Continuous flow study of isoeugenol to vanillin: A bio-based iron oxide catalyst

Layla Filiciotto, María Dolores Márquez-Medina, Antonio Pineda, Alina M. Balu, Antonio A. Romero, Carlo Angelici, Ed de Jong, Jan C. van der Waal, Rafael Luque



PII:	S0920-5861(19)30615-7
DOI:	https://doi.org/10.1016/j.cattod.2019.11.008
Reference:	CATTOD 12553
To appear in:	Catalysis Today
Received Date:	21 September 2019
Revised Date:	23 October 2019
Accepted Date:	8 November 2019

Please cite this article as: Filiciotto L, Márquez-Medina MD, Pineda A, Balu AM, Romero AA, Angelici C, de Jong E, van der Waal JC, Luque R, Continuous flow study of isoeugenol to vanillin: A bio-based iron oxide catalyst, *Catalysis Today* (2019), doi: https://doi.org/10.1016/j.cattod.2019.11.008

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier.

Continuous flow study of isoeugenol to vanillin: A bio-based iron oxide catalyst

Layla Filiciotto^{a,*}, María Dolores Márquez-Medina^a, Antonio Pineda^a, Alina M. Balu^a, Antonio A. Romero^a, Carlo Angelici^b, Ed de Jong^b, Jan C. van der Waal^{b,c}, Rafael Luque^{a,d*}

^aDepartamento de Quimica Organica, Universidad de Cordoba, Campus de Rabanales, Edificio Marie Curie (C-3), Ctra Nnal IV-A, Km 396, Cordoba, Spain.

^bAvantium Chemicals, Zekeringstraat 29, 1014 BV, Amsterdam, The Netherlands.

^cTNO Netherlands Organization of Applied Scientific Research, Leeghwaterstraat 44, 2628 CA, Delft, The Netherlands.

^dPeoples Friendship University of Russia (RUDN University), 6 Miklukho Maklaya str., 117198, Moscow, Russia

*: z62fifil@uco.es, q62alsor@uco.es

Graphical abstract



Abstract

The use of a biorefinery co-product, such as humins, in combination with an iron precursor in a solventfree method yields a catalytic material with potential use in selective oxidative cleavage reactions. In particular, this catalyst was found active in the hydrogen-peroxide assisted oxidation of a naturally extracted molecule, isoeugenol, to high added-value flavouring agent, vanillin. By carrying out the reaction in continuous flow, not only a better understanding of the reaction mechanism and of the catalyst deactivation can be achieved, but also important insights for optimised conditions can be developed. The findings of this paper could pave the way to a more sustainable process for the production of a valuable food and perfume additive, vanillin.

Keywords: Vanillin Production, Continuous flow catalysis

1. Introduction

Vanillin is one of the largest aroma chemicals, possibly the largest, with a current global consumption of over 18.000 ton/year (including vanilla pods/extract) [1], finding widespread application in food, beverages, pharmaceutical, and perfume industries [2]. Also, vanillin has been attracting more attention as a key intermediate in the production of a wide variety of bio-based polymers (from thermosets to thermoplastics) which can satisfy an incredible number of industries, including electronic or aeronautic. For more information on the different polymers, the readers are kindly referred to the skilful review by Caillol et al. [3]. With only ca. 1% of vanillin extracted from vanilla beans (agricultural production capacity of only 2000 ton/year), synthetic vanillin represents a major portion of the market [4, 5]. Presently, synthetic vanillin is obtained via the fossil-based route with a production capacity of ca. 17.000 ton/year [6, 7]. Nonetheless, current sustainability trends call for the dismissal of petroleum feedstocks and implementation of renewable chemical routes that are not competing with food resources. Lignin from the pulping industry, glucose, naturally-extracted ferulic acid and eugenol/isoeugenol are the substrates of choice for the sustainable production of such popular flavouring agent [6-10]. A more sustainable route is given by the conversion of sulphite liquors from the pulping industry with production capacities of ca. 1500 ton/year, as given by the Norwegian company Borregaard. However, this process relies on homogeneous catalysis and strong alkaline media [11, 12]. Biotechnological pathways of sustainable precursors may enable production via simple fermentation technologies or bacteria metabolic pathways; nevertheless, strain engineering is required due to substrate/product toxicity towards the microorganisms, raising the usual concerns of genetically modified organisms [10]. Biotransformations generally require higher plant capital investment and maintenance due to required sterilisation standards and difficulties in broths purification given by the aqueous media [13, 14]. Chemical conversions of potentially lignin-derived molecules such as isoeugenol can offer a cheap route to fulfil the required volumes of the synthetic vanillin market, with the particular advantage of using organic solvents (e.g. acetonitrile) as opposed to aqueous, thus low-energy intensive separation processes.

