25), 167 (100).

Compounds **2a**, **3a**, **3b**, **3c**, **3d** and **3e** (Chart 1) have been previously described and characterized by their spectral properties (28,29). In our experiments, ^{1}H-NMR and HPLC-MS analyses were used to confirm their structures. The *N,N* dimer of **3a** was also de-

scribed in the literature (30). Its MS was very characteristic: *m/z* 332 (M^+, 85), 166 ($M^+/2$, 100).

The structures of **1c**, **1d** and **2c** were also assigned by means of spectral data. The *p*-acetyl derivative **1c** was a viscous oil. HRMS: *m/z* 279.02182 (calculated for $C_{14}H_{11}NOCl_2$: 279.02177). It showed diagnostically important peaks in MS at *m/z* 283 ($M^+ + 4$, 3), 281 ($M^+ + 2$, 15), 279 (M^+, 20), 243 (M^+-HCl, 85), 228 (M^+-HCl,-CH_3, 100), 194 (M^+-2Cl, -CH_3, 60), 167 (M^+-2Cl, -$COCH_3$, 40). The most important signals in ^{1}H-NMR ($CDCl_3$) were: δ 8.24 (d, J = 8 Hz, 2H, $H_{3',5'}$), 8.02 (dd, J = 8 and 1 Hz, 2H, $H_{3,5}$), 7.53–7.37 (m, 3H, $H_{4,2',6'}$), 2.91 (s, 3H, CH_3). The *o*-acetyl derivative **1d** was a solid with melting point = 105–107°C. HRMS: *m/z* 279.02183 (calculated for $C_{14}H_{11}NOCl_2$: 279.02177). The corresponding data were: MS at *m/z* 283 ($M^+ + 4$, 8), 281 ($M^+ + 2$, 40), 279 (M^+, 60), 244 (M^+-Cl, 70), 229 (M^+-Cl, -CH_3, 100), 201 (M^+-Cl, -$COCH_3$, 20), 166 (M^+-2Cl, -$COCH_3$, 30); ^{1}H-NMR ($CDCl_3$): δ 10.42 (s, 1H, NH), 7.86 (dd, J = 8 and 2 Hz, 1H, $H_{3'}$), 7.42 (d, J = 8 Hz, 2H, $H_{3,5}$), 7.28 (dt, J = 8 and 2 Hz, 1H, $H_{5'}$), 7.17 (t, J = 8 Hz, 1H, H_4), 6.8 (dt, J = 8 and 1 Hz, 1H, $H_{4'}$), 6.36 (dd, J = 8 and 1 Hz, 1H, $H_{6'}$), 2.69 (s, 3H, CH_3). The carbazole **2c** was a solid with melting point = 230–232°C. HRMS: *m/z* 243.04618 (calcultated for $C_{14}H_{10}NOCl$: 243.04509). The spectral data were as follows: MS *m/z* 245 ($M^+ + 2$, 20), 243 (M^+, 50), 228 (M^+-CH_3, 100), 200 (M^+-$COCH_3$, 46), 164 (M^+-$COCH_3$, -HCl, 20); ^{1}H-NMR ($CDCl_3$) δ 8.73 (d, J = 2 Hz, 1H, H_5), 8.53 (s, 1H, NH), 8.14 (dd, J = 8 and 2 Hz, 1H, H_7), 8.04 (d, J = 8 Hz, 1H, H_8), 7.53 (d, J = 8 Hz, 1H, H_4), 7.47 (d, J = 8 Hz, 1H, H_2), 7.23 (t, J = 8 Hz, 1H, H_3), 2.74 (s, 3H, CH_3).

Fluorescence measurements. Fluorescence emission spectra were taken by means of a Hitachi, F-2000 fluorescence spectrophotometer, using dilute ethanol solutions of **1a**, **2a**, **3a** and **3e**, at room temperature under anaerobic and aerobic conditions. The emission intensity was detected at right angles by exciting optically thin solutions (absorbance ≅ 0.1 for a 10 mm path length) at ~300 nm and emission measurements were performed in the 315–500 nm region. Fluorescence quantum yields (Φ_F) were determined by comparison with **3a** as a standard (Φ_F = 0.42 in ethanol) (31).

