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NEW AND MORE SUSTAINABLE PROCESSES FOR THE SYNTHESIS OF PHENOLICS: 2-phenoxyethanol and hydroxytyrosol

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SUMMARY

GENERAL INTRODUCTION

The history of the modern fine chemicals industry dates back to the late 1800s, when the early chemical industry evolved from dyestuffs and explosives into modern pharmaceuticals.

Fine chemicals are generally organic compounds manufactured to high and well-defined standards of purity. They include pharmaceuticals, agrochemicals, dyes, pigments, vitamins, food additives, fragrances, flavors, intermediates, and performance chemicals. They are sold to companies, mostly other chemical companies, serving an immense range of end-user markets, on either a specification of purity or on their ability to deliver a particular effect.[1]

Fine chemicals are not always produced on a small scale. For some of them, the production may be measured in thousands of tonnes per year, especially for additives and drug intermediates. Often, the plants are not dedicated to a single process (a single plant could produce tens products) and they usually are multipurpose batch systems, followed by separation and purification steps.[2]

Fine chemicals have been produced for many years based upon conventional organic chemistry techniques that generate many wastes, are often insufficiently selective, use many hazardous species, and produce problems in scale-up, especially with respect to safe and economic operation of full-scale reactors (separations for removing undesirable by-products and impurities, and making suprapure fine chemicals constitute a major fraction of the production costs). For this reason, improving process selectivity is a fundamental factor in order to reduce the consumption of raw materials, minimize the amount of wastes and the purification steps, so the overall cost of the process.

Moreover, in the past, safety was a problem that was not tackled carefully enough, as illustrated by the disastrous Seveso incident and many other accidents in industry.[3]

The principle that it is preferable to have no waste than investing resources in an attempt to dispose of those products leads the chemical industry to a renewed interest towards what is known as 'green chemistry'.

The distinction is not between a “clean” and a “dirty” chemistry, but between a chemical production cheaper exploiting new synthesis routes and another penalized by the high environmental, energy and raw materials costs.

Public eye pressure, the shrinking international regulations, the availability of new technologies and new resources have led in recent years the chemical industry to develop a strong interest in that type of knowledge that make possible to realize chemical processes more sustainable from an environmental point of view without penalizing the economic aspect.

Here I report the 12 principles of the Green Chemistry (from the American Chemical Society website).

1) Waste Prevention: it is better to prevent waste than to treat or clean up waste after it has been created.
2) Atom Economy: synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3) Less Hazardous Chemical Syntheses: Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4) Designing Safer Chemicals: chemical products should be designed to affect their desired function while minimizing their toxicity.

5) Safer Solvents and Auxiliaries: the use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6) Design for Energy Efficiency: energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7) Use of Renewable Feedstocks: a raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8) Reduce Derivatives: unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
9) Catalysts (vs Stoichiometric): catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10) Design for Degradation: chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
11) Real-time analysis for Pollution Prevention: analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12) Inherently Safer Chemistry for Accident Prevention: substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.[4]

The role of heterogeneous catalysis in this context is related to various aspects, ranging from an improvement in the selectivity, to a reduction in the number of stages of the processes, to the simplification of the waste disposal, to the use of new synthesis routes with less expensive and renewable raw materials. Heterogeneous catalysis is considered one of the most effective tools to achieve cleaner and cheaper processes in the field of fine chemicals and pharmaceuticals. There are many reasons to choose a solid catalyst to replace stoichiometric or homogeneous catalytic processes: their easy separation from the reaction mixtures, the greater adaptability to continuous processes, the minor amount of liquid waste. Moreover, they are intrinsically more safe because of the elimination of corrosion problems and the minor contamination of the products.

RESEARCH OBJECTIVES

Phenolic compounds are widely used in household products and as intermediates for industrial synthesis. For example, phenol is used as a starting material to make plastics, explosives such as picric acid, and drugs such as aspirin. Phenols are common in nature. Many of the more complex phenols used as flavourings and aromas are obtained from essential oils of plants.[5]

My work was focused on the functionalization of phenolics compounds in order to obtain higher added-value products, namely 2-phenoxyethanol and hydroxytyrosol.

The common aspect of the two topics is the development of catalytic processes following the Green Chemistry principles of prevention of waste, less hazardous chemicals and synthesis, safer solvents (avoid the halogenated) and, when possible, use of heterogeneous catalysts.

There was also a third part during my research study, regarding the production of diesel additives (namely 2,5-bis(propoxymethyl)furan) from fructose. The work on diesel additives was carried out in the Instituto of Tecnologia Quimica (UPV-CSIC) in Valencia with prof. Corma and prof. Iborra, during a 4 months internship.

