Journal of Photochemistry and Photobiology A: Chemistry 211 (2010) 1–6

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

journal homepage: www.elsevier.com/locate/jphotochem

Photocyclization of 2,6-dichlorodiphenylamines in solution

Helmut Görner

Max-Planck-Institut für Bioanorganische Chemie, D-45413 Mülheim an der Ruhr, Germany

ARTICLE INFO

Article history:
Received 9 December 2009
Received in revised form 14 January 2010
Accepted 19 January 2010
Available online 1 February 2010

Keywords:
Diclofenac
Photocyclization
Quantum yield

ABSTRACT

The reactions of diclofenac, meclofenamic acid and 2,6-dichlorodiphenylamine were studied by pulsed and steady-state photolysis. The primary photoprocess of diclofenac is ring closure, the quantum yield of cyclization in dichloromethane and aqueous solution is Φ_{cyc} = 0.03 and 0.2, respectively. The results of the two related dichlorodiphenylamines are similar in the respect that the products are the corresponding 1-chlorocarbazoles and Φ_{cyc} is small in organic solvents and largest in aqueous solution.

1. Introduction

Diclofenac (Chart 1) is one of the most commonly used non-steroidal and anti-inflammatory drugs. However, it has also potentially harmful photosensitizing properties. Some fundamental photochemical features of diclofenac in solution have been reported [1–4]. The photodegradation of diclofenac in aqueous solution has been studied by various groups [5–14]. This is important for a better understanding of the UV treatment of wastewater [10]. The photodegradation of pharmaceuticals in aquatic environment has been reviewed [12]. The potential phototoxicity of diclofenac was ascribed to a biologically active photoproduct that is able to generate radicals upon photolysis, rather than to the parent drug [3,4]. Mechanistic studies indicate that the photochemistry of diclofenac involves electrocyclization to a monohalogenated carbazole [2–4]. In fact, 1-chlorocarbazole and carbazole are the respective initial and secondary photoproducts of 2,6-dichlorodiphenylamine (Cl_2DPA), which can be considered as the photoactive chromophore of diclofenac [3]. The photocyclization of 2,6-dichloroDPAs has been proposed to proceed via the triplet state [3,4]. For meclofenamic acid (*N*-(2,6-dichloro-*m*-tolyl)anthranilic acid: HO_2CCl_2DPA) which is another closely related amine, two cyclization products have been found [15]. A simplified mechanism of photoinduced ring closure of dichloroDPAs is illustrated in Scheme 1. The photoreactivity of 1-chlorocarbazole could be relevant to the understanding of the photobiological properties of diclofenac [1–4]. The photoreduction of 1-chlorocarbazole should be enhanced in the presence of an alcohol. Recently, the ozonation of diclofenac has been studied [7,16,17].

The photochemistry of diclofenac in solution may be compared to that of other diphenylamines, not containing chloro substituents. Parent diphenylamine (DPA), triphenylamine and *N*-methyldiphenylamine (MeDPA) have all been intensively studied by photochemical techniques [18–26]. They undergo an electrocyclic ring closure, and one rather unique property of DPAs is a photocyclization route in 4a,4b-dihydrocarbazoles via a triplet state [18–20]. The products of MeDPA are *N*-methylcarbazole (Scheme 2) and *N*-methyltetrahydrocarbazole, of which the latter is not stable and formed in deoxygenated solutions only [20]. The photocyclization of DPA has also been studied using thermal lensing [23] and time-resolved photoacoustic calorimetry [25]. A modified triplet state mechanism operates for the photoionization of DPA, when the two-pulse method is applied [24]. The photoinduced ring closure of DPAs in solution has recently been revisited and their oxygen uptake studied [26].

Here, the photochemistry of diclofenac was studied in several organic solvents and in aqueous solution. The effects of solvents, oxygen and pH concerning the quantum yield Φ_{cyc} of ring closure were outlined. These effects were compared with those of Cl_2DPA and HO_2CCl_2DPA, which are closely related to diclofenac since they also contain the 2,6-chloro substituents, see Chart 1. In fact, the 2-chloro group is a decisive element in the photocyclization of diclofenac. In contrast, the 1-carboxy group is not decisive, but the photoprocesses of meclofenamic acid (HO_2CMe_2DPA) and 2-carboxydiphenylamine (HO_2CDPA) differs from those of parent DPA.

2. Experimental

Diclofenac, 2-(2,6-dichloroanilino)phenylacetic acid, was from Heumann PSC [16]. The other compounds (EGA, Sigma)

E-mail address: goerner@mpi-muelheim.mpg.de.

1010-6030/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jphotochem.2010.01.010

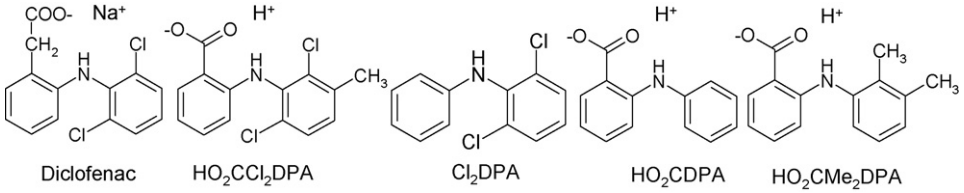
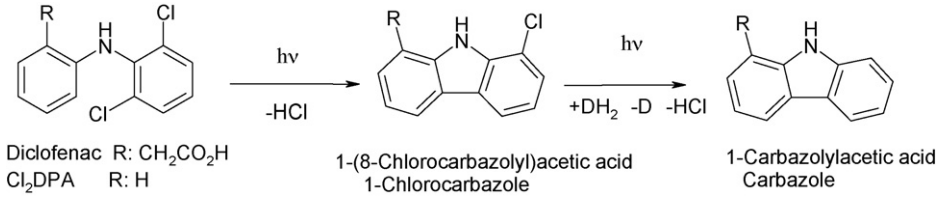
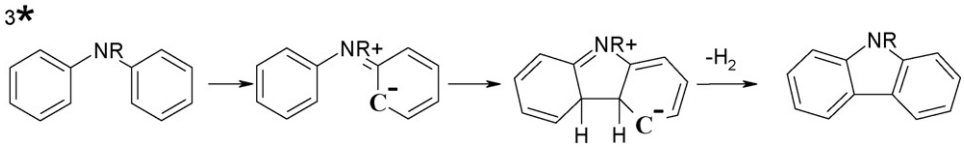