In fact, in our previous publication [15], we demonstrated the potential use of abundant iron oxides (in particular, hematite Fe_2O_3) in combination with a biorefinery co-product, humins [16] as active and selective catalyst in oxidative cleavage of isoeugenol assisted by the green oxidant, hydrogen peroxide. Humins, in particular, were found to enhance the catalytic activity of bare iron oxides (in the work, commercial nano Fe_2O_3 and Fe_3O_4 were tested) plausibly due to the oxygen-rich carbon functionalities of these furanic oligomers, showing the application potential of humins as catalyst support, peculiarly prepared *via* solvent-free methodologies (*i.e.* ball milling, thermal degradation). Similarly, different research groups have studied the conversion of isoeugenol with either homogeneous or heterogeneous

(photo)catalysts in combination with various oxidants (oxygen, hydrogen peroxide) [17-29]. However, to the best of our knowledge, isoeugenol conversion has yet to be studied in continuous flow to clarify temperature, pressure, concentration, and residence time effects, but also to have deeper insights into the mechanism. By using the catalyst that was found most active and stable in our previous publication, *i.e.* the one comprised of humins foams [30, 31] and iron(II) chloride, we herein propose the continuous flow conversion of isoeugenol in the presence of hydrogen peroxide. In parallel, another iron oxide-based catalyst prepared in our research group [17] was tested to ascertain differences between using humins foams or Al-SBA-15 as catalyst support.

2. Material and Methods

Humins foams [30, 31] were provided by Avantium Chemicals (The Netherlands); ferrous chloride tetrahydrate (99%), hydrogen peroxide (50 wt%) and isoeugenol (98%) were purchased from Sigma-Aldrich; acetonitrile (99.9%) was bought from Panreac Chemicals.

The humins-containing Fe₂O₃ catalyst was prepared *via* mechanochemical activation as described in our previous publication [15]. In brief, the iron precursor (FeCl₂·4H₂O) and the humins foams (weight ratio 1:2) were grinded in a planetary ball mill (Retsch, model PM 100) at 350 rpm for 45 minutes. The powder mixture was then dried for 12 h at 100 °C and calcined at 400 °C with a $\beta = 5$ °C min⁻¹. The Al-SBA-15 supported iron oxide was prepared as previously described [17]. The catalysts was synthesised using a mechanochemical process where Al-SBA-15 (1 g) was employed as support and iron (III) nitrate (30 wt%) as source of iron. Coffee waste (1 g) was used to activate the magnetic phase. After the milling process, the catalyst was calcined at 300 °C. XRD analyses were recorded on a Bruker D8 Discover diffractometer equipped with CuK_a radiation ($\lambda = 0.15406$ nm).

The reactions were carried out in a ThalesNano[®] Phoenix Flow ReactorTM (maximum operating temperature of 250 °C) equipped with 30 mm CatCarts[®] and a pressure moduleTM capable of generating system pressure up to 100 bar with the use of a back pressure regulator. Solutions with various concentrations of isoeugenol in acetonitrile were prepared and hydrogen peroxide added with a 1:2 molar ratio. The solutions are prepared only prior to the reaction, kept covered with aluminium foil to avoid light-induced conversion, and kept away from sources of heat. For the blank reaction, an inert titania (TiO₂) CatCart[®] provided by ThalesNano[®] was employed. For the catalytic testing, empty CatCarts[®] were packed under vacuum with the humins-based nanocomposite (0.25±0.02 g). Density of the humin-containing Fe₂O₃ catalyst was measured with a graduated cylinder, and recorded as 0.66 g mL⁻¹. Based on this value and the catalyst quantity used, contact time at a flow of 0.3 mL min⁻¹ is about 22

seconds. Same procedure was employed for the Fe-Al-SBA-15 catalyst [17] used for ascribing the support effect.

GC analyses were run on an Agilent 7890A fitted with a Supelco column heated at 200 °C with holding time of 70 minutes. Identification of vanillin, isoeugenol, and eugenol was confirmed by the use of standards. GC-MS analyses were carried out on an Agilent 5977B MSD equipped with an HP-5 column. The oven was set at 80 °C with a 3 °C min⁻¹ ramp to 200 °C, a 10 °C min⁻¹ ramp to 250 °C, and a 30 °C min⁻¹ ramp to 280 °C (50 min). Mass spectra of the by-products identified with corresponding reverse match factors (> 750) are given in Figures A1-4 (Appendix A).

3. Results and Discussion

The mechanochemically synthesised catalyst was tested under continuous flow conditions, as opposed to our original microwave-assisted reaction [15]. XRD analysis was employed to confirm the crystalline phase of the obtained catalyst (Figure A5, Appendix A). In our previous study, XPS analysis recorded a 46 wt% of superficial iron. Under microwave irradiation, the catalyst gave a 57% yield of vanillin at a temperature of 169 °C. However, due to the plausible exothermicity of the reaction and possible runaway decomposition of hydrogen peroxide at temperatures over 150 °C, the temperature of 120 °C was not exceeded for safety precautions. As such, lower vanillin yields can be expected and only the general catalytic trends will be taken into consideration. The isoeugenol to hydrogen peroxide ratio was fixed in our experiments (molar, 1:2), while changing flow rate, temperature, pressure, and concentration. Compared to the batch experiments, the isoeugenol to hydrogen peroxide ratio was increased (original, 1:5) [15] in order to save resources and plausibly have lower conversions, thus ascribing the reaction mechanism. These changes in conditions will allow a better understanding of the reaction mechanism by the possible detection of reaction intermediates.