Of course, this topic was not related to the field of phenolics, but it had in common with them the Green Chemistry principles. Moreover, in this case we also started from a renewable source, namely fructose.

NOTES AND REFERENCES

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[3] A. Cybulski, J.A. Moulijn, M.M. Sharma and R.A. Sheldon, "Fine Chemicals Manufacture", Technology and Engineering, 2001.

[4] Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University, 1998, 30.

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SYNTHESIS OF 2-PHENOXYETHANOL

This chapter takes cue from the following paper:

P. Ziosi[a,b], T. Tabanelli[a], F. Cavani[a,b], P. Righi[a,b], G. Fornasari[a], S. Cocchi[a], *Catal. Sci. Technol*, 2014, **4**, 4386-4395. DOI: 10.1039/C4CY00913D.

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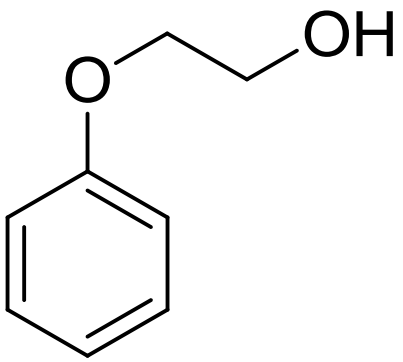
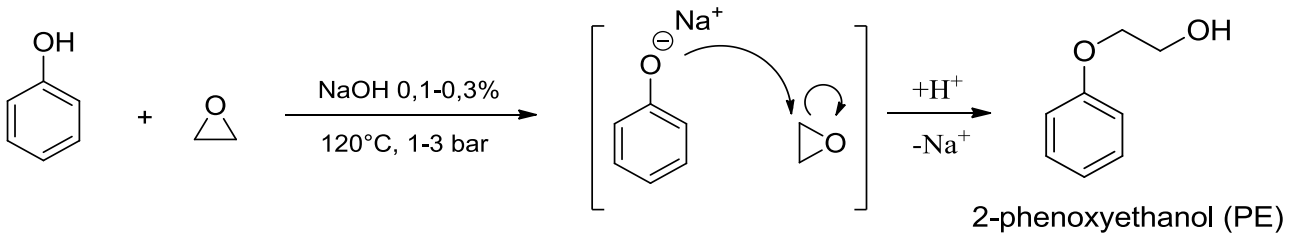
INTRODUCTION



2-Phenoxyethanol (PE, CAS No. 122-99-6) is an aromatic ether alcohol which conforms to the structure in figure; it is also known as phenoxyethanol, 2-phenoxy-1-ethanol, phenoxetol, phenyl cellosolve, ethylene glycol monophenyl ether. At room temperature, PE is a colourless oily liquid with a mild smell of roses. Glycol ethers in general and PE in particular find extensive use as solvent for dyes, inks, and resins; it is a synthetic intermediate in the production of plasticizers, pharmaceuticals, paraben-free and formaldehyde-free cosmetics (in a mixture with ethylhexylglycerine), soaps, textile detergents, and fragrances. PE shows also a balanced spectrum of effectiveness against bacteria, yeasts, and mould fungi, as well as being a solvent and fixative-extender for perfumes, as such or after esterification with isobutyric acid.[1]

The present global production capacity of PE is around 170,000 t/a, and it is manufactured by reaction of ethylene oxide with phenols (Scheme 1). This involves hazardous alkene oxide and often the basic

homogeneous catalysts used are corrosive, costly and sometimes low yields are achieved. In patents, the catalysts reported for this reaction are ammonia, urea, amines, phenates of Na and Li; there is also an heterogeneous catalyst example, based on hydroxide-exchanged resins. By the way, the most common catalysts employed are hydroxides of alkali metals, particularly sodium hydroxide, typically added in quantities of 0.1-0.3% by weight. The reactions are usually conducted in the range of temperature of 110-130°C and 1-3 bar pressure. In order to increase the selectivity towards the monoethoxylated product, the ethylene oxide is added slowly and the reactants are used in an equimolar amount.[2-11]



Scheme 1 The reaction between phenol and ethylene oxide catalyzed by NaOH.

In other examples, monochlorohydrins (such as 2-chloroethanol, as source of ethylene epoxide) are used for hydroxylation of phenol using trimethyl amine as a homogenous catalyst. However, very low yields (12–30%) are achieved using this method.

