

RSC Advances



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ARTICLE

Aerobic oxidation of aldehydes: selectivity improvement using sequential pulse experimentation in continuous flow microreactor.

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/advances

Laurent Vanoye,^a Mertxe Pablos,^a Neil Smith,^a Claude de Bellefon,^a Alain Favre-Régouillon^{*a,b}

The aerobic oxidation of aldehyde was investigated using a continuous flow microreactor under 5 bar of oxygen at room temperature. High-throughput screening of experimental conditions resulted in the development of an improved protocol. The synergistic use of a large range of salts and Mn(II) catalyst was found to be a very efficient catalytic system for selective aldehyde oxidation. Indeed for short residence time (*i.e.* 6 min.), a quantitative conversion of 2-ethylhexanal was obtained with a selectivity toward carboxylic acid of 98 %.

Introduction

The liquid phase oxidation of aldehyde by molecular oxygen (autoxidation) has been known for a long time. J. Liebig was the first to observe, in 1835, that benzaldehyde was transformed into benzoic acid in the presence of air. It was then shown by H. Bäckström, in 1927 that this reaction implies a radical chain mechanism.¹ Since then, this reaction has been extensively studied and is currently used for the commercial production of C₄-C₁₃ carboxylic acids from the corresponding aldehydes obtained by the hydroformylation of olefins (oxo synthesis).² Later it was demonstrated that this reaction is often limited by gas-liquid mass transfer and more recently we have shown that for some aldehyde autoxidation described in the literature, the rate limiting step was still the rate of oxygen transfer into the liquid.³ In such cases, the productivity and selectivity of the oxidation process is altered by oxygen starvation in the liquid phase. Taking advantages of the very efficient transfer properties of a continuous gas-liquid segmented flow process (Taylor flow), we have demonstrated that the productivity could be strongly improved. The oxidation of 2-ethylhexanal (2-EH) to 2-ethylhexanoic acid, one of the acids with the highest production capacity worldwide,⁴ was complete in less than 15 min using 5 bar of oxygen at 20°C neither using transition metal catalyst nor radical initiator.⁵ However, the selectivity towards the acid under those conditions were not improved (selectivity below 80%). Thus, catalytic system optimization is clearly needed to improve the selectivity.

Results and discussion

The uncatalysed aerobic oxidation of aldehyde could be performed in batch mode with pressurized air³ or in continuous flow microreactor under 5 bar of oxygen.⁵ At high conversion, the selectivity towards carboxylic acid could not be easily explain by the aldehyde structure and reactivity³ (Figure 1).

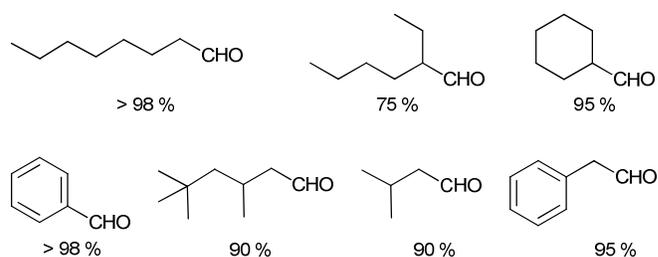


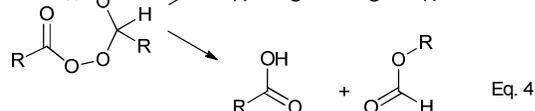
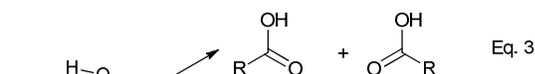
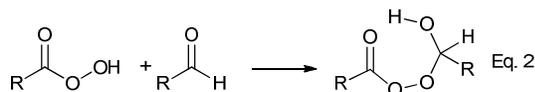
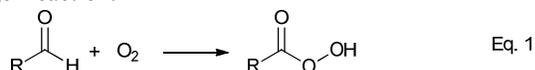
Figure 1. Selectivity towards carboxylic acid obtained for the uncatalysed aerobic oxidation of aldehydes in heptane (1.5 M, r.t.) in stainless steel autoclave with 40bar of air or in microreactor (PFA tubing, Taylor flow, O₂ 5 bar). Maximal standard deviations 5% see text.

