Metal-Free, Visible Light-Promoted Aerobic Aldehydes Oxidation

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An efficient and metal-free method for the oxidation of aldehydes to the corresponding carboxylic acids has been developed. In a simple continuous-flow photochemical reactor, the use of camphorquinone (CQ) irradiated with a white light-emitting diode (LED) source enhanced the autoxidation of aldehydes. Under 5 bar of oxygen, visible light, and 0.3 mol% of CQ, the rate of oxidation was increased from 6 times with 2-ethylhexanal to 30 times for *n*-nonanal. The large interfacial area generated by a segmented flow apparatus associated with radicals formed by photooxidation of CQ ensures metal-free high throughput of carboxylic acids under safe conditions.

Keywords: photooxidation, aldehydes, LED

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1. Introduction

The liquid phase oxidation of aldehydes by ground state dioxygen ($^3O_2$) into the corresponding carboxylic acid is a common process that could be easily observed when looking at an aldehyde bottle stored for a rather long time in a close chemical storage cabinet. The aldehyde oxidation pathway is summarized in Figure 1. This process has been first described by Wöhler and Liebig (1832), and it was noticed at the same time that the reaction is accelerated by light [1, 2]. Bayer and Villiger (1900) proposed that the reaction is not a single-step process, the first intermediate being a peracid. Bäckström (1934) showed that this reaction implies a radical chain reaction involving an acyl radical. Criegee (1935) suggested that a condensation between the peracid and a remaining aldehyde produced a tetrahedral adduct, the Criegee intermediate. Rearrangement of the latter produced the corresponding carboxylic acid.

On the lab-scale, the autoxidation of aldehydes has been catalyzed by numerous metallic ions in the form of salts, nanoparticles, or organic complexes [3, 4]. However, we have shown that, due to low transfer rate of O_2 in the liquid phase, the chemical performances of aerobic oxidation (productivity and selectivity) can be falsified by oxygen starvation in the liquid phase [4, 5]. One way this issue can be addressed is to operate at higher oxygen pressure but aldehyde oxidation is a strongly exothermic process ($\Delta_r H = -287$ kJ/mol) and proceeds via highly reactive free radical species. Thus, the combination of fuel, oxidant, and energy raise safety concerns [6, 7].

Flow chemistry has opened new exciting opportunities to perform gas–liquid reactions [8–13]. It provides advantages of fast mixing, enhanced mass and heat transfer, and large and well-defined interfacial area [12]. In the case of aldehyde oxidation, we have shown that aliphatic aldehyde could be safely and effectively oxidized into the corresponding carboxylic acid using 5 bar of O_2 at room temperature without using any catalyst. In less than 15 min, 2-ethylhexanal was totally converted into the corresponding carboxylic acids [14]. However, for less reactive aldehyde (unsubstituted aliphatic aldehydes or aromatic aldehydes), metal catalysts were required to get full conversion in less than 20 min [14, 15]. Under optimized conditions, neat 2-ethylhexanal could be oxidized into 2-ethylhexanoic acid in less than 1 min using 5 ppm of Mn(II) [6].

In a range of products, such as pharmaceuticals, chemicals, cosmetics, medical devices, and consumer products, metal contamination is a serious concern. Sources of metal contamination can include process components such as tanks, valves, piping, and metal catalysts used in synthesis. This is critical as trace metals can impact a product's toxicity and also affect how the substance interacts with other chemicals. Thus, metal-free oxidation methods are in high demand even if, in the particular case of Mn, Mn contamination is of low safety concern [16]. However, the will to suppress the possibility of metal contamination serves as the key motivation for us to tackle light-mediated protocol for the metal-free aerobic aldehydes oxidation.

2. Materials and Methods

2.1. Safety. It is worth mentioning that, in the case of oxidation reactions, fuel, oxidant, and energy are present at the same time in the reactor. Thus, the safety of the process should receive explicit attention.

2.2. Reagents. Benzaldehyde (>99.5%), 2-ethylhexanal (96%), and *n*-nonanal (99%) (Aldrich and Acros) were used as obtained from the supplier and stored at 4 °C under N_2 with protection from light. Analytical grade heptane, tetraphenylporphyrin (TPP), and camphorquinone (1,7,7-trimethylbicyclo [2.2.1]heptane-2,3-dione, CQ) were purchased from Aldrich and used without further purification. Pressurized oxygen (99.995%) was provided by Messer.

