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Mechanistic pathways of the photolysis of paracetamol in aqueous solution: an example of photo-Fries rearrangement†

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The mechanism of the photolysis of *N*-(4-hydroxyphenyl)ethanamide (paracetamol, PA), a widely prescribed analgesic and antipyretic drug, has been investigated in the absence and in the presence of oxygen. Identification of products and kinetic analyses were performed by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) and by ultra-performance liquid chromatography with a diode array detector (UPLC-PDA). The results show that, under irradiation at 254 nm and independently of the presence of oxygen, the predominant reaction pathway is a photo-Fries rearrangement (PFR), yielding the PA isomer 2′-amino-5′-hydroxyacetophenone (PAI). This reaction occurs from the singlet excited state of the molecule and involves the migration of the acetyl group onto the aromatic ring in the *ortho*-position to the amine moiety. The formation of 4-aminophenol (4-AP) was observed as a minor competitive pathway. The quantum yield of PA consumption (Φ_{-PA}) was determined to be $1.0(\pm0.1) \times 10^{-3}$ by chemical actinometry. As its concentration increases, the PFR product (PAI) competes with PA for light absorption and undergoes, in the presence of oxygen, a photooxygenation process leading to the formation of a peroxyester.

1 Introduction

Detection of pharmaceuticals in the environment was published for the first time in 1977.[1] Since then, through the development of more advanced analytical techniques such as chromatography coupled to tandem mass spectrometry, the persistence of a variety of drugs at very low concentrations (ng L^{-1}) in surface, ground and drinking water could be demonstrated.[2,3] This type of "Persistent Organic Pollutant (POP)" originates mainly from human and veterinary use as, after consumption, parent compounds are excreted unaltered and/or as metabolites in both urine and faeces.[4] Their presence in water bodies has been principally related to the fact that biological oxidation in Sewage Treatment Plants (STPs) achieves only their partial removal before release of the treated water into the environment.[5]

In the last few decades, increasingly stringent regulations for the protection of human health and the preservation of the environment have led to the development of Advanced Oxidation Processes (AOPs) that have improved the efficiency of oxidative degradation of toxic and non-biodegradable organic compounds. Among the AOPs, photochemical technologies based on the production of the hydroxyl radical, a powerful oxidizing intermediate, have proven most effective for the treatment of polluted water from diverse origins and containing a variety of organic pollutants, among them pharmaceuticals.[6–8]

N-(4-Hydroxyphenyl)acetamide, commonly called acetaminophen or paracetamol (PA), is an analgesic and antipyretic widely used in human and veterinary medical treatments. The top three drugs consumed in France contain paracetamol.[9] It has been reported to be present at concentrations up to 10 μg L^{-1} in natural waters in the USA, and even higher than 65 μg L^{-1} in the Tyne River in the UK.[10,11] Several studies have proposed to use AOPs for the oxidative degradation of this compound.[12–15] Among the processes investigated, the combination of hydrogen peroxide with ultraviolet radiation (H_2O_2/UV process)[6,16] has received considerable attention and the formation and fate of by-products have been investigated.[13,14] However, to the best of our knowledge, the photolysis of PA

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has not been studied, although this compound competes for light absorption at the wavelength generally used for the photolysis of H_2O_2 (254 nm, emission from commercial Hg arc lamps). Moreover, UV irradiation with so-called germicidal light sources (low pressure Hg lamps) is also used for disinfection of drinking water, as UV-C radiation (wavelength shorter than 280 nm) is harmful for microorganisms and may kill pathogens, such as bacteria and viruses.[17,18] Therefore, it is of particular interest to identify the intermediates formed during PA photolysis, as this process would also occur during photochemical processes involving UV-C irradiation.

In the present work, we have investigated the mechanistic pathways of the photolysis of PA at 254 nm in Ar- and in O_2-saturated aqueous solutions. Identification of products and kinetic analyses have been performed using a combination of analytical techniques: spectrophotometry, liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) and ultra-performance liquid chromatography with a diode array detector (UPLC-PDA). The main product of PA photolysis has also been identified by hydroxylation of a commercial compound using the UV/H_2O_2 process.

2 Experimental

2.1 Chemicals

N-(4-Hydroxyphenyl)ethanamide or paracetamol (PA, 98%), 4-aminophenol (4-AP, 98%), 2′-aminoacetophenone (2A-AP, 98%), 3′-aminoacetophenone (3A-AP, 98%), 1-β-D-ribofuranosyluracil or uridine (99%) and H_2O_2 (35% w/w in H_2O) were purchased from Sigma Aldrich and used without further purification. LC-MS Chromasolv grade methanol, acetonitrile, trifluoroacetic acid (TFA) and formic acid were purchased from Fluka Analytical (Sigma Aldrich). The working solutions (pH = 5.5) were prepared with ultrapure water (Milli Q Reagent Water System apparatus).

2.2 Photochemical reactors

The experiments were performed in an annular photochemical reactor. The laboratory batch reactor had a capacity of 300 mL (DEMA, Mangels, Bornheim-Roisdorf, Germany, internal radius: 3.6 cm; external radius: 5.5 cm; height: 27 cm). It was equipped with a low pressure Hg lamp positioned in a quartz well in the axis of the reactor and emitting at 254 nm (electrical power: 5 W; radiant power: 1.2 W; UV-Consulting Peschl, Mainz, Germany). The initial concentration of paracetamol was 2.65×10^{-4} mol L^{-1}.