GC analyses of the product mixtures showed the presence of four major products, only being *i*) vanillin, *iii*) vanillin methyl ketone (1), *iii*) eugenol (2), and *iv*) dehydrodiisoeugenol (3) (Scheme 1). Mass balances (based on molar concentrations) of > 98% were achieved. In particular, vanillin is the oxidative cleavage product; 1 results from the anti-Markovnikov oxidation of the alkene functionality; 2 is the product of isoeugenol isomerisation; and 3 is believed to be a radical condensation [23, 32, 33]. Traces of other products were detected via GC-MS analysis and will be discussed later. It should also be noted that gaseous products were observed in the reactor line but were not collected given the reactor's setup.



Scheme 1. Reaction products of the hydrogen peroxide-assisted oxidation of isoeugenol catalysed by humins-containing Fe₂O₃.

3.1. Initial activity and trend

An initial blank experiment (in the presence of a titanium-based inert provided by ThalesNano) was carried out at the chosen temperature of 100 °C, 15 bar of system pressure and 20 vol% of isoeugenol in the presence of hydrogen peroxide. Conversion and selectivities of the GC-detectable products are given in Figure 1. Low conversion (up to *ca.* 16%) and vanillin selectivity (up to *ca.* 10%) were observed in the absence of a catalyst, similarly to our previous study. A surprisingly high selectivity to vanillin methyl ketone was observed (> 80%) since the beginning of the reaction, signalling the importance of said molecule in the reaction mechanism. Isomerisation ($\mathbf{2}$, eugenol) and condensation ($\mathbf{3}$, dehydrodiisoeugenol) products were also observed in small percentages.



Figure 1. Column graph of isoeugenol conversion and selectivities to the major products over an inert CatCart® (ThalesNano). Reaction conditions: 100 °C, 15 bar, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H₂O₂ (50 wt%) in acetonitrile, up to 100 min time on stream.

With the same reaction conditions, the iron-based catalyst was tested and found active in the conversion of isoeugenol, improving vanillin yields by ca. 600% (Figure 2). Although steady-state conditions were not reached within 3 h of time on stream, a striking specular trend for vanillin (orange line, squares) and vanillin methyl ketone (pink line, triangles) is observed during the course of the reaction, showing a close relationship between the two molecules. Compared to the blank reaction, a *ca.* 100% increase of the formation of the isomerisation product (2, eugenol) and a *ca.* 200% increase of the formation of the condensation product (3, dehydrodiisoeugenol) was observed (based on molar concentrations), suggesting isomerisation activity as well as radical condensation.



Figure 2. Isoeugenol conversion (blue line, diamonds) and selectivities to *i*) vanillin (orange line, squares), *ii*) vanillin methyl ketone (pink line, triangles), *iii*) dehydrodiisoeugenol (purple line, crosses), and *iv*) eugenol (green line, circles) over a humins-containing Fe₂O₃ catalyst. *Reaction conditions*: 100 °C, 15 bar, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H₂O₂ (50 wt%) in acetonitrile, up to 180 min time on stream.

3.2. Contact time effect

In order to ascertain mass transfer limitations, the contact time of the feed was reduced by increasing the flow rate from 0.3 to 1 mL min⁻¹ (contact time between 85 and 22 seconds, respectively, based on catalyst density and loading). However, when the reaction was carried out at 1 mL min⁻¹, the system pressure dropped within 30 minutes of time on stream, while at 0.5 mL min⁻¹ within 50 minutes. This drop in pressure was caused by the failure of the catalytic bed seals and consequent blockage of the reactor, which could arise from the use of a viscous solution (as it is our case due to isoeugenol) and high flow rates. Nevertheless, no differences bigger than 10% in conversions and selectivities were observed at the three different flow rates, indicating little to no mass transfer limitation for the humins-containing Fe₂O₃. Indeed, from our previous textural properties studies [15], we observed from BET analysis a low surface area (*ca.* 8 m² g⁻¹) and pore volume (0.1 cm³ g⁻¹) which usually hints to low mass transfer limitations.



Figure 3. Stacked column graph of the effect of flow rate on the isoeugenol to vanillin conversion over a humin-containing Fe₂O₃ catalyst. *Reaction conditions*: 100 °C, 15 bar, 17 vol% isoeugenol and 13 vol% H₂O₂ (50 wt%) in acetonitrile, variable contact time (22, 45, and 85 seconds).

3.3. Temperature effect

The temperature effect was also studied in a range between room temperature and 120 °C (Figure 4) with a lower concentration of isoeugenol (9 vol%). A positive effect of increasing temperature can be observed up to 100 °C, both in terms of conversion and vanillin selectivity. Between 100 and 120 °C, instead, little change in conversion is observed while vanillin selectivity decreases (both reactions have nearly complete mass balances >99%). This slight decrease in selectivity could be given by either formation of condensation products that might foul the catalyst or increased desorption of key intermediates on the catalyst surface. Nonetheless, molar concentrations of the condensation product (**3**, dehydrodiisoeugenol) are similar at both temperatures, while vanillin methyl ketone (**1**) is favoured at higher temperatures becoming the predominant product. This difference in concentrations may again hint to a close relationship between the ketone and vanillin, suggesting that the ketone may be the kinetic product.