2.3. Experimental Setup. The modification of our experimental setup [15], i.e., adding a white light-emitting diode (LED) corn lamp, was easily performed. High-purity PFA with high light transmission (90–96% for visible light) (Upchurch Scientific) with an internal diameter of 750 μm and a length of 8.5 m was used as reactor. The organic phase (Harvard pumps PHD 4400) and the oxygen (Analyt-MTC mass flow controller) were fed via two separate lines and brought together using a T-mixer (IDEX - 632 ETFE tee for 1/16″ OD tubing). Typical flow rates set between 1 and 20 NmL/min for O_2 and up to 0.3 mL/min for the liquid phase were used. PFA tubing was wound around a white LED corn lamp (20 W, 6500 K, MENGS®, China) cooled by a fan (Figure 2). The outlet port of the microreactor was connected to a second T-mixer (IDEX) for dilution and quench by EtOH. A back pressure of 5 bar was applied using a home-made back pressure regulator controlled with nitrogen flow (Analyt-MTC mass flow controller) and micrometering valve. Liquid products were retrieved from backpressure regulator and were analyzed by an Agilent 6890 gas chromatograph (GC) equipped with flame ionization

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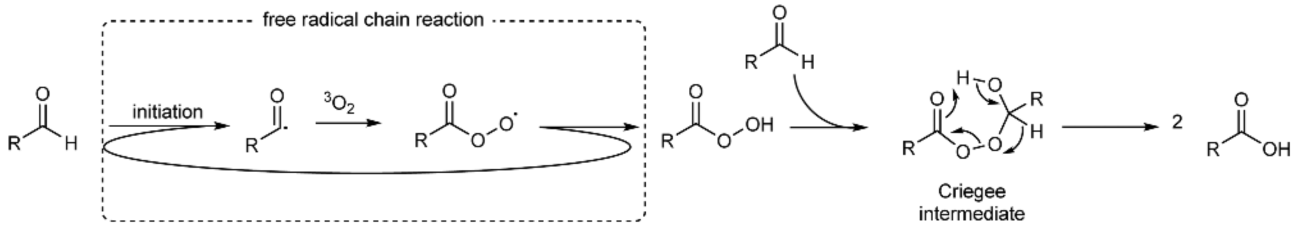

Figure 1. Aldehydes autoxidation pathway

detector (FID) and Zebro column (ZB50 10 m×0.1 mm× 0.1 µm). Conversion and selectivity toward the carboxylic acid were determined on the basis of the normalized peak areas for aldehyde, carboxylic acid, and side products.

The ultraviolet–visible (UV–vis) spectrum of CQ was recorded with a Perkin-Elmer Lamba 25 spectrometer using a 1-cm optical length quartz cuvette at room temperature (r.t.) and heptane as solvent. Emission spectra of 6500 K LED lamp was recorded with Shamrock SR-163 imaging spectrometer (Andor Technology) equipped with a CCD camera (Newton spectroscopic CCD 920 OE).

3. Results and Discussion

3.1. Aldehyde Oxidation Using Singlet Oxygen Generated by Visible Light Photocatalyst. The photooxidation of aldehydes in the liquid phases has already been studied [17, 18]. However, such direct photooxidation could only be observed using UV light due to the inability of aldehyde to absorb visible light. Visible-light photochemistry and, in particular, visible-light photochemistry in flow offer unique opportunities to perform photochemical process [19–22]. Among these processes, photochemically generated singlet oxygen, $^1O_2$, can provide a clean and sustainable route to photo-oxidized compounds with high atom efficiency. This activation mode of oxygen relies on the use of organometallic complexes or organic dyes to absorb photons and to, subsequently, engage in energy transfer processes with $^3O_2$. Practical oxidation of various substrates by $^1O_2$ in flow has been demonstrated by Seeberger [23] using tetraphenylporphyrin (TPP) as sensitizer. $^1O_2$ has been recently studied for the aldehydes oxidation in batch [24, 25]. However, the choice of $^1O_2$ for this particular type of oxidation may be somewhat inappropriate. $^1O_2$ is a powerful electrophile [26] and can react rapidly with olefins (ene reactions, [4+2] and [2+2] cycloadditons) and heteroatoms (organosulfur and organophosphorus compounds, amines, …) [21–23, 26–28]. Indeed the formation of an acyl radical by reaction of singlet oxygen with aldehyde as suggested by Safari [24] and Cho [25] would violate the principle of spin conservation. Nevertheless, total conversion of benzaldehyde was observed in batch using $^1O_2$ [24, 25]. Thus, the oxidation of benzaldehyde by $^1O_2$ using microreactors was evaluated. For this purpose, the emission spectral characteristics of the white LED light sources make TPP an interesting photocatalyst as the broad emission band of white LED source (480–700 nm) encompasses the entire visible region of the absorption spectrum of the photocatalyst TTP (500–670 nm) [29].