For the UV/H_2O_2 experiments, a given volume of an aqueous solution of H_2O_2 at the required concentration was introduced into the reactor containing the solution of 2A-AP or 3A-AP just before starting the irradiation. 2A-AP, 3A-AP and H_2O_2 absorb at 254 nm, the molar absorption coefficients of 2A-AP and 3A-AP (determined in this work) being much higher (6930 L mol^{-1} cm^{-1} and 7290 L mol^{-1} cm^{-1}, respectively, 5% experimental error) than that of H_2O_2 (18.7 L mol^{-1} cm^{-1}).[16] The amount of H_2O_2 used in this work was such that 5% of the incident photons were absorbed by H_2O_2 ($[H_2O_2]_0 = 3.18 \times 10^{-3}$ mol L^{-1}, $[A\text{-}AP]_0 = 1.55 \times 10^{-4}$ mol L^{-1}). Conversion was kept low enough, so that further oxidation was minimized. Solutions were continuously bubbled with oxygen, air or argon and the experiments were performed at a temperature of 20(±1) °C. Samples (800 μL) were withdrawn from the reactor at regular intervals and analyzed by UV-Visible spectrophotometry, UPLC and liquid chromatography coupled with mass spectrometry (LC-MS/MS, § 2.4).

2.3 Actinometry and quantum yield determination

Uridine (1-β-D-ribofuranosyluracil) was used as an actinometer.[19,20] The quantum yield of uridine photolysis at 254 nm was taken as $\Phi_{uridine} = 0.018$.[21] The molar absorption coefficients of uridine (determined in this work) at 254 nm and 262 nm are 8520 L mol^{-1} cm^{-1} and 9970 L mol^{-1} cm^{-1} respectively (5% experimental error). To ensure total absorption of the radiation by the actinometric solution at 254 nm on 1 cm, a 2.37×10^{-4} mol L^{-1} solution of uridine was used. The incident photon flux (P_0) defined as the number of photons entering the solution per unit of time and unit volume was calculated from eqn (1). A value of 1.5×10^{-5} einstein L^{-1} s^{-1} (incident photon flux emitted by the lamp: 4.5×10^{-6} einstein s^{-1}) was obtained.

$$-\mathrm{d}[\text{uridine}]/\mathrm{d}t = \Phi_{\text{uridine}}\, P_0\, (1 - 10^{-A_{\text{uridine}}}) \quad (1)$$

where $-\mathrm{d}[\text{uridine}]/\mathrm{d}t$ is the initial rate of uridine disappearance (mol L^{-1} s^{-1}), $\Phi_{uridine}$ is the quantum yield of uridine photolysis at 254 nm, P_0 is the incident photon flux (einstein L^{-1} s^{-1}) and $A_{uridine}$ is the absorbance of uridine at 262 nm.

The value of the quantum yield of PA consumption (Φ_{-PA}) at low conversion (≤30%) was calculated using eqn (2).

$$\Phi_{-PA} = (\mathrm{d}[PA]/\mathrm{d}t)_0/P_a \quad (2)$$

where $(\mathrm{d}[PA]/\mathrm{d}t)_0$ is the initial rate of PA disappearance (mol L^{-1} s^{-1}) and P_a is the photon flux absorbed by PA (einstein L^{-1} s^{-1}). The initial rate of PA disappearance was calculated to be 1.5 (±0.1) × 10^{-8} mol L^{-1} s^{-1} ($[PA]_0 = 2.6 \times 10^{-4}$ mol L^{-1}).

2.4 Analytical methods

UV/Visible absorption spectra were registered on an HP-8452A diode array single beam spectrophotometer from Hewlett Packard. Quartz cells of 1 cm or 1 mm optical path length were employed.

Chromatographic analyses of the reaction systems were performed using an ACQUITY UPLC from Waters with a PDA detector, and an Acquity UPLC BEH C_{18} column (2.1 × 100 mm, 1.7 μm, Waters). The optimized mobile phase for PA consisted of a mixture of two solutions: 98% of a 0.1% TFA aqueous solution (A) and 2% of acetonitrile containing 0.1% TFA (B). Runs were carried out in isocratic mode at a flow rate of 0.3 mL min^{-1}. In the case of aminoacetophenones, the flow rate was the same, but the eluent consisted of a mixture of A and B at a ratio of 98/2 for only 2.5 min, the A/B ratio was

then changed to 65/35 within 1 min, maintained at this value for 2.5 min, changed back to 98/2 within 0.5 min and kept constant until the end of the run. The detection range of the PDA detector was set between 190 nm and 500 nm. Samples of 3 μL were injected into the UPLC system. Data acquisition was handled by the Empower2 software.

Preparative chromatography was performed using an Autopurif Waters system with a PDA 2998 detector, an injector collector 1767 and a pump 2545. Beforehand, the 300 mL solution was lyophilized (Lyoph Alpha 1–2, Fisher Bioblock Scientific) and redissolved in 1.5 mL of methanol. Chromatographic conditions were optimized on an analytical column (XBridge C_{18}, 4.6 × 150 mm, 5 μm, Waters); the flow rate was 1.2 mL min^{-1} in isocratic mode with 95% of A and 5% of B. These conditions were then transposed on a preparative column (XBridge C_{18}, 19 × 150 mm, 5 μm, Waters), the flow rate was 20 mL min^{-1}, the eluent consisted of a mixture of A and B at a ratio of 95/5 during 7 min, the A/B ratio was then changed to 100% of B within 1 min, maintained at this value for 3 min, changed back to 95/5 within 1 min and kept constant until the end of the run. The detection range of the PDA detector was set between 200 nm and 400 nm. Samples of 500 μL were injected into the preparative system. Data acquisition was handled by the MassLynx and FractionLynx softwares. 21 fractions were collected and checked on the ACQUITY UPLC system with the same method described above for the analysis of PA. The solvent from the various fractions was evaporated by Speed-Vacuum.