Figure 4. Stacked column graph of isoeugenol conversion and vanillin selectivity at various temperatures (25, 80, 100, and 120 °C). *Reaction conditions*: 15 bar, 0.3 mL min⁻¹, 9 vol% isoeugenol and 7 vol% H₂O₂ (50 wt%) in acetonitrile, up to 100 min time on stream, variable temperature.

3.4. Pressure effect

The pressure effect on the reaction was then studied in a 5-30 bar range. A positive effect on isoeugenol conversion and vanillin selectivity can be clearly evidenced up to 15 bar of pressure, with a decrease at 30 bar (Figure 5). Increasing the pressure from 5 to 15 bar, in fact, improves collision between plausible OH-species and isoeugenol, thus improving conversion. At 30 bar, where conversions are comparable, selectivity to vanillin is lower. It should be noted that already at an applied pressure of < 2 bar, the system is in the liquid phase (based on the Clausius-Clapeyron equation) [34], so that pressure has a limited effect compared to reactions in the gas phase. Nevertheless, application of 30 bar of system pressure shows a decrease in conversion and selectivity after 100 min of time on stream, signalling a deactivation process. By analysing the selectivities to the other major products (Figure 6), a relatively higher selectivity to the condensation product (**3**, dehydrodiisoeugenol) is observed at higher pressures after 60 minutes of reaction time while eugenol selectivities are independent on pressure, again hinting to a simple thermal effect. In fact, dehydrodiisoeugenol is believed to be a radical condensation between two molecules of isoeugenol, thus higher pressures will increase molecular collisions and plausibly the selectivity to **3**.

The reaction profiles of isoeugenol conversion at 30 bar (Figure 7) shows again a specular trend of vanillin and vanillin methyl ketone, but also catalyst deactivation. In fact, after an initial improvement in isoeugenol conversion and vanillin selectivity (up to 60 minutes of time on stream), conversion decreases and selectivity to vanillin methyl ketone increases again. XRD analysis of the catalyst after the reaction



(Figure A6, Appendix A), shows the disappearance of the (021) plane ($2\theta = 23.85$) and the formation of a broad shoulder typical of deposition of carbon species, hence catalyst fouling.

Figure 5. Stacked column graph of isoeugenol conversion and vanillin selectivity at various pressures (5, 15, 30, and 50 bar). *Reaction conditions*: 100 °C, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H_2O_2 (50 wt%) in acetonitrile, up to 180 min time on stream, variable pressure.



Figure 6. Stacked column graph of by-products selectivities at various pressures (5, 15, 30, and 50 bar). *Reaction conditions*: 100 °C, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H_2O_2 (50 wt%) in acetonitrile, up to 180 min time on stream, variable pressure.



Figure 7. Isoeugenol conversion (blue line, diamonds) and selectivities to *i*) vanillin (orange line, squares), *ii*) vanillin methyl ketone (pink line, triangles), *iii*) dehydrodiisoeugenol (purple line, crosses), and *iv*) eugenol (green line, circles) over a humins-containing Fe₂O₃ catalyst. *Reaction conditions*: 100 °C, 30 bar, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H₂O₂ (50 wt%) in acetonitrile, up to 180 min time on stream.

3.5. Isoeugenol concentration effect

The concentration effect of isoeugenol was also studied (maintaining the isoeugenol:hydrogen peroxide ratio constant) from a 10 vol% (C) to a 30 vol% (3 C) of isoeugenol in acetonitrile (Figure 8). Although conversions are not really affected by varying isoeugenol concentration, vanillin selectivity is boosted at higher concentrations. In particular, by observing the reaction trend over time and focussing on the vanillin and vanillin methyl ketone selectivities between 40-60 minutes of time on stream the two selectivities reverse (Figure 9). This inverse trend could again hint that vanillin is the thermodynamic product, hence favoured at higher concentrations and longer reaction times. Nevertheless, the relatively high viscosity of the pump solution caused the reactor seals failure between 130-140 minutes of time on stream.



Figure 8. Stacked column graph of isoeugenol conversion and vanillin selectivity at isoeugenol concentrations (C = 10 vol%). *Reaction conditions*: 100 °C, 0.3 mL min⁻¹, 1:2 isoeugenol to H₂O₂ (50 wt%) ratio in acetonitrile, up to 100 min time on stream, variable isoeugenol concentration (10 vol%, 20 vol% and 30 vol%).



Figure 9. Isoeugenol conversion (blue line, diamonds) and selectivities to *i*) vanillin (orange line, squares) and *ii*) vanillin methyl ketone (pink line, triangles) over a humins-containing Fe₂O₃ catalyst. *Reaction conditions*: 100 °C, 15 bar, 0.3 mL min⁻¹, 24 vol% isoeugenol and 18 vol% H₂O₂ (50 wt%) in acetonitrile, up to 120 min time on stream.