As expected from previous experiments [14], without catalyst, the aerobic benzaldehyde oxidation in neat heptane even using pure oxygen in a Taylor flow is a slow reaction and conversion into benzoic acid below 5% is reached in 14 min (Figure 3). The use of TPP as photocatalyst involves the use of 10 vol% of CH_2Cl_2 as solvent in order to solubilize TPP. The introduction of small amount of TTP (0.01 mol%) has a significant inhibitory effect, and no conversion could be noticed in the dark under those conditions (Figure 3). When visible light was turned on, surprisingly, no conversion could be observed even with a residence time of 14 min. We check that, under our conditions, $^1O_2$ was photochemically generated by studying the oxidation of citronellol under the conditions of Seeberger [23]. As expected, high conversion of citronellol could be obtained under the irradiation of white LED lamp using TPP as photocatalyst. From these experiments, we can conclude that photochemically generated $^1O_2$ does not improve the oxidation of aldehydes contrarily to what Safari [24] and Cho [25] claim.

With these disappointing results in hand, we performed an extensive literature research and we found that it has already been demonstrated in the late 1970s that $^1O_2$ was not liable to lead to the initiation of the photooxidation on aldehydes [17]. When methylene blue was used as photocatalyst, an important inhibition of the oxidation was observed [17].

As mentioned previously, aldehyde autoxidation is a slow spontaneous process which is highly dependent on the presence of inhibitors [4, 14]. Thus, we could expect that the in situ

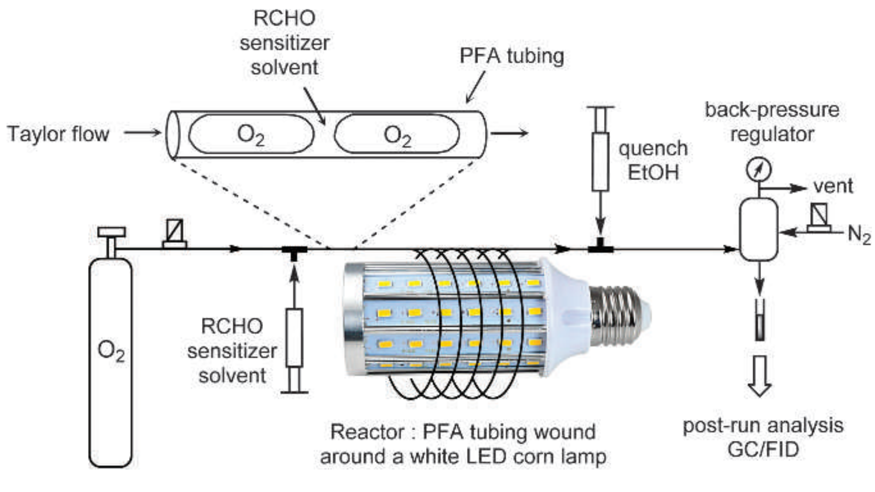

Figure 2. Experimental setup for the visible light-promoted aerobic aldehydes oxidation