Linear aldehydes have a very high selectivity (98% for octanal) and as expected, the influence of the α -substitution of the starting aldehyde is crucial for the selectivity (75 % for 2-ethylhexanal). However, the selectivity observed with cyclohexane-carboxaldehyde and benzaldehyde is high (95 and 98% respectively). β -substituted aldehyde gave intermediate selectivity close to 90%.

The factors affecting the selectivity of aerobic aldehydes oxidation appear to be rather poorly understood. The general

reaction scheme takes place in three consecutive and parallel stages as described below (Eqs 1 to 4).^{1,3}

Aldehydes are transformed into the corresponding peracids via a free radical chain-reaction (Eq. 1). Condensation of the peracid and an aldehyde produce a tetrahedral adduct (Eq. 2) similar to the Criegee intermediate observed in the Baeyer-Villiger reaction.



Rearrangement of the latter by migration of the hydrogen (Eq. 3) or alkyl(aryl) group from the aldehyde (Eq. 4) lead to two carboxylic acid (Eq. 3) or one carboxylic acid and one formate (Eq. 4). Formate is eventually hydrolysed into formic acid (non-quantified) and alcohol that can be further oxidized by oxygen radicals into ketone. By-products formed by homolytic cleavage of the radicals intermediate or by termination reactions can be neglected under our reaction conditions (*i.e.* excess of O₂ and low reaction temperature).

Despite numerous investigation of the mechanism of the Baeyer-Villiger reaction, the factors that control the migratory aptitude of the two carbon group are still not completely understood.⁶ The situation should be much simpler in the case of aldehyde where the migratory aptitude of hydrogen is expected to be higher than the carbon group.

Surprisingly, very little work report studies dealing with the selectivity of such oxidation despite the industrial importance of such process. Lehtinen *et al.* have studied the influence of solvents, salts, metal catalysts and oxidant and they also performed computational studies.⁷ Nevertheless, only slight improvement of the selectivity for 2-ethylhexanal oxidation (75 to 84%) was obtained using Mn(II)acetate and octanoic acid as solvent.¹² The improvement of the selectivity was attributed by the ability of the metal catalyst to decompose the peracid into the corresponding acid before formation of the Criegee intermediate (Eq. 2).

Microreactors and continuous flow technology in general represents an important opportunity towards greening chemical production.⁸ One of the main advantages of continuous flow processing is the enhanced heat- and mass transfer characteristics in particular for biphasic reactions. Gas-liquid reactions have been dramatically improved using microreactor technology owing to an enhanced mass transfer of gaseous reactants into the liquid phase and among them oxidations.^{5,9} This prompt us to upgrade our continuous segmented flow

reactor already used for aldehyde aerobic oxidation⁵ for high-throughput experimentation. High-throughput screening of catalysts/ligands in gas-liquid asymmetric hydrogenation have previously been evaluated in microdevice in our laboratory.¹⁰ Unlike hydrogenation where the price and the availability of ligand and/or metal catalyst as well as the number of chiral inductor available are the key-points, in the case of oxidation, the safety of the process is essential since fuel, oxidant and energy are present at the same time in the reactor. However, it is now demonstrated that performing gas-liquid oxidation reactions in micro-reactors in the presence of catalyst at high O₂ and organics partial pressures is safe due to the small dimensions of the channels, the enhanced heat transfer and a small reactor inventory of hazardous chemicals.⁸

A sample loop was added in the experimental setup (Figure 2) which allows us to screen the effect of different catalysts and/or additives on the selectivity towards carboxylic acid. It should be notice that our device does not allow us to evaluate solvent effect since hydrodynamic properties (wetting, viscosity, ...) are too different to get a regular segmented flow (Taylor flow) with different composition of the liquid slugs. However, solvent effect has already been evaluated and no improvement of the selectivity was noticed.⁷