3.6. Comparison with an Iron Oxide @Al-SBA-15 catalyst

In our research group, a catalyst with 30% of iron over an Al-SBA-15 support (*see* 30%FeMagN300) was prepared and found active at room temperature in the conversion of isoeugenol [17]. In particular,

relatively high surface areas (*ca.* 300 m² g⁻¹) and a synergistic effect of the Fe-Al bond were accounted for the high activity. Parallel to the humins-containing catalyst presented in this study [15], both catalysts show Fe(III) superficial species in the form of oxide. Thus, we tested this catalyst in continuous flow at both 100 °C (Figure 10) and 30 °C (Figure 11) to ascertain the reactivity of Fe(III) species and the influence of the support for iron oxide catalysts. In both cases, blockage of the continuous flow system was observed within 50 and 190 minutes for the reaction carried out at 100 °C and 30 °C, respectively, with mass balances of *ca.* 96%. By employing this mesoporous aluminosilicate catalyst at 100 °C, a striking specularity of the vanillin methyl ketone and dehydrodiisoeugenol is observed as opposed to vanillin (*see 3.1*), signalling condensation as the main thermodynamic product at this temperature for this room temperature catalyst.



Figure 10. Isoeugenol conversion (blue line, diamonds) and selectivities to *i*) vanillin (orange line, squares), *ii*) vanillin methyl ketone (pink line, triangles), *iii*) dehydrodiisoeugenol (purple line, crosses), and *iv*) eugenol (green line, circles) over an Al-SBA-15-containing iron oxide catalyst. *Reaction conditions*: 100 °C, 15 bar, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H₂O₂ (50 wt%) in acetonitrile, up to 40 min time on stream.

When the temperature is decreased to 30 °C, improvement of isoeugenol conversion and vanillin selectivity is observed, signalling the exothermic character of the reaction and high activity of the catalyst. Lower vanillin yields (here up to 13%) than the ones reported in batch conditions (56%) were observed, but again a lower hydrogen peroxide concentration was employed. Nevertheless, the specularity



observed for the humins-containing nanocomposite between vanillin and vanillin methyl ketone is not observed by using an Al-SBA-15 based iron oxide, hinting at a support effect in the reaction mechanism.

Figure 11. Isoeugenol conversion (blue line, diamonds) and selectivities to *i*) vanillin (orange line, squares), *ii*) vanillin methyl ketone (pink line, triangles), *iii*) dehydrodiisoeugenol (purple line, crosses), and *iv*) eugenol (green line, circles) over an Al-SBA-15-containing iron oxide catalyst. *Reaction conditions*: 30 °C, 15 bar, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H₂O₂ (50 wt%) in acetonitrile, up to 180 min time on stream.

In fact, Fe-doped Al-SBA-15 was found as an effective catalyst for styrene/phenol hydroarylation given its combination of Lewis and Brønsted acidity [35] which may explain the condensation activity to dehydrodiisoeugenol of the aluminosilicate.

3.7. By-products and mechanism

Even if mass balances were high considering the products depicted in Scheme 1 (> 98%) for the humins-containing catalyst, GC-MS analyses of the reaction mixture showed three other molecules in traces. In particular, i) one identified as methyl (3-hydroxy-4-methoxyphenyl)acetate (**4**, Scheme 2), ii) one of atomic mass of 212 which is identified as methyl hydroxy(3-hydroxy-4-methoxyphenyl)acetate (**5**, Scheme 2) and iii) one of atomic mass unit (amu) of 198 which could be identified as 3-hydroxy-4-methoxyphenylacetic acid (**6**, Scheme 2) or 1-3-hydroxy-4-methoxyphenyl)-1,2-propanediol (**7**, Scheme 2). Vanillin alcohol and vanillic acid were not detected in our reaction mixtures, which may arise from overoxidation or Cannizzaro/Dakin-type of reactions [36, 37]. In fact, these reactions are

usually base catalysed (either hydroxyl or hydroperoxyl anions), whereas the catalysts employed herein have acidic properties.



Scheme 2. Trace products of the isoeugenol conversion detected by GC-MS. In order: 4, methyl (3-hydroxy-4-methoxyphenyl)acetate; 5, methyl hydroxy(3-hydroxy-4-methoxyphenyl)acetate; 6, 3-hydroxy-4-methoxyphenylacetic acid; and 7, 1,3-hydroxy-4-methoxyphenyl)-1,2-propanediol.

In our previous study in batch under microwave irradiation, we had attributed the molecule with mass 198 to the diol (7, Scheme 2) which was detectable by GC analysis (selectivities of *ca.* 3%). In fact, the diol had already been proposed as intermediate of an epoxide route under oxidation with hydrogen peroxide [28] or molecular oxygen [24] but in our conditions the epoxide was never detected. Detection of the ester product 4 (Scheme 2) instead suggests the occurring of a Baeyer-Villiger reaction of the vanillin methyl ketone (1, Scheme 1). Even if only few reports exist on the iron-catalysed Baeyer-Villiger oxidation [38], the reaction is usually carried out under molecular oxygen and at milder temperatures (50 °C), supporting the formation of the ester product 4 in our conditions. If this latter product is an intermediate of the vanillin synthesis, it could undergo a series of steps involving nonconcerted radical hydrogen abstraction, hydroxylation, ester hydrolysis, and cleavage to form vanillin and formic acid (Scheme 3). It should also be noted that the ester 5 could decompose directly to vanillin given the hydroxyl in the α position, thus lower stability. The contribution of the metal oxide has been neglected given the lack of in situ spectroscopic data, but coordination of the Fe³⁺ superficial species with oxygen functionalities should be expected. In particular, the disappearance of the (021) XRD peak (see 3, Figure A5, Appendix A) upon deactivation (Figure A6, Appendix A) at 30 bar may suggest carbonyl coordination through this face. Overall, this proposed route will allow the formation of formic acid which not only is a better leaving group as compared to the ethanol from product 7, but also its formation may further catalyse the formation of vanillin via Fenton-type reactions as well as the hydrolysis of the intermediate ester. In fact, all of the considered steps would be acid-catalysed, thus solid acid catalysts not only will induce the formation of radicals, but also improve overall vanillin synthesis over time on stream. The proposed radical intermediate (first step, Scheme 3) could also react with another radical molecule giving the diol

