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Mechanism of the photochemical degradation of amlodipine

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Abstract

A mechanistic investigation on the photodegradation of amlodipine, the corresponding besylate and a simple analogue lacking the β-aminoethoxy group has been carried out in water and in organic solvents. Irradiation leads to aromatization to the corresponding pyridines through an oxygen-independent process. The quantum yield for amlodipine base is $\Phi \cong 0.001$ under UV-A light, about one order of magnitude larger than that for the model bearing no amino group, supporting intramolecular assistance by that group. The value of Φ increases up to *ca.* 0.01 at shorter wavelength. The photolability of this drug according to ICH criteria is justified by the high absorptivity in the UV-A range ($\varepsilon_{\text{UV-A}}$), despite the low quantum yield. Some comments are added about the fact that product $\Phi \times \varepsilon_{\text{UV-A}}$ is more significative than Φ alone for the photolability (in solution) and about the lacking possibility to quench the photoreactivity where, as in the present case, this involves only short-lived intermediates.

Keywords: Photochemistry; Amlodipine; Mechanism; Quantum yield; Dihydropyridine; Photolability

1. Introduction

Photostability is a concern for drugs that absorb strongly in UV-A and in the visible. After the introduction of the ICH Guidelines (ICH, 1996) on this topic, several determinations and some comments have appeared in the literature (Tønnesen, 1996, 2004; Beijersbergen van Henegouwen, 1997; Albini and Fasani, 1998, 2003, 2004; Fasani and Albini, 2005; Fasani et al., 2006a,b). Isolated measurements have no predictive value, however, and it is important that reports on single drugs or groups of drugs are accompanied by mechanistic investigations, where a rationalization of the observed reactivity and of its dependence on changes in the structure and in the medium is offered. 1,4-Dihydropyridines antihypertensive drugs are a typical case. These absorb intensively in the UV-A (some derivatives also in the visible) and are known to be photolabile (Yeung et al., 1991; Marinkovic et al., 2000; Ragno et al., 2002, 2003). Furthermore, the efficiency of various methods for their protection from light has been tested (Skowronski et al., 1984; Thoma and Klimek, 1991; Béchard et al., 1992; Hasan, 1992; Jang et al., 2006). However, in front of a large number of photostability determinations under various conditions, there are only a few quantum yield measurements and the mechanism has been discussed in detail practically only for some 4-(2′-nitrophenyl) derivatives, in particular for nifedipine (Fasani et al., 2006a; Shim et al., 1988; Fujii and Berliner, 1999; Taiwo et al., 1999). These compounds, however, are clearly a special case. The efficient photoreaction in this case is due to the interaction of the nitro group with the easily accessible hydrogen in position 4 of the dihydropyridine ring, a mechanism that has no bearing on the photochemistry of derivatives with the nitro group in a different position (as demonstrated for some 4-(3′-nitrophenyl)-1,4-dihydropyridines) or lacking such group (Fasani et al., 2006b).

We were attracted by amlodipine, a term of the 1,4-dihydropyridine class of antihypertensive drugs used in the treatment of hypertension and angina. This acts as a calcium antagonist and inhibits the transmembrane influx of calcium ions into vascular smooth muscles and cardiac muscles, which in turn affects their contractile process and results in reduced blood pressure (Naidu et al., 2005). The structure characteristics that made this particular derivative worth studying were: (i) the fact that no nitro group was present, but rather a chloro atom in 2′, thus making it possible to test whether a different substituent in 2′ may exert any effect and (ii) the presence of an aliphatic amino group in the side chain. The latter moiety, an electron donor and a base, may on one hand introduce new paths in the

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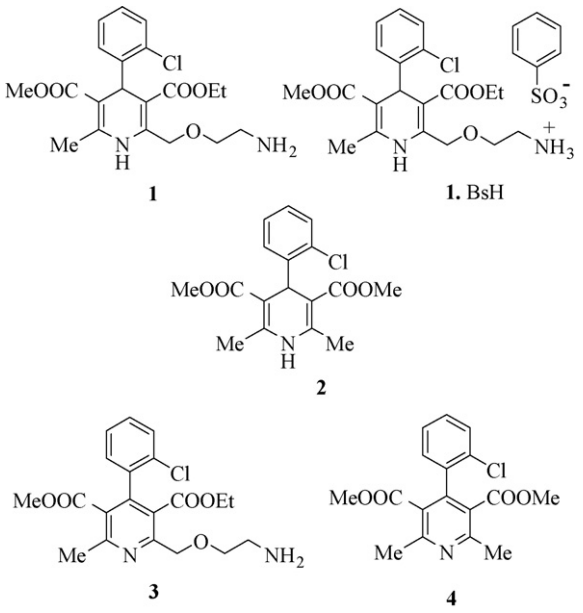

Fig. 1. Chemical structures of the studied compounds.

photochemical reaction and on the other widen the scope of solvents that could be tested, because the corresponding salts were more soluble in polar media than dihydropyridines generally are.

Therefore, we decided to explore in some detail the photoreaction in solution of amlodipine [3-ethyl-5-methyl-4-(2′-chlorophenyl)-2-(2-aminoethyloxymethyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate, **1**, see Fig. 1] and of the corresponding besylate (**1.BsH**), a salt that is one of the used pharmaceutical forms, as well as of a simple analogue lacking the amino group, viz. dimethyl 4-(2′-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, **2**.