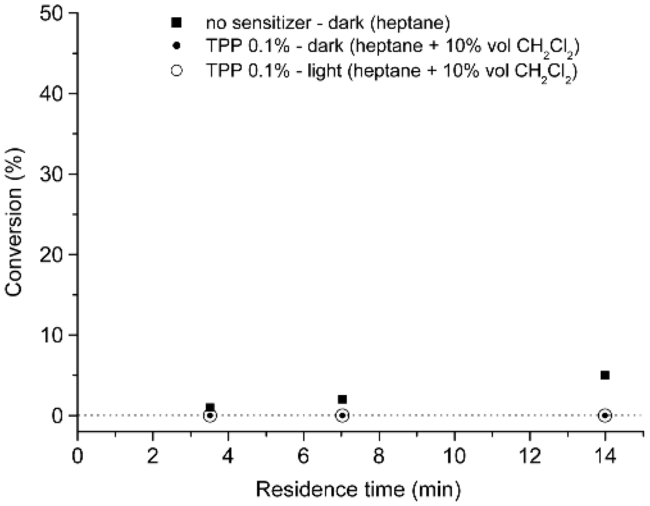

Figure 3. Aerobic oxidation of benzaldehyde in a segmented flow apparatus in the dark or under irradiation of white LED lamp. Reaction conditions: benzaldehyde 1 M in heptane or heptane/10 vol% CH_2Cl_2, PFA tubing (8.5 m × 0.75 mm), Taylor flow, r.t., 5 bar of O_2, O_2/aldehyde molar ratio of 2.5, photocatalyst: TPP 0.01 mol%, white LED 20W

generation of $^1O_2$ could remove these inhibitors, leading to an inhibitors-free solution of aldehydes. Then, the aldehydes could be slowly oxidized as observed by Safari [24] and Cho [25]. It should be noticed that the time needed to reach full conversion of benzaldehyde under those conditions using $^1O_2$ is between 4 h [25] (0.5 mol% of $Ru(bpy)_3Cl_2$ in MeCN, O_2 atmosphere) to 72 h [24] (87% conversion, 0.1 mol% of TPP in MeCN–CH_2Cl_2 with continuous oxygen bubbling). The presence of inhibitors in the solution could explain why no oxidation was noticed in a blank experiment [25] (dark experiment without photocatalyst, O_2 atmosphere).

3.2. Aldehyde Autoxidation Using Visible Light Absorption by Photoinitiator. Camphorquinone (1,7,7-trimethylbicyclo[2.2.1]heptane-2,3-dione, CQ) belongs to the aliphatic α-diketones and is used as a photoinitiator for visible-light photo crosslinking. CQ absorbs light in the UV region at 200–300 nm and in the visible light region at 467 nm (Figure 4). Emission band of white LED encompasses the visible light absorption region of CQ (Figure 4) and could lead to the formation of two excited states: (1) the “singlet state,” which does not involve reversal of electron spin, and (2) the “triplet state,” which is the one relevant to free radical formation and which has a very short half-life (Figure 5).

In the presence of tertiary amines, it gives an effective photoinitiating system widely used for the crosslinking of methacrylate-based dental restorative polymers [30]. The addition of molecular oxygen to the excited triplet state of CQ forms 1,4-biradicals [31–33]. Rearrangement of the latter furnish variety of oxygen and carbon-centered radicals [33, 34] (Figure 5) that could initiate the oxidation of aldehyde through the formation of an acyl radical (Figure 1).

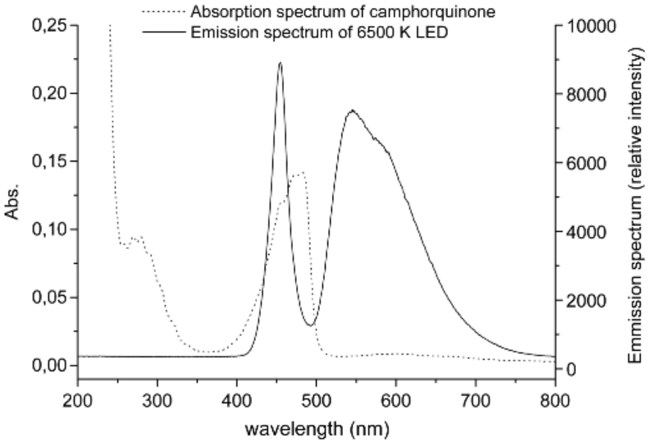

Figure 4. Comparison between the emission spectra of white LED source and absorption spectra of CQ 0.3 mol% in heptane

Thus, photooxidation of benzaldehyde using CQ as photocatalyst was evaluated (Figure 6). As expected, in the dark and in the presence of 0.3 mol% of CQ, no improvement of benzaldehyde oxidation could be noticed for a residence time of 14 min (Figure 6).