(7, Scheme 2) which can cleave to give vanillin and ethanol. However, the oxidative cleavage of the diol by radical mechanism would prefer forming carboxylic acids [39], thus vanillin formation *via* this mechanism would rather be sustained by a non-radical mechanism involving superficial oxygen species. In fact, first row transition metals generally catalyse the oxometal pathway were hydrogen peroxide increases the oxidation state of the metal which then coordinates to the reactive molecule [40].



Scheme 3. Proposed radical mechanism of the conversion of isoeugenol to vanillin (in bold).

Utter identification of the governing mechanism requires further investigation, as for instance with the use of the herein identified intermediates, of oxygen-labelled hydrogen peroxide or addition to radical

scavengers in solution, as well as identification of gases and other by-products that are not detected by GC-MS (*e.g.* ethanol, formic acid). Nevertheless, the occurring of a radical mechanism was also proposed for vanadium-based systems [25]. Also, in our previous study we saw that simply the humins (thermally treated as foams) [30, 31] could catalyse the reaction with high conversion but low selectivity, typical of radical mechanisms, whereas commercial (nano) iron oxides gave low conversions (< 30%) as well as low vanillin selectivity (<20%) [15]. The remarkable difference in reactivity and the findings of this paper support the occurrence of a radical mechanism without excluding an oxometal contribution as a parallel mechanism. Given the multiple consecutive steps herein, thus, vanillin yields will be improved by longer contact times (or simply catalytic bed) and presence of radical initiators. Overall, it can be concluded that future optimisation reactions should be carried in batch given the viscosity of the solution, hence chances of plugging the reactor. A particular focus should be given to catalysts with radical-inducing activity, which can be obtained by the addition of bio-based carbon sources (*e.g.* humins) to Fenton-like metal oxides. Thus, this work suggests the positive effect of using sustainable carbon sources in the development of active catalysts in selective oxidations.

4. Conclusions

Catalytic conversion of isoeugenol by a cheap and abundant catalyst, *i.e.* a humin-containing iron oxide, can be carried out in the presence of hydrogen peroxide. Carrying out the reaction in continuous flow at reduced conversions allowed the identification of the key intermediate molecules involved in the reaction mechanism. Particularly, a predominantly radical mechanism can be envisioned, followed by a series of consecutive steps to the desired product, vanillin; nonetheless, contribution *via* an oxometal pathway may also occur in parallel. These findings support the use of solid acid catalysts with multiple oxidation states in the presence of environmentally-friendly oxidant, hydrogen peroxide, and a bio-carbon source as radical enhancer. Development of an efficient catalytic system can thus remarkably improve the sustainable production of the widespread flavouring agent, vanillin.

Declaration of interests

 \boxtimes The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Acknowledgements

We gratefully acknowledge P. Tosi (University of Nice) for providing the humins foams and the European Commission for funding the HUGS project. L.F. would also like to acknowledge Prof. Francesco Arena (University of Messina) for having inspired the work. The publication has been prepared with support from RUDN University Program 5-100. This work was supported by the European Framework Programme Horizon 2020 (EID-ITN-HUGS G. A. 675325).

References

[1] M. M. Bomgardner, Chem. Eng. News 94 (2017) 38-42.

[2] M. J. W. Dignum, J. Kerler, R. Verpoorte, Food Rev. Int. 17 (2001) 199-219.

[3] M. Fache, B. Boutevin, S. Caillol, Eur. Polym. J. 68 (2015) 488-502.

[4] C. Branzinha, D.S. Barbosa, J.G. Crespo, Green Chem. 13 (2011) 2197-2203.

[5] F. Cavani, G. Centi, Sustainable Development and Chemistry, in: C. Ley (Ed.) Kirk-Othmer Encyclopedia of Chemical Technology, John Wiley & Sons, Inc., Hoboken, 2011, pp. 1-61.

[6] R. Ciriminna, A. Fidalgo, F. Meneguzzo, F. Parrino, L. M. Ilharco, M. Pagliaro, ChemistryOpen 8 (2019) 660-667.

[7] D. Havikin-Frenkel, Vanillin, in: C. Ley (Ed.) Kirk-Othmer Encyclopedia of Chemical Technology, John Wiley & Sons, Inc., Hoboken, 2018, pp. 1-61.

[8] M. Fache, B. Boutevin, S. Caillol, ACS Sustainable Chem. Eng. 4 (2016) 35-46.

[9] BGN TECH LLC, WO Pat., WO066722 A1, 2015.

[10] N. J. Gallage, B. L. Møller, Mol. Plant 8 (2015) 40-57.

[11] Borregaard Industries Limited, US Pat., US4151207A, 1979.