LC-electrospray ionization (ESI) – MS/MS analyses were carried out on an instrument consisting of an Agilent 1100 LC (Waters) equipped with a UV/visible detector and a Q-trap Applied Biosystems mass spectrometer with an ESI source in positive mode. Data acquisition was handled by the Analyst 1.4.2 software. A Symmetry C_{18} column (4.6 × 75 mm, 3.5 μm, Waters) was used for HPLC analyses with a 0.1% formic acid aqueous solution as the eluent (C) or pure methanol (eluent D) at a flow rate of 0.3 mL min^{-1}. The mobile phase gradient was changed as follows. Elution was started with a volumetric ratio C/D of 90/10, changed to 20/80 after 5 min and to 90/10 at 5.5 min and held for 9 min. The UV/visible detector was set at 254 nm. The mass spectrometer was operated in a positive ionization mode. The source temperature was set at 400 °C and the ionization source at 5 kV. MS analyses were performed using extracted ion current (XIC) and multiple reaction monitoring (MRM) of specific product and parent ions (tandem mass spectrometry). The parameters for the MRM mode were optimized for each compound (Table 1).

Table 1 Optimized parameters for the ionization of paracetamol (PA) and its photolysis products (PAI, 4-AP and PAIO)

	PA and PAI[a]	PAIO[a]	4-AP
Transition MRM	152/110	184/166	110/65
Declustering potential (V)	57	81	51
Entrance potential (V)	5	6	10
Collision energy (V)	21	11	28

[a] PAI: 2′-amino-5′-hydroxyacetophenone (2A5H-AP); PAIO: peroxyester (Scheme 3).

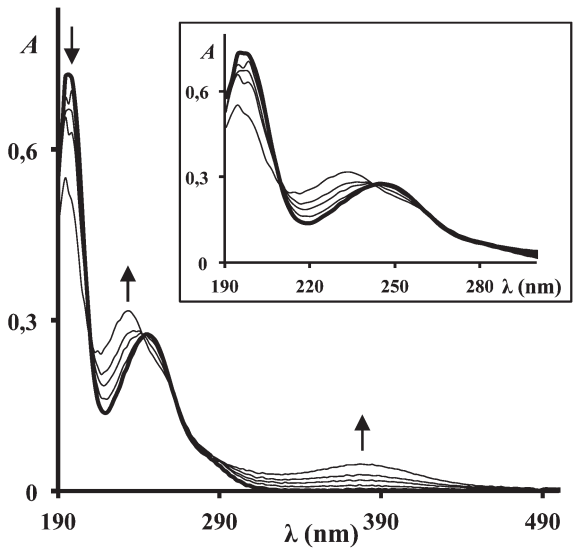


Fig. 1 Evolution of the absorption spectrum of an Ar-saturated solution of PA during 3 hours of irradiation at 254 nm ($[PA]_0 = 2.65 \times 10^{-4}$ mol L^{-1}); PA absorption spectrum in bold; arrows indicate increase or decrease of corresponding absorption bands.

3 Results and discussion

3.1 Photolysis of paracetamol in the absence of oxygen

The absorption spectrum of paracetamol (PA) in aqueous solution shows two absorption bands centered at 196 nm and 244 nm (Fig. 1), with molar absorption coefficients (determined in this work) of 13 660 L mol^{-1} cm^{-1} and 9680 L mol^{-1} cm^{-1}, respectively (experimental error of 5%). Irradiation of an Ar-saturated solution at 254 nm induced significant changes in the absorption spectrum (Fig. 1). Evolution of the latter during irradiation shows two distinct isosbestic points at 208 nm and 240 nm, suggesting that PA is transformed into one main product under these conditions. The solution changed from colorless to yellow due to a new absorption band centered at 380 nm and extending into the visible spectral range.

The disappearance of PA during irradiation was followed by liquid chromatography coupled to mass spectrometry (LC-MS/MS), using the multiple reaction monitoring (MRM) mode. The concentration of PA was calculated from the peak area of the MRM transition 152/110, between the parent ion at 152 (MH^+ of PA) and the fragment ion at 110 (loss of the acetyl group).

The major product formed during the photolysis of PA in an Ar-saturated solution had the same MRM transition 152/110 as PA, but a different retention time on the chromatogram. The same MRM transition means that this product is a configuration isomer of PA (PAI). The minor product of PA photolysis was identified by UPLC-PDA and mass spectrometry as

4-aminophenol (4-AP) by comparison to a commercial standard. Fig. 2 represents the evolution of the concentrations of PA, its isomer (PAI) and 4-AP during irradiation at 254 nm in Ar-saturated solutions. Under these conditions, the isomer concentration increased during irradiation time. After 5 hours of irradiation, the conversion rate of PA was approx. 80% with formation of 73% of PAI and 6% of 4-AP.

3.2 Photolysis of paracetamol in the presence of oxygen

When the PA aqueous solution was saturated with O_2 and irradiated, changes in the absorption spectrum were similar to those in an Ar-saturated solution (identical isosbestic points) up to 3 hours of irradiation at 254 nm. PA disappearance followed the same kinetics within experimental error (Fig. 3a).