Chart 1.



Scheme 1.



Scheme 2.

were used as received after checking for impurities. Benzene, dichloromethane and acetonitrile (Merck) were Uvasol quality, water was from a millipore (milliQ) system. The absorption spectra were monitored on an UV/vis spectrophotometer (HP, 8453). The molar absorption coefficient of diclofenac in neutral water at 285 nm is $\varepsilon_{285} = 0.82 \times 10^4\,M^{-1}\,cm^{-1}$ [1], that of Cl_2DPA is $\varepsilon_{280} = 1.1 \times 10^4\,M^{-1}\,cm^{-1}$ [3]. In addition, HO_2CMe_2DPA and HO_2CDPA were briefly studied. Note that the solution of HO_2CCl_2DPA becomes opaque on addition of $HClO_4$ at pH 3. A spectrofluorimeter (Cary, eclipse) was employed to measure the fluorescence spectra. For photoconversion, a 1000-W high-pressure Hg–Xenon lamp and a monochromator were used for irradiation at 270–313 nm. Alternatively, a 200-W Hg lamp and suitable band-pass filter were used for irradiation at 313 nm. Irradiation at 254 nm (using a low-pressure Hg lamp) could be considered as an alternative. This is, however, limited by a too low conversion due to large absorption of the carbazole photoproduct at 254 nm, and was therefore not employed. For HPLC analyses a reverse phase ODS-3HD PerfectSilTarget 3 μm column (0.8 ml min^{-1}) with eluent gradient was used, the mobile phases were composed of 0.5% trifluoroacetic acid and either a 1:5 mixture of acetonitrile and water or neat acetonitrile. The dichloroDPAs and their main products have retention times of 17.6/16.7 19.0/17.2 and 18.7/19.1 min for diclofenac, Cl_2DPA and HO_2CCl_2DPA, respectively. The two product peaks for the latter [15] were not separated under our conditions. The quantum yield of cyclization was determined from plots of the absorption at appropriate wavelength or the HPLC signals vs dose using the aberchrome 540 actinometer for λ = 308/313 nm [27]. The experimental error of Φ_{cyc} is ±20%. The solutions were generally used without buffer and the initial pH was shifted by addition of protons ($HClO_4$) or hydroxyl ions; in a few cases buffers (<5 mM) were used. The oxygen concentration was measured by a Clark electrode (Hansatech). The relative yield of oxygen consumption was determined from the slope of $[O_2]$ vs irradiation time [28]. An excimer laser (Lambda Physik, EMG 201 MSC, pulse width of 20 ns and energy <100 mJ) was used for excitation at 308 nm. The absorption signals were measured with two digitizers (Tektronix 7912AD and 390AD) and an Archimedes 440 computer for data handling was used as in previous work [28]. The transient conductivity set-up was as used elsewhere [29]. All measurements refer to 24 °C.

3. Results

3.1. Photoconversion

The absorption spectrum of diclofenac in acetonitrile exhibits a maximum at λ_{DPA} = 282 nm, those of Cl_2DPA and HO_2CCl_2DPA have maxima at 280 and 320 nm, respectively. The absorbance of diclofenac at 282 nm decreases upon continuous irradiation at 313 nm or pulsed excitation at 308 nm, whereas those at maxima of the products, e.g. λ_C = 250 or 300 nm, increase markedly. Two or three isosbestic points (λ_i) result at low conversion, indicating a minor effect of secondary photolysis. The absorption spectra of diclofenac are similar in acetonitrile or methanol (Table 1). Generally, the spectral changes of each of the dichloroDPAs are comparable in methanol, water and their mixtures. Examples of these changes prior to and after UV photolysis are shown in Figs. 1–3 (insets) for diclofenac, HO_2CCl_2DPA and Cl_2DPA, respectively. The absorbances at λ_{DPA} decrease upon irradiation, whereas those at λ_C increase markedly. One major photoproduct of Cl_2DPA and diclofenac in polar solvents was detected by HPLC. The assignment to 1-chlorocarbazole and the corresponding derivative, respectively, is well established [1–4]. Likewise, the photoproducts of DPA or triphenylamine have the corresponding carbazole

Table 1
Spectral properties of dichloroDPAs[a].

	Diclofenac	Cl_2DPA	HO_2CCl_2DPA
λ_{DPA} (nm)	282	280[b]	340
λ_C (nm)	290, 340	290, 335[b]	305, 360
λ_i (nm)	268, 285, 305	266, 286, 300	320, 345
λ_f^{exc} (nm)	290, 338	290, 335	300, 365
λ_f^{em} (nm)	368	370	440

[a] In acetonitrile.
[b] Same values in methanol.