Triplet-state measurements. Ethanol solutions of **1a**, **2a** and **3e** (2×10^{-4} *M*) were studied by the laser flash photolysis technique at $\lambda_{excitation}$ = 266 nm. Parallel experiments were carried out under aerobic (air) and anaerobic (N_2) conditions, to detect quenching of the transient species by oxygen. A kinetic treatment such as a Stern–Volmer plot was used to get kq values for **2a** and **3e**, measuring the triplet lifetime variations in the presence of oxygen.

In order to perform these measurements, a pulsed Nd:YAG SL404G-10 Spectrum Laser Systems was used for excitation at 266 nm. The single pulses were ~10 ns duration and the energy was ~20 mJ/pulse. A Lo255 Oriel xenon lamp was employed as detecting light source. The laser flash photolysis apparatus consisted of the pulsed laser, the Xe lamp, a 77200 Oriel monochromator, an Oriel photomultiplier (PMT) system made up of 77348 side-on PMT tube, 70680 PMT housing and a 70705 PMT power supply. The oscilloscope was a TDS-640A Tektronix. The ouput signal from the oscilloscope was transferred to a personal computer to study it.

RESULTS AND DISCUSSION

It is known that the carboxylic group is not affected in the photolytic degradation of diclofenac (**I**) and meclofenamic acid (**II**) in methanolic solution; hence, the aliphatic chain remains in all the photoproducts (10,16). For this reason, the present study has been made with 2,6-dichlorodiphenylamine (**1a**), which is the most simple compound containing the reactive chromophore common to both drugs.

Photochemistry of 1a

When irradiation of **1a** was performed in both deaerated and aerated methanolic solutions, a mixture of **2a** and **3a** was obtained. The latter was the major photoproduct. Besides, trace amounts of the *N,N* dimer of **3a** were detected. Under inert atmosphere the yield of **3a** was higher. Thus, the photochemical behavior of compound **1a** is similar to that previously reported for **I** and **II**, as it involves cyclization and loss of a chlorine atom; this confirms the suitability of **1a** as a model to study the photodegradation and phototoxicity mechanism of **I** and **II**.

It was not possible to detect the fluorescence emission of **1a**; likewise the laser flash photolysis experiments did not allow detection of the triplet state nor any other transient species.

As the attempts to achieve direct detection of the excited states were unsuccessful, some other experiments were designed. In principle, **1a** could be converted into **2a** *via* the singlet or triplet states, although the abovementioned quenching by oxygen is suggestive of a triplet photoreaction. In order to assess this point, photosensitization with acetophenone was attempted. Acetophenone triplet energy ($E_T \cong$ 75 kcal/mol) (32) should be enough to generate the diphenylamine triplet ($E_T \cong$ 70 kcal/mol) (33).

Although a singlet pathway cannot be completely ruled out on this basis, the results confirmed involvement of the triplet excited state, because the photoproduct distribution was similar to that obtained without sensitizer. In this respect, the photochemical conversion of **1a** into **2a** could be similar to the well-known behavior of diphenylamines, whose cyclization also involves the excited triplet states (20–25,34,35).

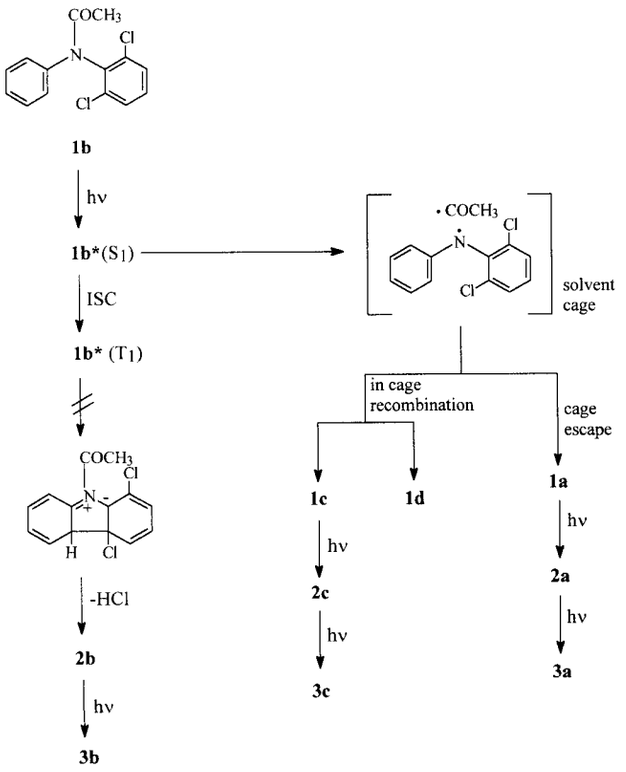
Nature of the primary photochemical step: 6π electrocyclization