However, we were pleased to see that, under the irradiation of a white LED lamp, benzaldehyde in heptane could be selectively oxidized into benzoic acid. A conversion of up to 45% was obtained for a residence time of 14 min at room temperature under 5 bar of oxygen using 0.3 mol% of CQ (Figure 6). An oversaturated solution of benzoic acid was obtained for conversion above ~10%. However, the reaction mixture is diluted by EtOH at the outlet of the reactor, preventing any crystallization of benzoic. We could thus hypothesize that the in situ formation of radicals (Figure 5) could help to break the weak C(=O)–H bond of aldehyde generating the acyl radical followed by the well-known aldehydes autoxidation pathway (Figure 1). It is worth noting that benzaldehyde could not act as a sensitizer because benzaldehyde did not absorb light above 400 nm (Figure 4). Different aldehydes were then evaluated under those conditions (Figure 7).

As expected [4, 14, 15], aliphatic aldehydes oxidation was faster than the oxidation of aromatic aldehydes (Figure 7). In the dark and in the presence of CQ, the conversion of 2-ethylhexanal was already close to 60% for a residence time of 2 min. Those results are comparable to uncatalyzed aerobic oxidation of aldehyde in flow [14]. Under the irradiation of a white LED lamp, the reaction was 6 times faster. The conversion of 2-ethylhexanal for a residence time of 2 min reached 90%. Under those conditions, no improvement of the selectivity towards 2-ethylhexanoic acid (<80%) could be detected [15]. This could be explained as the reaction pathway (Figure 1) was not modified by the use of photocatalyst. Visible light irradiation of CQ produces radicals that only initiated the free radical chain reaction. The selectivity is linked to the rearrangement of the Criegee intermediate, and thus, no improvement of the selectivity could be expected and was noticed. However, reaction rate is greatly enhanced compared to uncatalyzed aerobic oxidation in flow [14].

The same improvement of conversion was observed with unsubtituted aliphatic aldehydes, i.e., *n*-nonanal. In the dark, a conversion of *n*-nonanal below 10% could be achieved with a residence time of 7 min, whereas, under visible light irradiation, a conversion of *n*-nonanal higher than 80% was obtained under the same conditions. Thus, irradiation with visible light in the presence of 0.3 mol% of CQ increases the reaction rate of *n*-nonanal oxidation above 30 times. It should be noticed that the oxidation of *n*-nonanal to the corresponding carboxylic acid is always selective (>98%) [15]. Smaller effect can be observed for benzaldehyde with an increase of the conversion to benzoic acid for a residence time of 14 min from less than 5% to higher than 45% in the dark and under visible light irradiation, respectively (Figure 7). However, the effect is less pronounced than the use of Mn(II), i.e., a conversion up to 95% was obtained for a residence time of 17 min using 100 ppm of Mn(II) [14]. The oxidation of *n*-nonanal was then studied as the function of photocatalyst concentration (Figure 8).

The oxidation of *n*-nonanal was shown to be dependent on the photocatalyst concentration (Figure 8). In order to determine the optimum CQ concentration, a series of experiments was performed and the *n*-nonanal conversion obtained for a residence time of 30 s against the concentration of CQ was plotted in Figure 9.

As expected from previous experiments, the reaction rate increased with the concentration of CQ until a plateau was reached