Under prolonged irradiation, O_2-saturated solutions of PA became light brown and no distinct band was present in the absorption spectrum after 7 hours, in contrast to Ar-saturated solutions (Fig. 3b and S1†). This result suggests that, in the presence of O_2, the reaction proceeds to yield secondary products. This was confirmed by LC-MS/MS measurements, showing that the PAI concentration reached a maximum value after 3 hours of irradiation, and then decreased (Fig. 4).

The product of PAI oxidation (PAIO) was analyzed by mass spectrometry. Its molecular mass (183 g mol^{-1}) is equal to that of PA (and PAI) (151 g mol^{-1}) plus 32 g mol^{-1}. The concentration of PAIO was followed by measuring the peak area of the MRM transition 184/166, between the parent ion at 184 (MH^+ of PAIO) and the fragment ion at 166 (loss of H_2O). Fig. 4 confirms that PAI underwent an oxygenation process in a secondary reaction step under UV irradiation in the presence of O_2: the PAIO formation was shifted at longer times than that of

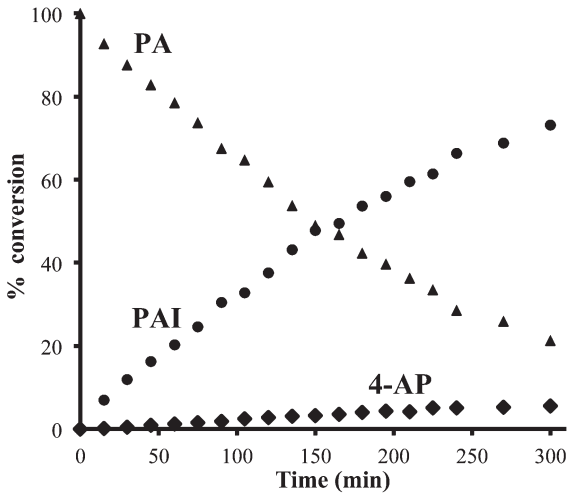


Fig. 2 Consumption of PA (triangles) and formation of its isomer PAI (dots) and of 4-AP (diamonds) during irradiation at 254 nm in an Ar-saturated aqueous solution; $[PA]_0 = 2.65 \times 10^{-4}$ mol L^{-1}; analysis by LC-MS/MS in the MRM mode: transitions 152/110 (PA and PAI) and 110/65 (4-AP).

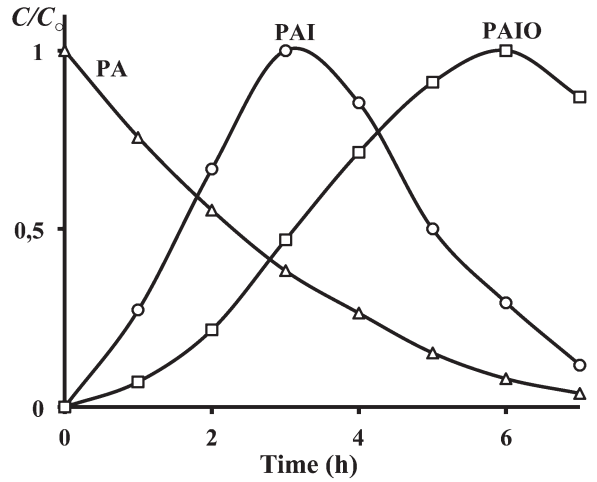


Fig. 4 Evolution of the relative concentrations of PA (triangles), of its isomer PAI (circles) and of the PAI oxygenation product (squares) during irradiation at 254 nm in an O_2-saturated aqueous solution; $[PA]_0 = 2.65 \times 10^{-4}$ mol L^{-1}; analysis by LC-MS/MS in the MRM mode: transitions 152/110 (PA and PAI) and 184/166 (PAIO).

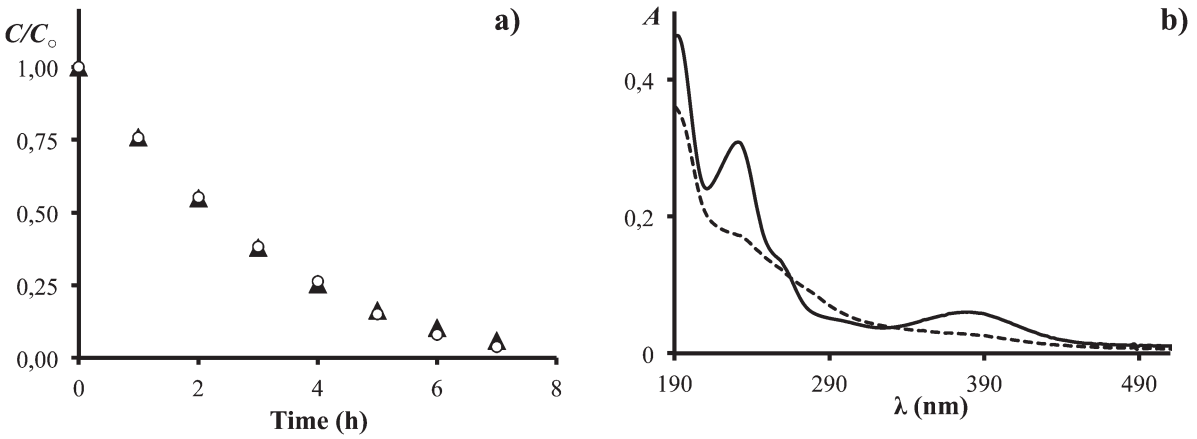


Fig. 3 (a) Evolution of the relative concentration of PA in Ar-saturated (filled triangles) and in O_2-saturated (open circles) solutions during irradiation at 254 nm. (b) Comparison of the absorption spectra of PA after 7 hours of irradiation in Ar-saturated (full line) and O_2-saturated (dotted line) solutions; $[PA]_0 = 2.65 \times 10^{-4}$ mol L^{-1}; analysis by LC-MS/MS in the MRM mode for the transition 152/110.