As **1a** is a substituted diphenylamine, its photocyclization could be an electrocyclic process (19). Such photocyclization would represent a photochemical six-electron pathway, where the heteroatom (N) contributes with its unshared electron pair (25). Hence, a good model to check this possibility could be compound **1b**, where the six-electron pathway would be disfavored by the lower avalaibility of the N electron pair, due to delocalization toward the *N*-acetyl group.

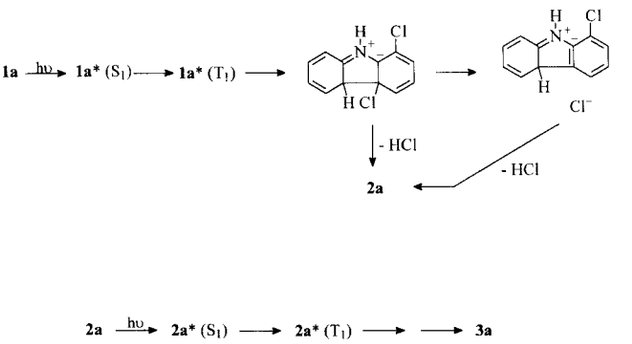
Irradiation of **1b** in methanolic solution, both under aerobic and anaerobic conditions, gave completely different photoproduct distributions as compared with **1a**. It is remarkable that not even traces of chlorocarbazoles **2b** or **3b** were detected. Instead, the products arising from the photo-Fries rearrangement of the acetyl group to the *ortho* (**1d**) and *para* (**1c**) positions with respect to the nitrogen group were obtained. Compound **1c** was present in a lower amount, because it partially photocyclized to **2c** and **3c**. Deacetylation to **1a** and subsequent photocyclization to **2a** and **3a** also took place as side reactions.

The above results can be accounted for as indicated in Scheme 2. The major photochemical pathway would involve cleavage of the carbonyl–nitrogen bond from the excited singlet state. The resulting radical pair would recombine to **1c** or **1d**; cage escape followed by hydrogen abstraction would lead to **1a**. Similar photo-Fries rearrangements of anilides have been previously reported; it is generally accepted that they are also singlet state reactions (36).

Due to the aromatic ketone character of **1c**, its photocyclization to **2c** should occur from the triplet state. The same would be true for the subsequent dehalogenation of **2c** to **3c**. The lack of photocyclization of **1d** can be explained on the



Scheme 2. Photochemistry of 2,6-dichlorodiphenylacetamide (**1b**).



Scheme 3. Mechanistic pathways for the **1a** and **2a** photochemistry.

basis of the known photostability of *o*-hydroxy or *o*-amino aromatic ketones, where an energy-wasting tautomerization channel is operating (37).

The lack of cyclization of **1b** to **2b** strongly suggests that this is a 6π electrocyclization requiring a higher availability of the N lone pair. However, it could be conceivable that, if the reaction has to take place from the triplet, this state is not efficiently populated due to photocleavage of the amide bond from the excited singlet, competing with intersystem crossing (ISC). To rule out this possibility, acetophenone was again used as triplet photosensitizer. No photoreaction was observed, confirming our mechanistic proposal. This experiment also showed that the Fries process does not take place from the triplet state.

In summary, these results support that photocyclization of **1a** is a 6π-electrocyclic process mainly occurring from the triplet state (see Scheme 3).