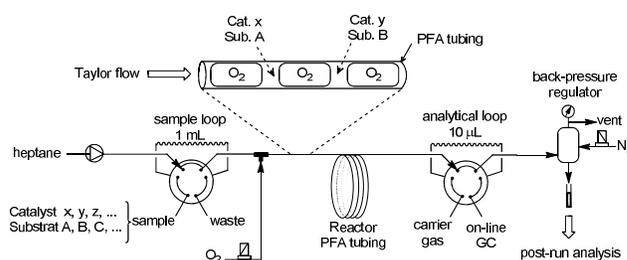


Figure 2. Experimental setup for the sequential pulse evaluation of catalyst and/or additives for aldehyde oxidation

For the first set of experiments the residence time was adjusted to get 80% of conversion of 2-ethylhexanal (*i.e.* 6 min.) for a 1.5 M solution in heptane at 20°C under 5 bar of oxygen and without any catalyst or additive. Under those conditions the selectivity towards carboxylic acid was 75% (Figure 3), while the experimental error based on the standard deviation relative to the mean of multiple experiments were 3% and 5% for conversion and selectivity respectively. Such relatively high measurement uncertainty is not a consequence of the sequential pulse experiments because lower standard deviation could be obtained with others catalytic system but is probably due to the free radical-chain mechanism involved in this oxidation process. Despite this, transition metal exhibit differentiated activities and selectivities for 2-ethylhexanal oxidation. As expected from literature data,^{1,7,11} 100 ppm of first-row transition metal (*e.g.* V to Cu) and Pd enhance the conversion while the selectivity was not modified. This could be explained by an enhanced formation of Criegee intermediate rate (Eqs 1 and 2), whereas metals have little effect on the rearrangement

of the latter. Near quantitative conversion were obtained with Mn(II), Mn(III), Cr(III) and Pd(II). Surprisingly an enhancement of the selectivity up to 90% could be observed using Cu(II). Mixtures of metals were also evaluated, but all the results were disappointing except for a mixture of Cu(II) and Mn(III) (1/1 mixture, 100 ppm of metals yielding to a conversion above 95% with a selectivity of 90%). The result

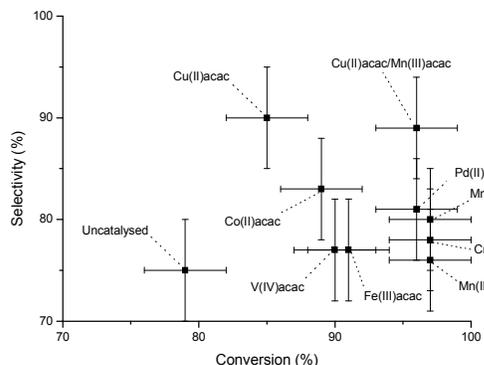


Figure 3. Influence of catalyst on conversion and selectivity for the aerobic oxidation of 2-ethylhexanal. (2-EH 1.5 M in heptane, Taylor flow, PFA tubing 5m, r.t., O₂ 5bar, catalyst 100 ppm, residence time 6 min.)

After optimising the catalyst, the salt effect was studied. Indeed while Lehtinen *et al.* have shown that the selectivity was slightly decrease in the presence of salts,⁷ but patents¹² claims that the presence of alkali metals salts (2% wt), increase the selectivity towards 2-ethylhexanoic acid up to 95% in industrial advanced reactor that enables efficient mixing and chemical rates up to 300 mmol/L/min. So the effect of the concentration of sodium 2-ethylhexanoate as additive was re-evaluated in our microreactor (Figure 4).

In order to study the selectivity for nearly quantitative conversions, the residence time was increase to 15 min. (Figure 4). The conversion of 2-ethylhexanal under those conditions was higher than 95% and the selectivity towards carboxylic acid was around 75% as expected. A decrease of the conversion could be noticed (Figure 4) with the increase of the concentration of sodium 2-ethylhexanoate salt.