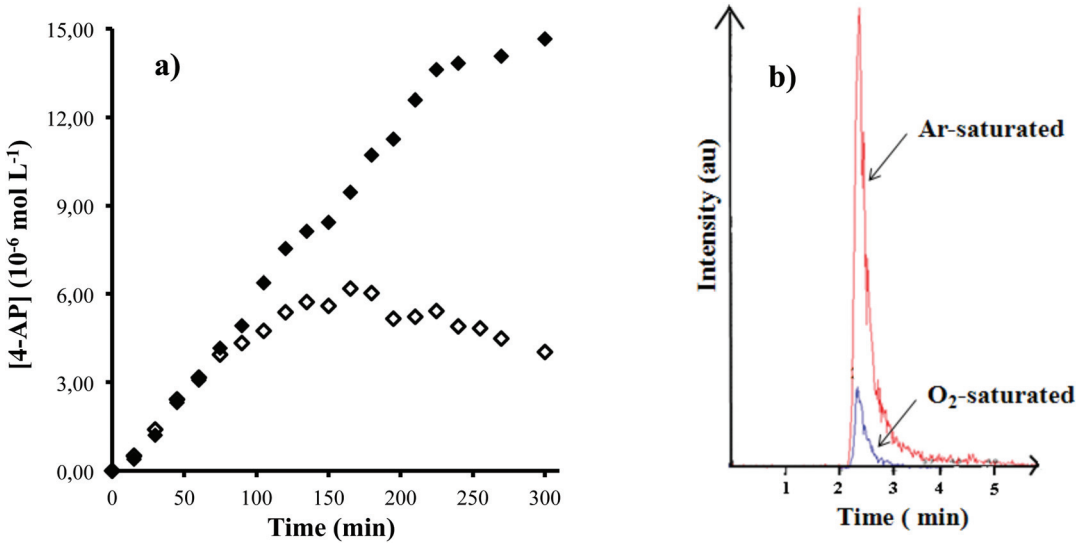
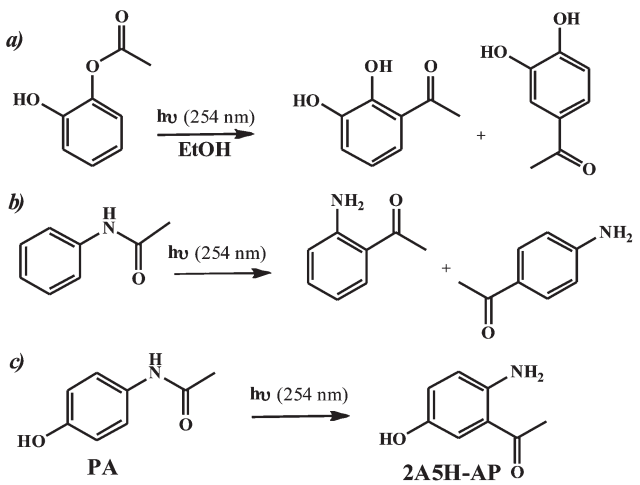


Fig. 5 (a) Evolution of the concentration of 4-AP in Ar-saturated (filled diamonds) and in O_2-saturated (open diamonds) solutions of PA under irradiation at 254 nm. (b) XIC (extracted ion chromatogram) of 110 (MH^+ of 4-AP, retention time: 2.4 min) after 7 hours of PA irradiation in Ar- and O_2-saturated aqueous solutions; $[PA]_0 = 2.65 \times 10^{-4}$ mol L^{-1}; analysis by LC-MS/MS in the MRM mode for the transition 110/65.

PAI and reached its maximum when the PAI concentration had significantly decreased (Fig. 4).

Formation of 4-AP was also observed in O_2-saturated solutions. The kinetics of its formation at the beginning of the irradiation time were the same in Ar-saturated and O_2-saturated solutions (Fig. 5a). After 7 hours of irradiation at 254 nm, 4-AP was less concentrated in the presence of O_2 than in its absence (Fig. 5b); a maximum concentration of 4-AP of 6.2×10^{-6} mol L^{-1} (2.3% of $[PA]_0$) was achieved after 3 hours of irradiation, then the 4-AP concentration decreased. This compound is known for its poor stability in the presence of oxygen and undergoes an autooxidation process in the dark, in particular at alkaline pH.[22,23] A product with a molecular mass of 107 g mol^{-1} was detected by mass spectrometry (ESI, positive ionization, MH^+ = 108); such a mass, corresponding to that of 4-AP minus 2, may be attributed to the quinonoid structure formed by autooxidation of 4-AP.[23] This reaction may explain the yellow-brownish color of the solution at long irradiation times.



Scheme 1 Photo-Fries rearrangement (PFR): (a) products formed by photolysis of catechol monoacetate,[24] (b) of acetanilide[34] and (c) potential product of PA photolysis.