[12] The flavour that carries – Vanillin for 50 years, https://www.borregaard.com/News/The-flavor-that-carries-Vanillin-for-50-years, (accessed September 2019).

[13] R. A. Sheldon, J. M. Woodley, Chem. Rev. 118 (2018) 801-838.

[14] P. Domínguez de María, F. Hollmann, Front. Microbiol. 6 (2015) 1257 [Online]. https://doi.org/10.3389/fmicb.2015.01257

[15] L. Filiciotto, A. M. Balu, A. A. Romero, E. Rodríguez-Castellón, J. C. van der Waal, R. Luque, Green Chem. 19 (2017) 4423-4434.

[16] S. Kang, J. Fu, G. Zhang, Renew. Sust. Energ. Rev. 94 (2018) 340-362.

[17] M. D. Márquez-Medina, D. Rodríguez-Padrón, A. M. Balu, A. A. Romero, M. J. Muñoz-Batista, R. Luque, Catalysts, 9 (2019) 290 [Online]. https://doi.org/10.3390/catal9030290

[18] M. D. Márquez-Medina, P. Prinsen, H. Li, K. Shih, A. A. Romero, R. Luque, ChemSusChem 11 (2018) 389-396.

[19] F. Saberi, D. Rodríguez-Padrón, A. Garcia, H. R. Shaterian, R. Luque, Catalysts 8 (2018) 167[Online]. https://doi.org/10.3390/catal8040167

[20] S. Ostovar, A. Franco, A. R. Puente-Santiago, D. Rodríguez-Padrón, H. R. Shaterian, R. Luque, Front. Chem. 6 (2018) 77 [Online]. https://doi.org/10.3389/fchem.2018.00077

[21] A. Franco, S. De, A. M. Balu, A. A. Romero, R. Luque, ChemistrySelect 2 (2017) 9546-9551.

[22] A. Franco, S. De, A. M. Balu, A. Garcia, R. Luque, Beilstein J. Org. Chem. 13 (2017) 1439-1445.

[23] A. Bohre, D. Gupta, M.I. Alam, R.K. Sharma, B. Saha, ChemistrySelect 2 (2017) 3129-3136.

[24] I. B. Adilina, T. Hara, N. Ichikuni, S. Shimazu, J. Mol. Catal. A 361-362 (2012) 72-79.

[25] E.V. Gusevskaya, L. Menini, L.A. Parreira, R.A. Mesquita, Y. N. Kozlov, G. B. Shul'pin, J. Mol. Catal. A 363-364 (2012) 140-147.

[26] V. Augugliaro, G. Camera-Roda, V. Loddo, G. Palmisano, F. Parrino, M. A. Puma, Appl. Catal. B 111-112 (2012) 555-561.

[27] A. Salanti, M. Orlandi, E.-L. Tolppa, L. Zoia, Int. J. Mol. Sci. 11 (2010) 912-926.

[28] W. A. Herrmann, T. Weskamp, J. P. Zoller, R. W. Fischer, J. Mol. Catal. A 153 (2000) 49-52.

[29] R. S. Drago, B. B. Corden, C. W. Barnes, J. Am. Chem. Soc. 108 (1986) 2453-2454.

[30] P. Tosi, G. P. M. van Klink, A. Celzard, V. Fierro, L. Vincent, E. de Jong, A. Mija, ChemSusChem, 11 (2018) 2797-2809.

[31] Avantium Knowledge Centre B.V., WO Pat., WO2017074183 (A8), 2017.

[32] L. Hernández-Vázquez, M. T. de Jesús Olivera-Flores, H. Luna, A. Navarro-Ocaña, TIP 20 (2017) 15–22.

[33] R. Bortolomeazzi, G. Verardo, A. Liessi, A. Callea, Food Chem. 118 (2010) 256–265.

[34] U. Krey, A. Owen, Basic Theoretical Physics, Springer, Berlin, 2007.

[35] R. Hosseinpour, A. Pineda, A. Garcia, A. A. Romero, R. Luque, J. Mol. Catal. A 407 (2015) 32–37.

[36] M. Fache, E. Darroman, V. Besse, R. Auvergne, S. Caillol, B. Boutevin, Green Chem. 16 (2014) 1987-1998.

- [37] I. A. Pearl, J. Org. Chem. 12 (1947) 79-84.
- [38] C. Jiménez-Sanchidrián, J. R. Ruiz, Tetrahedron 64 (2008) 2011-2026.
- [39] F. Mecozzi, J. J. Dong, P. Saisaha, W. R. Browne, Eur. J. Org. Chem. 46 (2017) 6919-6925.
- [40] H. Wójtowicz-Młochowska, Arkivoc 2017 (2016) 12-58.

Captions to Illustrations (in order)

Figure 12. Column graph of isoeugenol conversion and selectivities to the major products over an inert CatCart® (ThalesNano). Reaction conditions: 100 °C, 15 bar, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H_2O_2 (50 wt%) in acetonitrile, up to 100 min time on stream.

Figure 13. Isoeugenol conversion (blue line, diamonds) and selectivities to *i*) vanillin (orange line, squares), *ii*) vanillin methyl ketone (pink line, triangles), *iii*) dehydroisoeugenol (purple line, crosses), and *iv*) eugenol (green line, circles) over a humins-containing iron oxide catalyst. *Reaction conditions*: 100 °C, 15 bar, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H_2O_2 (50 wt%) in acetonitrile, up to 180 min time on stream.