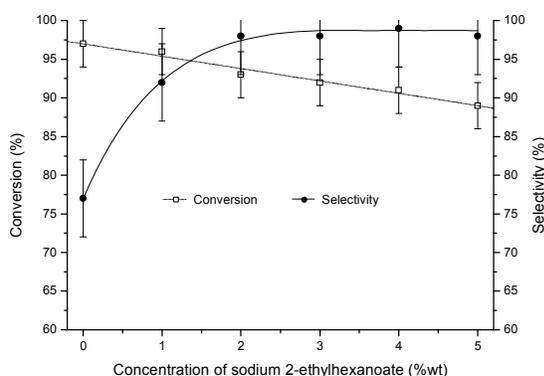


Figure 4. Influence of sodium 2-ethylhexanoate on conversion and selectivity on uncatalysed aerobic oxidation of 2-ethylhexanal. (2-EH 1.5 M in heptane, Taylor flow, PFA tubing 5m, r.t., O₂ 5bar, residence time 13 min.). The lines in the figure are only a guide to the eye.

However, we were pleased to see in parallel an enhancement of the selectivity. Indeed for concentration of sodium 2-ethylhexanoate above 2%wt, selectivities higher than 98% were obtained. Increasing further the concentration of salt was of none interest as the selectivity remained high (> 98%) but lower conversions were obtained.

Then, the synergetic effect of sodium 2-ethylhexanoate as additive and Mn(II) as catalyst was evaluated as reported in Figure 5. The residence time was then decreased to 6 min., and we were pleased to see that the selectivity was not affected at all by the presence of 100 ppm of Mn(II) while the higher activity was maintained.

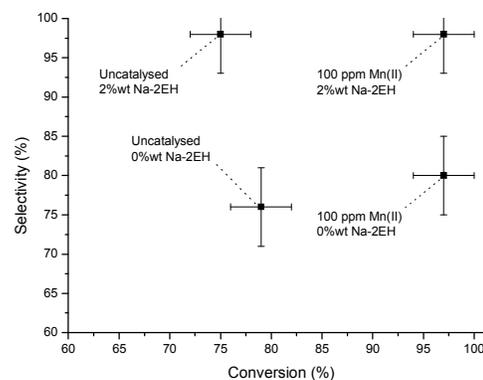


Figure 5. Synergetic effect on aerobic 2-ethylhexanal oxidation (2-EH 1.5 M in heptane, Taylor flow, PFA tubing 5m, r.t., O₂ 5bar, catalyst 100 ppm, residence time 6 min., Na-2EH : sodium 2-ethylhexanoate)

Different salts were then evaluated as additive but the results were not unambiguous. Using sodium trifluoroacetate (pKa - 0.3) or sodium acetate (pKa 4.7), high selectivity towards carboxylic acid were obtained (a concentration of 4 %wt was needed for the latter) clearly showing that deprotonation of the intermediates was not involved. Surprisingly 98% selectivity was also obtained with 1-butyl-3-methylimidazolium acetate clearly showing that alkaline or alkaline earth salts are not necessary to enhance the selectivity.¹³ On the opposite, the use of ammonium acetate or tetrabutylammonium bromide had limited effect on selectivity.

The results present here clearly shows the potential of gas-liquid microreactors for the safe screening of homogeneous oxidation catalysts. Though some important advances have been made here, there is more to do to understand how the salt affects the reaction mechanism and inhibits the formation of by-products. This synergistic use of salt and catalyst need to be further studied and the scope and limitation of this synergistic system is in due course.

Experimental

Analytical grade heptane (Aldrich) was used. Aldehydes (Aldrich and Acros) were used as obtained from the supplier and stored at 4°C under N₂ with protection from light. Pressurized oxygen (99.995 %) was provided by Messer.

Oxidation of aldehyde in autoclave³

The reactions were performed in a 135 mL thermo-regulated stainless steel autoclave (120 mL useful capacity) operating in batch mode. Four baffles were mounted to the reactor walls. The reaction medium was stirred by a Rushton turbine or a self-suction turbine. A total volume of 40 mL of the desired mixture of aldehyde (1.5 M in heptane) were placed in the reactor. The temperature was set to 25 °C and the reactor was then pressurized with reconstituted air (O₂ 21%wt and N₂ 79%wt). The time-course of the gas pressure decrease was measured with a pressure transducer and recorded on-line using Labview. The reaction mixture was analysed at the end of each experiment using a Shimadzu 2010 GC-MS system equipped with a DB-5 column.