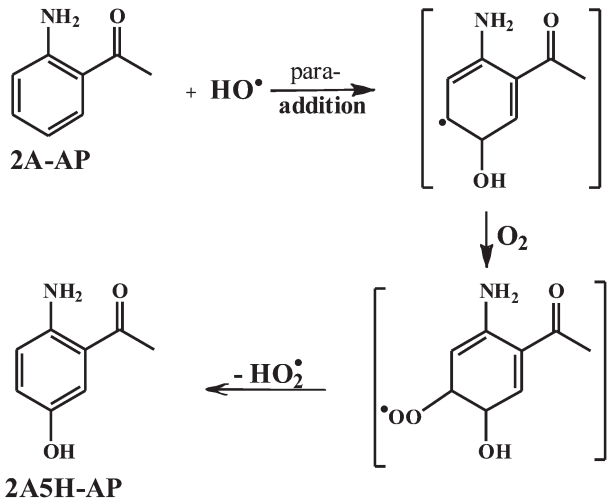
3.3 Identification of the configuration isomer formed during photolysis of paracetamol

Taking into account the structure of PA and the absence of the O_2 effect on the formation of its configuration isomer, the hypothesis of a photo-Fries rearrangement (PFR) occurring from the singlet excited state of PA may be formulated. This type of rearrangement was first observed by Anderson and Reese in 1960,[24,25] when they reported that 2-hydroxyphenylacetate rearranged to 2,3- and 3,4-dihydroxyacetophenone upon UV irradiation in ethanol (Scheme 1a). Similarly, Kobsa[26] showed that the photolysis of *p*-(*tert*-butyl) phenyl esters of aromatic carboxylic acids gave the corresponding *o*-hydroxyphenyl ketones. Such rearrangements were later investigated for a large variety of phenyl esters in organic solvents.[27] They imply the cleavage of the C–O bond in the α-position to the carbonyl group (α-cleavage, Norrish type I reaction)[28,29] and migration of the acyl group to the *ortho*- and/or *para*-positions on the aromatic ring (not *meta* due to electronic factors).[30] Although there are much less literature reports on PFR of aromatic amides (anilides) than on analogous esters,[27] a few early studies on acetanilide have shown that, similarly to phenyl acetate, acetanilide may undergo PFR with cleavage of the C–N bond and migration of the acetyl group.[31–36] A mixture of *ortho* and *para* isomers (2-amino and 4-aminoacetophenone) was obtained (Scheme 1b).[34]

In the case of PA, due to the presence of a hydroxyl substituent in the *para* position of the amide moiety, a PFR should lead to the formation of only one rearrangement product: 2′-amino-5′-hydroxyacetophenone (2A5H-AP) (Scheme 1c). To

the best of our knowledge, this compound is not commercially available for comparison with PAI. Nevertheless, the corresponding non-hydroxylated derivative, 2′-aminoacetophenone (2A-AP), could be purchased. 2A5H-AP might be obtained from 2A-AP by hydroxylation of the aromatic ring in the *para* position to the amino group.

Hydroxylation of 2A-AP was performed in aqueous solution using the UV/H_2O_2 process (irradiation at 254 nm) (§ 2.2). In this process, photolysis of H_2O_2 results in the homolytic cleavage of the oxygen–oxygen bond, producing hydroxyl radicals ($HO^{\cdot}$) with a quantum yield of 1.[16] The $HO^{\cdot}$ radical is a highly reactive species, and the first step of its reaction with aromatic compounds is generally electrophilic addition to the aromatic ring yielding intermediate hydroxycyclohexadienyl radicals.[37]



Scheme 2 Hydroxylation of 2′-aminoacetophenone (2A-AP) by addition of $HO^{\cdot}$ in the *para* position to the amino group in the presence of oxygen.

The latter are efficiently trapped by O_2 and the peroxy radicals thus formed undergo re-aromatization to hydroxylated derivatives by elimination of $HO_2^{\cdot}$ (hydroperoxyl radical) (Scheme 2).

Taking into account the electronic effects of the substituents on 2A-AP, electrophilic addition of $HO^{\cdot}$ on the *ortho* and *para* positions relative to $-NH_2$ should be favored (activation by $-NH_2$ of these positions that are also less deactivated by the electron attracting effect of $-COCH_3$),[38] thus yielding 2A5H-AP as one of the main products.

In fact, PAI and the main product obtained by the hydroxylation of 2A-AP were found to be the same compound. This conclusion was supported by the results of LC-MS/MS and UPLC-PDA analyses (same retention time, same mass spectrum and same UV-visible absorption spectrum) (Fig. 6). The only possible common product resulting from the PFR of PA with migration of the acetyl group to the *ortho*-position on the aromatic ring (Scheme 1c) and from the hydroxylation of 2A-AP on the *para*-position to the $-NH_2$ (Scheme 2) is 2A5H-AP (=PAI). The difference in the absorption spectra observed in Fig. 3b (PAI, main product of PA photolysis under Ar) and in Fig. 6 (chromatographic peak of PAI) is due to a pH difference: water at natural pH in the former case and elution solvent (pH approx. 2) in the latter case. A control experiment using preparative HPLC (§ 2.4) confirmed this pH effect on the absorption spectrum (Fig. S2†).

It could be confirmed that PFR of PA involving migration of the acetyl group to the *meta* position on the aromatic ring did not occur. Indeed, hydroxylation of 3′-aminoacetophenone yielded a mixture of hydroxylated products (because of opposite electronic effects of the two substituents, $-NH_2$ and $-COCH_3$) but none of these compounds could be identified as a product of PA photolysis.