One significant disadvantage of the current industrial process is that the product obtained needs to be treated because of its pungent metal odour (due to the residues of alkali metal catalysts), not acceptable for the cosmetic and fragrance industry. This problem is quite complex because it is not completely solved even by means of a subsequent distillation, which is carried out in order to separate the product from unconverted

phenol and heavy by-products. Also, post-treatments with sodium borohydride have been proposed;[12] the alkali metal borohydride can be directly added in the reaction medium, with the alkali metal hydroxide.[13] Another drawback of the current industrial production with ethylene oxide is the formation of polyethoxylated by-products containing 2 to 80 condensed ethylene oxide molecules; also polymeric glycol ethers of phenols are formed from a multi-consecutive reaction of PE with ethylene oxide. These by-products make the final product darker and require post- or in-situ treatments. There are patents which report maximum conversions of phenol around 99%, but with variable selectivity towards the 2-phenoxyethanol (from 88 to 96%), depending on the reaction conditions used.[2-10]

Alternatively, phenol is reacted with ethylene carbonate (EC), again in the presence of alkalies.[14] This last route was claimed in early patents to be a smooth, controllable reaction that makes it possible to obtain phenoxyethyl alcohols with high yields[15-18]

More recently, it was also used for introducing aryl nuclei into the chemical structure of acrylic esters (phenoxyethyl alcohols can easily condense with acrylic acid).[19,20] In addition to the non-hazardous nature of alkylene carbonates, hydroxyalkoxylation employing cyclic alkylene carbonate does not require the high-pressure equipment often necessary when working with the highly volatile alkene oxide like ethylene and propylene oxides. In most cases, the carbonate acts both as a reactant as well as a solvent. In previous literature, ethylene carbonate was reported as alkylating agent for phenol using catalysts such as alkali carbonates, LiH, tetraethyl ammonium iodide, alkaline metal iodides and phosphorous containing catalysts for synthesis of glycol phenyl ethers. Although, these catalysts are effective, often yield tarry reaction products and are difficult to recycle. Moreover, these soluble catalysts

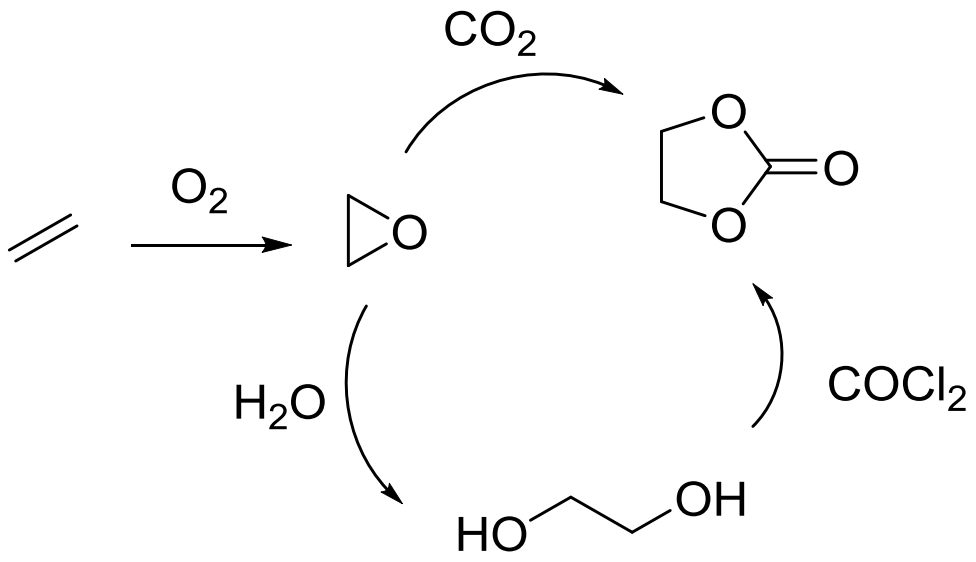
pose several technical and environmental issues such as difficulty in recycle-recovery and waste disposal. Often the products are coloured due to presence of halide trace impurities and phosphorous compounds. Side products such as polymeric glycol ethers of phenols are formed due to further unselective reaction of glycol ethers with ethylene carbonate.[21,22,23]

The use of carbonates as reactants for the synthesis of fine chemicals and intermediates has now become one of the research areas of major scientific and applied interest. Reasons are, for example, that their employment avoids the use of toxic compounds and prevents the generation of waste effluents which need to be disposed. Carbonates also may offer advantages regarding the selectivity to the desired compounds; very important examples are the use of dimethyl carbonate for the O-methylation and the carboxymethylation of phenolic compounds.[24-29]

The organic carbonates are divided according to their structure into cyclic carbonates and linear; both categories are interesting from the industrial point of view and are currently mainly produced from phosgene, for a total market of about 18 million tons per year.