Oxidation of aldehyde in microreactor⁵

A PFA tubing (Upchurch Scientific) (internal diameter of 1000 µm, length 5 m) was used as reactor. Sample were injected via HPLC sample injector (Rheodyne) using an external PEEK loops of 1 mL. The organic phase (Harvard pumps PHD 4400) and the oxygen (Analyt-MTC massflow controller) were fed via two separate lines and brought together using a T-mixer (Interchim). A back pressure of 5 bar was applied using a home made back pressure regulator controlled with nitrogen flow (Analyt-MTC massflow controller) and micro-metering valve. The outlet port of the microreactor was connected to a 6-way gas sampling injection valve (Agilent) for on line analysis by Agilent 6890 GC equipped with FID detector and Red dot FFAP column (5 m x 0.05 mm x 0.05 µm). Liquid products were retrieved from back-pressure regulator and could be further analysed by a Shimadzu 2010 GC-MS system equipped with a DB-5 column (15 m x 0.1 mm x 0.1 µm.).

The general experimental procedure is as follows. Heptane was loaded in 50 mL syringes. Heptane (Harvard pump) and oxygen (Analyt-MTC massflow controller) were delivered into the microreactor via a T-mixer. A portion of a freshly prepared solution of aldehyde (1.5 M in heptane), catalyst (0 to 100 ppm) and salt (0 to 5 wt%) is introduced into the sampling loop and injected into the microreactor. The residence time control was achieved by varying the flow rate of the organic phase and/or oxygen. Conversion and selectivity toward the carboxylic acid were determined on the basis of the normalized peak areas for aldehyde, carboxylic acid and side products obtained by on-line GC. By-products were identified and quantified using post-run analysis of the liquid phase by GC-MS.

Conclusions

In conclusion, we were able to demonstrate that aldehyde could be safely and selectively transformed into the corresponding carboxylic acid using molecular oxygen in flow. The reaction conditions were optimized and full conversion with almost full selectivity toward carboxylic acid was obtained under mild conditions through the use of synergistic effect of salt and Mn(II). The usual by-products obtained via the rearrangement of the Criegee intermediate (*i.e.* formate) could be nearly completely eliminated. Finally it was also demonstrated that

microflow reactors are interesting tools for high-throughput screening of experimental conditions in gas-liquid reactions.

Notes and references

^a LGPC, UMR CNRS 5285, CPE Lyon, 43 bld du 11 nov 1918, 69100 Villeurbanne, France; E-mail: afr@lgpc.cpe.fr

^b CASER, SITI, CNAM, 2 rue Contié, 75003 Paris, France.