It should be noted that the same secondary product as found during PA photolysis in the presence of O_2 (PAIO) was

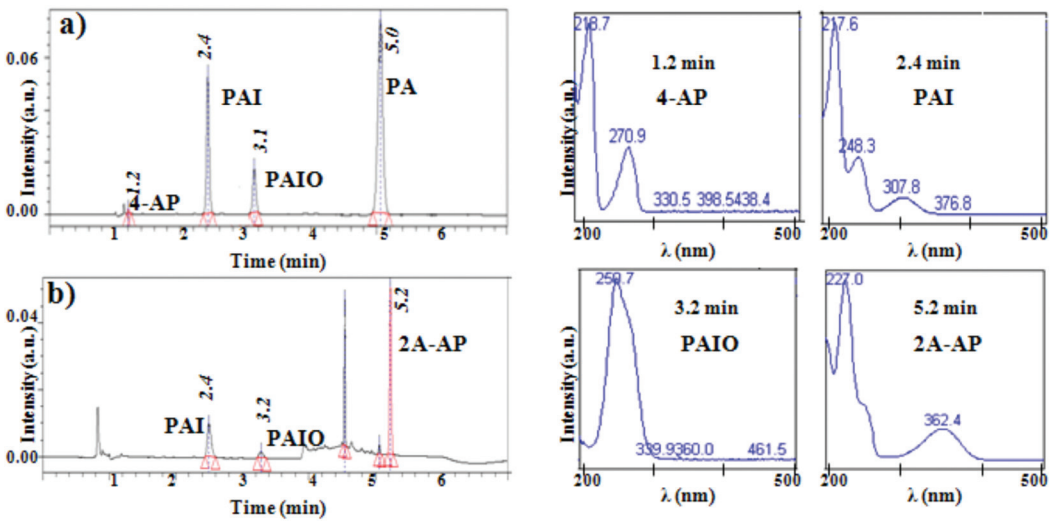


Fig. 6 UPLC-PDA chromatograms (left) and absorption spectra corresponding to the different peaks observed (right): (a) chromatogram obtained after photolysis of PA ($[PA]_0 = 2.65 \times 10^{-4}$ mol L^{-1}) during 3 h; (b) chromatogram obtained after hydroxylation of 2′-aminoacetophenone ($[2A\text{-}AP]_0 = 1.55 \times 10^{-4}$ mol L^{-1}) by the H_2O_2/UV process during 15 min; O_2-saturated aqueous solutions; irradiation at 254 nm.

observed during the hydroxylation of 2A-AP to 2A5H-AP (=PAI), thus confirming that PAIO comes from the oxygenation of PAI during the PFR of PA in the presence of O_2 (Fig. 6).

3.4 Mechanistic pathways of the photolysis of paracetamol

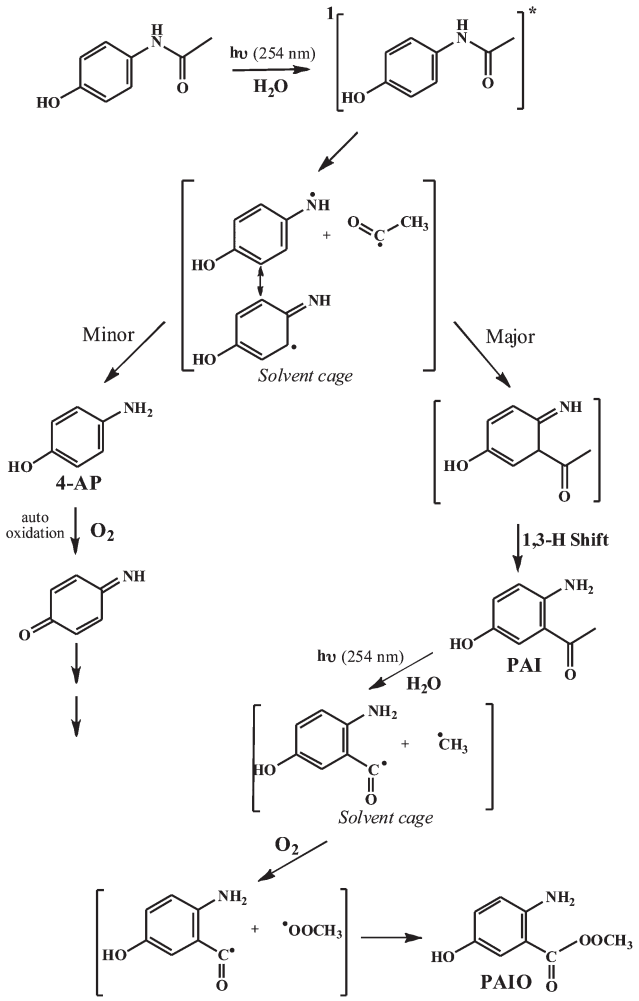
Mechanism in the absence of oxygen. We have shown that the excitation of PA at 254 nm in de-aerated aqueous solution leads to a photo-Fries rearrangement with formation of 2′-amino-5-hydroxyacetophenone (2A5H-AP) as the main product (§ 3.3). The lack of sensitivity of PA disappearance to the presence of oxygen (Fig. 3a) confirms that the reaction occurs from the singlet excited state of the molecule, as is most often observed in PFRs.