2. Materials and methods

2.1. Chemicals

The sample of amlodipine besylate (**1.BsH**) used was a generous gift by Pfizer Ltd., Sanwick, Kent (UK). The free base was prepared by treatment of the besylate with NaOH 5 M (pH 11) in CH_2Cl_2/H_2O under stirring, as indicated in a previous work (McDaid and Deasy, 1996). The corresponding pyridine **3** was prepared by oxidation of **1**, according to the literature (Beresford et al., 1989), and isolated as a difumarate salt, m.p. 135–138 °C (lit: 135–140 °C);

^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.83$ (t, 3H, C**H**$_3$CH$_2$COO, $J = 7$ Hz); 2.57 (s, 3H, C**H**$_3$-Py); 2.9 (t, 2H, –C**H**$_2$NH$_2$, $J = 5$ Hz); 3.49 (s, 3H); 3.58 (t, 2H, –OC**H**$_2$CH$_2$NH$_2$, $J = 5$ Hz); 3.94 (q, 2H, –COOC**H**$_2$CH$_3$, $J = 7$ Hz); 4.77 (AB quartet, 2H, Py-C**H**$_2$–O–, $^2J = 13$ Hz); 6.46 (s, 2H); 7.17-7.55 (m, 5H, aromatic protons).

^{13}C NMR (DMSO-d_6): $\delta = 13.2$ (CH_3); 22.8 (CH_3); 38.4 (CH_2); 52.3 (CH_3); 60.9 (CH_2); 67.7 (CH_2); 72.1 (CH_2); 126.1 (C); 126.6 (CH); 129.0 (CH); 130.3 (CH); 130.5 (CH); 131.7 (C); 134.1 (C); 135.0 (CH fumarate); 144.2 (C); 155.4 (C); 155.5 (C); 165.6 (C, carboxyl group); 166.5 (C, carboxyl group); 167.6 (2 C, fumarate carboxyl groups).

Samples of dihydropyridine **2** and pyridine **4** were prepared according to published procedures and showed spectroscopic characteristics as reported (Carabateas et al., 1984; Böcker and Guengerich, 1986; Salehi and Guo, 2004).

2.2. Photochemistry

Small-scale experiments were carried out on 3 mL samples of 2.5×10^{-4} M solutions of the dihydropyridines in MeCN or MeOH in quartz tubes after argon flushing when appropriate. These were irradiated by means of 15 W low-pressure mercury arcs (254 nm) or 15 W phosphor-coated lamps (center of emission, 366 nm; mid-height width of the emission range, 35 nm). The course of the reaction was monitored by TLC on silica gel (Fluka Silica gel/TLC-cards; F254, 0,2 mm thick) by eluting with cyclohexane/ethyl acetate 7:3 for compound **2** (R_f 0,15, fluorescent under UV_{366}), dichloromethane/methanol/ammonia 60/40/2 for compound **1** ($R_{f.}$ 0,4, fluorescent under UV_{366}) and by HPLC (Jasco PU1580, UV 1575 system) by using a C-18 reverse-phase Supelco Discovery 14518, 250 mm × 4.6 mm, 5 μm column and eluting with acetonitrile–water mixture (50:50, flow 1.3 mL/min, $\lambda_{an} = 250$ nm for compound **2**, r.t. 11,3 min) or phosphate buffer-triethylammine pH 3.14/MeCN mixture (65:35, flow 1 mL/min, $\lambda_{an} = 250$ nm for compounds **1**, r.t. 10,6 min, and **1.BsH**, r.t. 9,1 min). The phosphate buffer was prepared by dissolving 7.0 mL of triethylammine in 1 L of water adding H_3PO_4 to adjust the pH to 3.14).

Absorption spectra were registered on 5×10^{-5} M solutions in spectrophotometric cuvettes (1 cm optical path) on the range of 200–450 nm on a Jasco V-550 UV-Vis Spectrophotometer, using Spectra Manager as software UV, with scan rate 1 nm s^{-1}.

2.3. Quantum yields

The quantum yields of the reaction were measured in quartz tubes on 3 mL samples of 2.5×10^{-4} M solutions of the dihydropyridines in MeCN or MeOH after argon flushing when appropriate irradiated by means of a multilamps apparatus (Helios Italquartz Multirays apparatus). This was fitted with twelve 15 W phosphor-coated lamps (center of emission, 366 nm; mid-height width. 35 nm) or four 15 W low-pressure mercury arcs (254 nm), until a 10–25% conversion was reached (HPLC). The light flux was measured by ferrioxalate actinometry (Hatchard and Parker, 1956).

3. Results and discussion

The absorption spectrum of **1** (Fig. 2) exhibited a long-wavelength band with a maximum in the region 350–360 nm (in MeOH, $\varepsilon_{361} = 5740$ M^{-1} cm^{-1}) that tailed beyond 400 nm, as well as a more intensive band at shorter wavelength (in MeOH, $\varepsilon_{238} = 16850$ M^{-1} cm^{-1}). The spectrum of compound **2** was almost identical ($\varepsilon_{238} = 20400$, $\varepsilon_{359} = 7300$).

Irradiation of a 5×10^{-5} M solution of **1** in methanol at 366 nm (see Section 2 for detail) caused the decrease of both