Figure 14. Stacked column graph of the effect of flow rate on the isoeugenol to vanillin conversion over a humin-containing iron oxide catalyst. *Reaction conditions*: 100 °C, 15 bar, 17 vol% isoeugenol and 13 vol% H₂O₂ (50 wt%) in acetonitrile, variable contact time (22, 45, and 85 seconds).

Figure 15. Stacked column graph of isoeugenol conversion and vanillin selectivity at various temperatures (25, 80, 100, and 120 °C). *Reaction conditions*: 15 bar, 0.3 mL min⁻¹, 9 vol% isoeugenol and 7 vol% H₂O₂ (50 wt%) in acetonitrile, up to 100 min time on stream, variable temperature.

Figure 16. Stacked column graph of isoeugenol conversion and vanillin selectivity at various pressures (5, 15, 30, and 50 bar). *Reaction conditions*: 100 °C, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H_2O_2 (50 wt%) in acetonitrile, up to 180 min time on stream, variable pressure.

Figure 17. Stacked column graph of by-products selectivities at various pressures (5, 15, 30, and 50 bar). *Reaction conditions*: 100 °C, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H_2O_2 (50 wt%) in acetonitrile, up to 180 min time on stream, variable pressure.

Figure 18. Isoeugenol conversion (blue line, diamonds) and selectivities to *i*) vanillin (orange line, squares), *ii*) vanillin methyl ketone (pink line, triangles), *iii*) dehydroisoeugenol (purple line, crosses), and *iv*) eugenol (green line, circles) over a humins-containing iron oxide catalyst. *Reaction conditions*: 100 °C, 30 bar, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H_2O_2 (50 wt%) in acetonitrile, up to 180 min time on stream.

Figure 19. Stacked column graph of isoeugenol conversion and vanillin selectivity at isoeugenol concentrations (C = 10 vol%). *Reaction conditions*: 100 °C, 0.3 mL min⁻¹, 1:2 isoeugenol to H₂O₂ (50 wt%) ratio in acetonitrile, up to 100 min time on stream, variable isoeugenol concentration (10 vol%, 20 vol%, and 30 vol%).

Figure 20. Isoeugenol conversion (blue line, diamonds) and selectivities to *i*) vanillin (orange line, squares) and *ii*) vanillin methyl ketone (pink line, triangles) over a humins-containing iron oxide catalyst. *Reaction conditions*: 100 °C, 15 bar, 0.3 mL min⁻¹, 24 vol% isoeugenol and 18 vol% H₂O₂ (50 wt%) in acetonitrile, up to 120 min time on stream.

Figure 21. Isoeugenol conversion (blue line, diamonds) and selectivities to *i*) vanillin (orange line, squares), *ii*) vanillin methyl ketone (pink line, triangles), *iii*) dehydroisoeugenol (purple line, crosses), and *iv*) eugenol (green line, circles) over an Al-SBA-15-containing iron oxide catalyst. *Reaction conditions*: 100 °C, 15 bar, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H_2O_2 (50 wt%) in acetonitrile, up to 40 min time on stream.

Figure 22. Isoeugenol conversion (blue line, diamonds) and selectivities to *i*) vanillin (orange line, squares), *ii*) vanillin methyl ketone (pink line, triangles), *iii*) dehydroisoeugenol (purple line, crosses), and *iv*) eugenol (green line, circles) over an Al-SBA-15-containing iron oxide catalyst. *Reaction conditions*: $30 \,^{\circ}$ C, 15 bar, 0.3 mL min⁻¹, 17 vol% isoeugenol and 13 vol% H₂O₂ (50 wt%) in acetonitrile, up to 180 min time on stream.

Scheme 4. Reaction products of the hydrogen peroxide-assisted oxidation of isoeugenol catalysed by humins-containing iron oxide.

Scheme 5. Trace products of the isoeugenol conversion detected by GC-MS. In order: 4, methyl (3-hydroxy-4-methoxyphenyl)acetate; 5, methyl hydroxy(3-hydroxy-4-methoxyphenyl)acetate; 6, 3-hydroxy-4-methoxyphenylacetic acid; and 7, 1,3-hydroxy-4-methoxyphenyl)-1,2-propanediol.

Scheme 6. Proposed radical mechanism of the conversion of isoeugenol to vanillin (in bold).



Figure A1. Mass fragmentation pattern of vanillin methyl ketone (1). Reverse Match: 888.



Figure A2. Mass fragmentation pattern of dehydrodiisoeugenol (3). Reverse Match: 786.



Figure A3. Mass fragmentation pattern of methyl hydroxy(3-hydroxy-4-methoxyphenyl)acetate (5). Reverse Match: 828.



Figure A4. Mass fragmentation pattern of 3-hydroxy-4-methoxyphenylacetic acid (6). Reverse Match: 796.



Figure A5. XRD pattern of the as-synthesised humins-containing Fe₂O₃ catalyst.



Figure A6. XRD pattern of the humins-containing Fe₂O₃ catalyst after reaction.