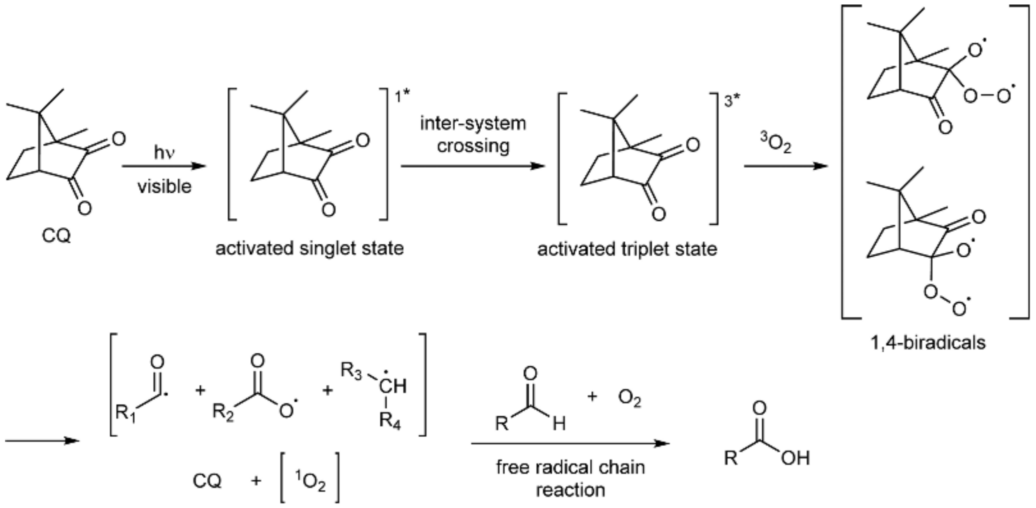

Figure 5. Generation of oxygen and carbon centered radicals by photooxidation of CQ that could initiate the autoxidation of aldehydes

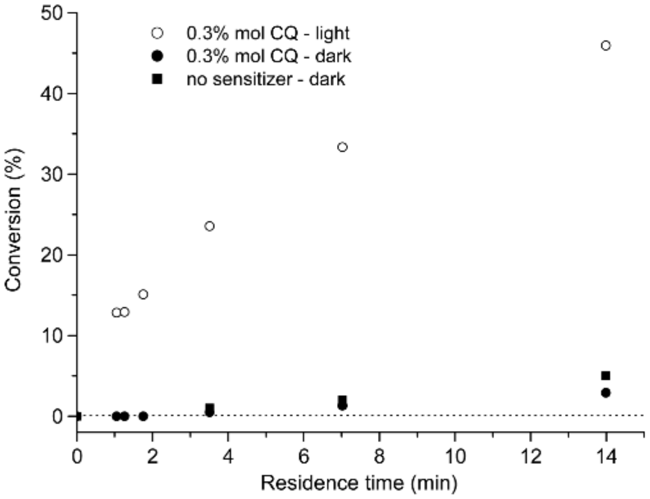

Figure 6. Aerobic oxidation of benzaldehyde in a segmented flow apparatus in the dark or under irradiation of white LED lamp. Reaction conditions: benzaldehyde 1 M in heptane, PFA tubing (8.5 m × 0.75 mm), Taylor flow, r.t., 5 bar of O_2, O_2/aldehyde molar ratio of 2.5, photocatalyst: CQ 0.3 mol%, white LED 20W

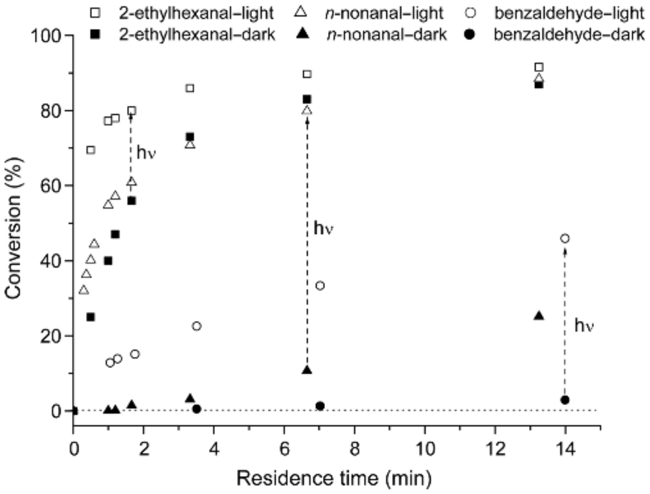

Figure 7. Comparison of the aerobic oxidation of aldehydes in a segmented flow apparatus in the dark or under irradiation of white LED lamp. Reaction conditions: Aldehyde 1 M in heptane, PFA tubing (8.5 m × 0.75 mm), Taylor flow, r.t., 5 bar of O_2, O_2/aldehyde molar ratio of 2.5, photocatalyst: CQ 0.3 mol%, white LED 20W