Cleavage of the C–Cl bond in the second photochemical step

As stated above, the irradiation of **1a** gives **3a** as the major product, even after short irradiation times, accompanied by a lower amount of its precursor **2a**. This fact, together with the low lifetimes of the nondetectable **1a** triplets and the lack of radical formation in the primary photochemical process of **1a**, suggested that the photochemistry of the chlorocarbazole chromophore could play a key role in the photobiological properties of **I** or **II**. Actually, the phototoxicity of carprofen (whose simple model is chlorocarbazole **3e**) has been related to formation of radicals by carbon–halogen cleavage. Therefore, it appeared interesting to study the photochemical behavior of **2a** and to compare it with that of **3e** (17).

Photodehalogenation of **2a** did indeed occur in methanolic solution, under both aerobic (Φ = 0.1) and anaerobic (Φ = 0.3) atmospheres. The kinetics of this process was very similar to that observed in the photodehalogenation of **3e** (Fig. 1). In both cases, photodehalogenation was more rapid under inert atmosphere than in the presence of air; thus, oxygen behaves as quencher of the reaction, indicating the triplet nature of the process. A simplified mechanism for the photodehalogenation of **2a** is shown in Scheme 3.

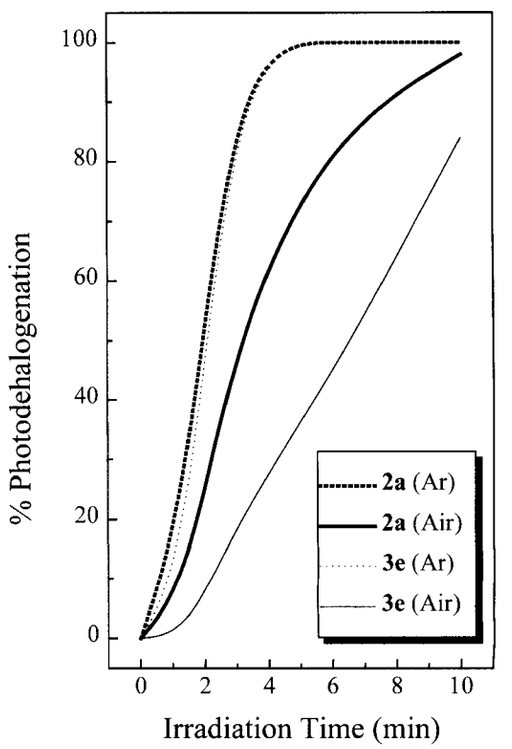


Figure 1. Photodehalogenation of **2a** and **3e** at different irradiation times, both under aerobic and anaerobic atmospheres. The compounds **2a** and **3e** (0.001 *M*) were irradiated in methanol and the photomixture analyzed by GC after 1.5, 3, 6 and 10 min.

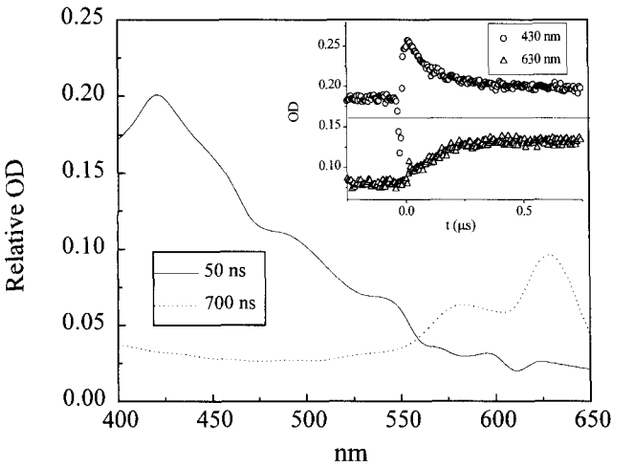


Figure 2. Transient absorption spectra of a nitrogen-saturated ethanolic solution of **2a** (2×10^{-4} *M*) measured 50 ns and 700 ns after the laser pulse (266 nm). Insert: decay of the triplet monitored at 430 nm and formation of the carbazolyl radical, monitored at 630 nm.