The value of the quantum yield of PA consumption (Φ_{-PA}) up to 30% conversion was calculated to be 1.0 (±0.1) × 10^{-3}, from the rate of PA disappearance (Fig. 2 and 3a) and the photon flux absorbed by PA determined by actinometry (§ 2.3). This low value is in agreement with earlier measurements for acetanilide showing that the quantum yield for the PFR with *ortho* migration of the acetyl group was 0.004 in water, 4 times lower than in ethanol and more than 15 times lower than in cyclohexane.[34] The OH substituent in the *para* position in PA further decreases its reactivity compared to acetanilide. These results confirm the much lower photoreactivity of anilides compared to that of analogous phenyl esters.

The accepted PFR mechanism for aromatic esters involves the homolytic scission of the O–CO bond to give a radical pair (phenoxy and acyl radicals) enclosed in a solvent cage, followed by an intramolecular recombination with migration of the acyl group to form intermediate cyclohexadienones that tautomerize to the final products.[27] A similar mechanism may explain the formation of 2A5H-AP by PFR of PA. The homolytic cleavage of the N–CO bond leads to the formation of a cyclohexadieneimine intermediate I that undergoes a 1,3-H shift to yield PAI (Scheme 3).

The formation of 4-aminophenol (4-AP) represents a minor competitive pathway. The origin of the corresponding phenol observed in the case of phenyl esters was attributed to the out-of-cage escape of the phenoxy radical to form phenol by hydrogen abstraction from the organic solvent.[27] However, in the case of PA in aqueous solution, hydrogen abstraction from water by the Ph–(H)N˙ radical is unlikely but an in-cage redox reaction (H-transfer) between the two radicals could explain the formation of 4-AP with low yield (Scheme 3). The reported yield of aniline (18%) in the case of the photolysis of acetanilide in absolute ethanol in the absence of oxygen supports this interpretation.[32]

Mechanism in the presence of oxygen. As already discussed (§ 3.2), the presence of oxygen does not affect the PFR of PA to yield PAI (2A5H-AP), but PAI undergoes an oxygenation process leading to the formation of PAIO (Fig. 4). Since PAI absorbs at the irradiation wavelength (254 nm) as does PA (Fig. 1), the fraction of photons absorbed by PAI increases as its concentration increases and that of PA decreases. Therefore, PAI itself may undergo a photochemical transformation. The homolytic cleavage of the C–C bonds in the α-position to the carbonyl group (Norrish type I cleavage) has been reported to occur from n,π^* or π,π^* excited states of aromatic (and aliphatic) ketones.[28,29,39] PAI being an acetophenone derivative, cleavage of the C–CH_3 bond, weaker than the C–Ph bond, is expected.[40] In aqueous solution (no source of hydrogen atoms) and in the absence of oxygen, the radical pair recombines and no product formation is observed. However, in the presence of oxygen, the radical(s) may be trapped by oxygen in the solvent cage and subsequent recombination may lead to the formation of a peroxyester (PAIO, molecular mass of 183 g mol^{-1}) (Scheme 3).



Scheme 3 Mechanistic pathways of PA photolysis at 254 nm in the absence and presence of oxygen.

4 Conclusion

We have investigated the photolysis of paracetamol (PA) at 254 nm in aqueous solution and we have elucidated the main mechanistic pathways following excitation of PA in the presence and in the absence of oxygen (Scheme 3). Independently of the presence of O_2, the major reaction product is a PA isomer (PAI), identified as 2′-amino-5′-hydroxyacetophenone

(2A5H-AP) by combining different analytical techniques. This compound results from a photo-Fries rearrangement (PFR), involving cleavage of the C–N bond in the α-position to the carbonyl group (α-cleavage, Norrish type I reaction) and migration of the acetyl group to the *ortho*-position relative to the amino group on the aromatic ring. This reaction proceeds with a low quantum yield, as expected from a few earlier studies on the PFR of acetanilide.

In a minor pathway, 4-aminophenol (4-AP) was formed with a yield more than 10 times lower than the PFR product (PAI), most probably through a cage disproportionation of the two radicals resulting from the initial cleavage of the C–N bond. In the presence of oxygen, 4-AP underwent an autooxidation reaction.

The photo-Fries rearrangement of PA to yield PAI is not affected by the presence of O_2. However, in O_2-saturated solutions, the formation of a secondary product (PAIO) resulting from the oxygenation of PAI was observed under prolonged irradiation. This result was explained by the photochemical reactivity of PAI. Indeed, as its concentration increases, PAI competes more and more efficiently with PA for light absorption and, as an acetophenone derivative, may undergo cleavage of the C–O bond in the α-position to the carbonyl group (α-cleavage). In the absence of O_2, the radicals formed recombine and PAI is stable. However, in O_2-saturated solutions, the radical(s) may be trapped by O_2, leading to the formation of a peroxyester (PAIO).

It should be noted that, although the quantum yield of PA photolysis is low, both reaction products (major and minor) are aromatic amines (anilines). These compounds are known to be toxic, in particular for fish[41] and also for humans,[42] and UV-C (254 nm) disinfection under prolonged irradiation in the presence of PA may induce their formation. More generally, this raises the question of the use of 254 nm irradiation alone for disinfection of water containing organic aromatic residues that absorb at this wavelength (such as drugs or pesticides). Under these conditions, the use of an adequate amount of additive absorbing at 254 nm (*e.g.* H_2O_2, O_3, TiO_2) for producing hydroxyl radicals and ensuring pollutant mineralization to CO_2, H_2O and inorganic acids would be required.

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