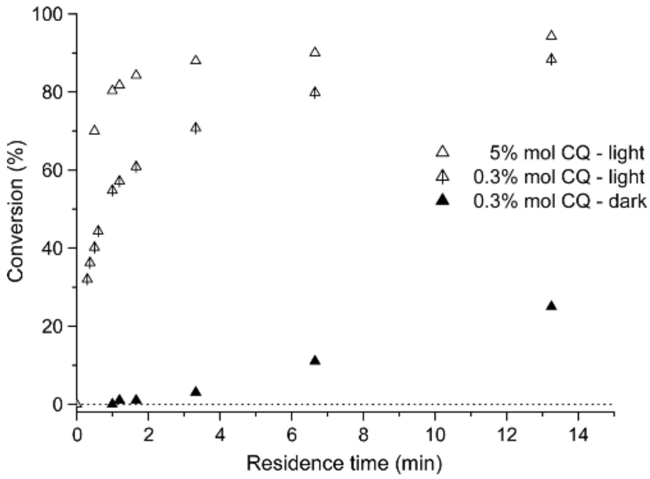

Figure 8. Aerobic oxidation of *n*-nonanal in a segmented flow apparatus in the dark or under irradiation of white LED lamp. Reaction conditions: *n*-nonanal 1 M in heptane, PFA tubing (8.5 m × 0.75 mm), Taylor flow, r.t., 5 bar of O_2, O_2/aldehyde molar ratio of 2.5, photocatalyst: CQ 5 or 0.3 mol%, white LED 20W

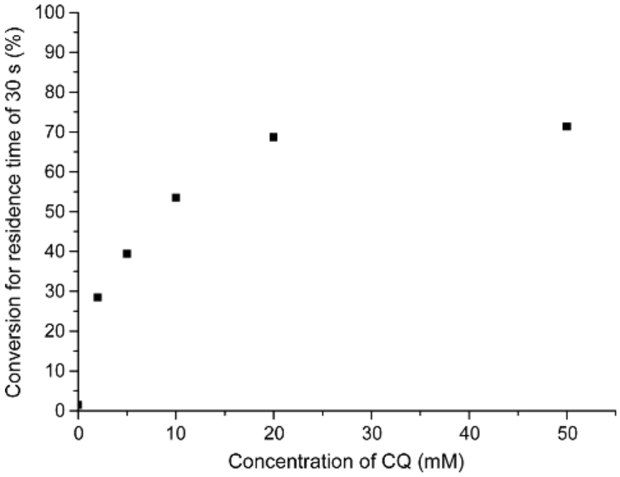

Figure 9. Aerobic oxidation of *n*-nonanal in a segmented flow apparatus as the function of CQ concentration under irradiation of white LED lamp. Reaction conditions: *n*-nonanal 1 M in heptane, PFA tubing (8.5 m × 0.75 mm), Taylor flow, r.t., 5 bar of O_2, O_2/aldehyde molar ratio of 2.5, photocatalyst :CQ, white LED 20W

above 20 mM (2 mol%). This optimum might be explained by O_2 transfer limitations or by recombination of radicals.

4. Conclusion and Outlook

The liquid phase autoxidation of aldehydes by air/oxygen has been known for more than 180 years, and the reaction mechanism and kinetics of the oxidation have been widely studied. Recently, new catalysts and news processes have been reported for this oxidation. However, in most cases, we can suspect that the reaction rates are limited by oxygen mass transfer and/or by the presence of inhibitors. Such phenomena could lead to much confusion in the interpretation of the results, and microreactors are clearly interesting tools for the evaluation of these new gas–liquid experimental conditions.

We have developed a simple and inexpensive continuous-flow reactor system that enables the metal-free catalyzed aerobic oxidation of aldehydes. The use of a photoinitiator, camphorquinone (CQ), irradiated with broad emission band of white LED source (480–700 nm) enhanced the autoxidation of aliphatic aldehyde as well as aromatic aldehydes by generating a variety of oxygen and carbon centered radicals.

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