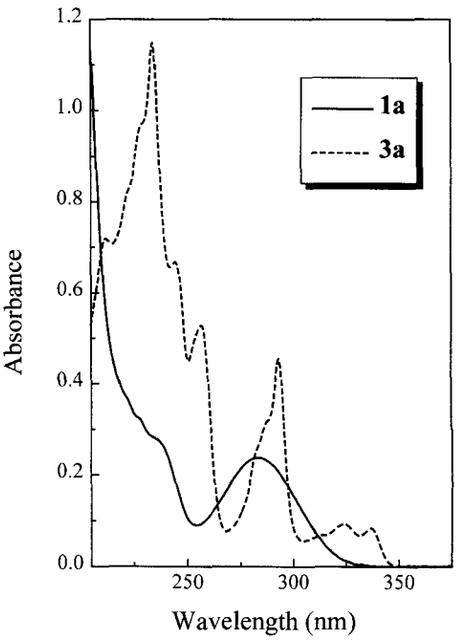


Figure 3. Absorption spectra of **1a** and **3a** in ethanol at 2×10^{-5} *M* concentration.

Excited-state measurements

Fluorescence measurements showed that the first excited singlet state has the same behavior in both chlorocarbazoles **2a** and **3e**. The spectrum (not disclosed) showed two emission bands around 367 and 352 nm. Thus, the singlet energies are close to 80 kcal/mol. The fluorescence quantum yield in ethanolic solution was ~0.06, taking the parent carbazole (**3a**) as reference (17). No significant quenching of the singlet states by oxygen was observed.

As regards the first triplet excited state, its characterization was done by means of laser flash photolysis experiments. Both halogenated carbazoles present a triplet absorption maximum at ~420 nm in deaerated ethanolic solutions; this is shown in Fig. 2 for **2a**. The triplet lifetimes (τ_T = 0.17 μs for **2a** and 0.86 μs for **3e**) were markedly lower than that reported for the parent carbazole under analogous conditions (~40 μs). The reason has to be attributed to the possibility of carbon–halogen bond cleavage from the triplet state of **2a** and **3e**. Also, the rate of ISC to the ground state should increase by the presence of a chlorine substituent.

Both triplets were quenched by oxygen, with similar rate constants (3–4 × 10^9 M^{-1} s^{-1}). The triplet decay was concomitant with the appearance and increase of a new transient with absorption maximum at ~630 nm (see Fig. 2 and insert). The new species was assigned to be the carbazolyl radical on the basis of literature data (17,38,39).

Photobiological implications

The present photophysical and photochemical studies on 2,6-dichlorodiphenylamine (**1a**) are relevant to the understanding of the photobiological properties of diclofenac (**I**) and meclofenamic acid (**II**). Although the presence of the carboxy group in these drugs might in principle have some influence on the photochemical and photobiological properties in water or biological fluids, the fact that the drug photoproducts **III–V** are not decarboxylated supports the suitability of **1a** as a model compound.

Previously, it has been hypothesized that the primary photochemical process of **I** and **II** is cleavage of the carbon–halogen bond of the 2,6-dichlorodiphenylamine moiety. The resulting aryl/halogen radicals would be the intermediates responsible for the observed photobiological effects. The present work clearly shows that the first reaction of **1a** is rather a very rapid 6π-electrocyclization, and hence no radicals are formed at this stage. Instead, cleavage of the carbon–halogen bond occurs in the 1-chlorocarbazole photoproduct.

The reduced lifetime of the **2a** triplet (as compared with the unsubstituted carbazole) and the observed quenching of the reaction by oxygen are in agreement with the reaction occurring from the excited triplet state. In this connection, the properties of **2a** would be very similar to those of carprofen, which is also a chlorocarbazole.

Overall, the above results obtained with model compounds suggest that the potential phototoxicity of diclofenac and meclofenamic acid is due to a photobiologically active photoproduct, rather than to the parent compound. Further studies with the carboxyl-containing drugs appear necessary to check the validity of this hypothesis. Besides, the light absorption by the 1-chlorocarbazole chromophore in the UVA region is more efficient than that of a 2,6-dichlorodiphenylamine (see Fig. 3).

The involvement of phototoxic photoproducts has also been demonstrated in the case of related NSAID, such as benoxaprofen (40) or tiaprofenic acid (41,42).

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