- For select reviews, see: (a) J. R. McNesby and C. A. Heller, *Chem. Rev.*, 1954, **54**, 325. (b) L. Sajus and I. Séré De Roch, in *Liquid-Phase Oxidation*, eds. C. H. Boamford and C. F. H. Tipper, Elsevier, Amsterdam, 1980, vol. 16, pp. 89. (c) E. T. Denisov and I. B. Afanas'ev, *Oxidation and antioxidants in organic chemistry and biology*, Taylor & Francis, Boca Raton, 2005.
- W. Riemenschneider, in *Ullmann's Encyclopedia of Industrial Chemistry*, 6th Ed., Wiley-VCH, 2003, vol. 6, p. 493.
- L. Vanoye, A. Favre-Réguillon, A. Aloui, R. Philippe and C. de Bellefon, *RSC Advances*, 2013, **3**, 18931.
- (a) C. Kohlpaintner, M. Schulte, J. Falbe, P. Lappe and J. Weber, in *Ullmann's Encyclopedia of Industrial Chemistry*, 6th Ed., Wiley-VCH, 2003, vol. 2, p. 65. (b) T. Seki, J.-D. Grunwaldt and A. Baiker, *Chem. Commun.*, 2007, 3562.
- L. Vanoye, A. Aloui, M. Pablos, R. Philippe, A. Percheron, A. Favre-Réguillon and C. De Bellefon, *Org. Lett.*, 2013, **15**, 5978.
- (a) J. R. Alvarez-Idaboy and L. Reyes, *J. Org. Chem.*, 2007, **72**, 6580. (b) R. D. Bach, *J. Org. Chem.*, 2012, **77**, 6801.
- (a) C. Lehtinen and G. Brunow, *Org. Process Res. Dev.*, 2000, **4**, 544. (b) C. Lehtinen, V. Nevalainen and G. Brunow, *Tetrahedron*, 2000, **56**, 9375. (c) C. Lehtinen, V. Nevalainen and G. Brunow, *Tetrahedron*, 2001, **57**, 4741.
- (a) R. L. Hartman, J. P. McMullen and K. F. Jensen, *Angew. Chem. Int. Ed.*, 2011, **50**, 7502. (b) V. Hessel, D. Kralisch, N. Kockmann, T. Noël and Q. Wang, *ChemSusChem*, 2013, **6**, 746.
- For recent papers on gas-liquid reactions in microreactors, see: (a) T. Fukuyama, T. Totoki, I. Ryu, *Green Chem.*, 2014, **16**, 2042. (b) J. Wu, J. A. Kozak, F. Simeon, T. A. Hatton, T. F. Jamison, *Chem. Sci.*, 2014, **5**, 1227. (c) A. Nagaki, Y. Takahashi, J.-I. Yoshida, *Chem. Eur. J.*, 2014, **20**, 7931. For select examples on oxidation in microreactors, see: (d) A. Leclerc, M. Alame, D. Schweich, P. Pouteau, C. Delattre and C. de Bellefon, *Lab Chip*, 2008, **8**, 814. (e) C. Aellig, D. Scholz and I. Hermans, *ChemSusChem*, 2012, **5**, 1732. (f) M. Hamano, K. D. Nagy and K. F. Jensen, *Chem. Commun.*, 2012, **48**, 2086. (g) T. P. Petersen, A. Polyzos, M. O'Brien, T. Ulven, I. R. Baxendale and S. V. Ley, *ChemSusChem*, 2012, **5**, 274. (h) B. Pieber and C. O. Kappe, *Green Chem.*, 2013, **15**, 320. (i) S. L. Bourne and S. V. Ley, *Adv. Synth. Catal.*, 2013, **355**, 1905. (j) X. Ye, M. D. Johnson, T. Diao, M. H. Yates and S. S. Stahl, *Green Chem.*, 2010, **12**, 1180-1186. (k) Z. He and T. F. Jamison, *Angew. Chem. Int. Ed.*, 2014, **53**, 3353. (l) U. Neuenschwander and K. F. Jensen, *Ind. Eng. Chem. Res.*, 2014, **53**, 601.
- C. de Bellefon, N. Tanchoux, S. Caravieilhès, P. Grenouillet and V. Hessel, *Angew. Chem. Int. Ed.*, 2000, **39**, 3442.
- (a) W. Partenheimer, *Adv. Synth. Catal.*, 2005, **347**, 580. (b) C. F. Hendriks, H. C. A. van Beek and P. M. Heertjes, *Ind. Eng. Chem. Prod. Res. Dev.*, 1978, **17**, 260. (c) D. R. Larkin, *J. Org. Chem.*, 1990, **55**, 1563.

12. (a) *K. Fisher and G. Fritz, US Patent N°5,504,229, (BASF), 1996.*
(b) *H. F. Koch and R. P. Reed, Patent WO 01/46111, (Celanese International Corporation), 2001.*
13. *A. Favre-Réguillon, L. Vanoye and C. De Bellefon, France priority patent application FR1455588, (CNRS-CNAM), 2014.*

The selectivity of the aerobic oxidation of aldehydes can be strongly enhanced by means of a synergistic use of salts and catalyst.