However, being toxic and hazardous, these processes are switching to routes of synthesis from carbon dioxide. This methodology, named "The green carbonyl route", replaces the phosgene and reduces the emission of CO_2 into the atmosphere by about seven times (0,92 t per tonne of product against 6,62 t at present).[30]

As shown in Scheme 2, the CO_2 is able to react with epoxides leading to the formation of the corresponding cyclic carbonates. The catalysts mostly used are halide quaternary ammonium salts (Et4NBr) and potassium iodide (KI).



Scheme 2 Comparison between EC synthesis.

The most synthesized cyclic carbonates are:

- Ethylene carbonate (EC), the most widespread and simple among the cyclic carbonates, it is used as a solvent in preparations for pharmaceuticals and cosmetics, and as an electrolyte in lithium batteries;
- Propylene carbonate (PC);
- Cyclohexane carbonate (CHC);
- Styrene carbonate (SC).

They have important industrial applications, mainly as monomers for the synthesis of polymers (such as polycarbonates and polyols), for the synthesis of hydroxyesters and hydroxyamines.

The most common linear carbonates are dimethyl carbonate (DMC), diallyl carbonate (DAC), diphenyl carbonate (DPC).

In the presence of nucleophiles, such as phenolic compounds, primary amines, thiols, sulfones etc., DMC can react both as a methylating or methoxycarbonylation agent, depending on the temperatures.[31]

For most of these processes the carbonates act both as reactant and solvent.

Recently, some authors have reported the alkylation of phenol with ethylene carbonate on heterogeneous basic catalysts (namely alkali-loaded large-pore zeolites), achieving a very good PE yield of 98.5%.[32] However, the paper does not report any in-depth study on how the reaction parameters (for example temperature, molar feed ratio, amount of catalyst etc) or the catalyst properties influence the performance of the process.

OUR AIM

Our aim was to develop a more sustainable process for the synthesis of PE reacting phenol and EC, avoiding any solvent and using heterogeneous basic catalysts such as Na-mordenite, which did not contaminate the product, and could be easily recovered and reused.[33-36]

In order to improve the selectivity to PE, we in-depth investigated the reaction parameters, the different behaviors of the catalysts, and we compared the homogeneous with the heterogeneous catalysis.

RESULTS

Identification of the best reaction conditions

Preliminary experiments were aimed at finding the reaction conditions necessary for obtaining high conversion of the substrate using the Na-mordenite catalyst. The catalyst used for reactivity experiments was a "CBV 10A" sodium mordenite molecular sieve from ZEOLYST International with a SiO_2/Al_2O_3 mole ratio of 13 (Na_2O weight% = 6.5; surface area = 425 g/m^2). Before the experiments, the catalyst was thermally pre-treated at 400 °C for 3 h in air flow.

X-ray diffraction patterns of zeolites were carried out using a Philips PW1710 instrument, Ni-filtered CuKα radiation, (λ= 0.15418 nm), interval 2Θ 5-80°, step 0.1°.

Ar adsorption/desorption isotherms (77K) were carried out in a Micromeritics ASAP 2020 instrument. Samples were previously outgassed for 120 minutes at 423K and 30 μmHg, and then heated for 240 minutes at 623K. Specific surface area values were obtained by multi-point BET equation in the 0.05-0.2 p/p^0 range and total pore volume values were calculated at 0.95 p/p^0. The micropore size distribution was calculated with the NLDFT-statistic method.

Figure 1 Picture of the reactor system.

Reactivity experiments were carried out as follows: in a round bottom pyrex cylinder equipped with an internal cooling circuit (see Figure 1), phenol (3 mmol), EC (6 mmol) and Na mordenite (0.5% weight with respect to the phenol fed, if not otherwise specified) were added. The reaction mixture was usually stirred at the given temperature for 7 h under nitrogen atmosphere. 50 µL samples were taken without interrupting the reaction; they were then brought to a 10 mL volume with acetone (HPLC grade, Sigma-Aldrich); then an aliquot (approx. 2 mL) was filtered (0.45µm PTFE filter) to separate the catalyst, and then

analysed by means of GC. The analysis of the reaction mixture was performed using an Agilent GC6850 instrument, equipped with HP-1 capillary column (30m x 320 µm x 0.25 µm), and a FID held at 280 °C (H_2 40 mL/min, air 450 mL/Min); carrier gas was H_2 (108 mL/min). The injector was held at 250 °C, in the split mode (50:1). The volume of the sample injected was 1 µL. The oven temperature was the following: 50 °C (2 min), ramp 10 °C/min, 120 °C, ramp 25 °C/min, final T 280 °C (3 min).

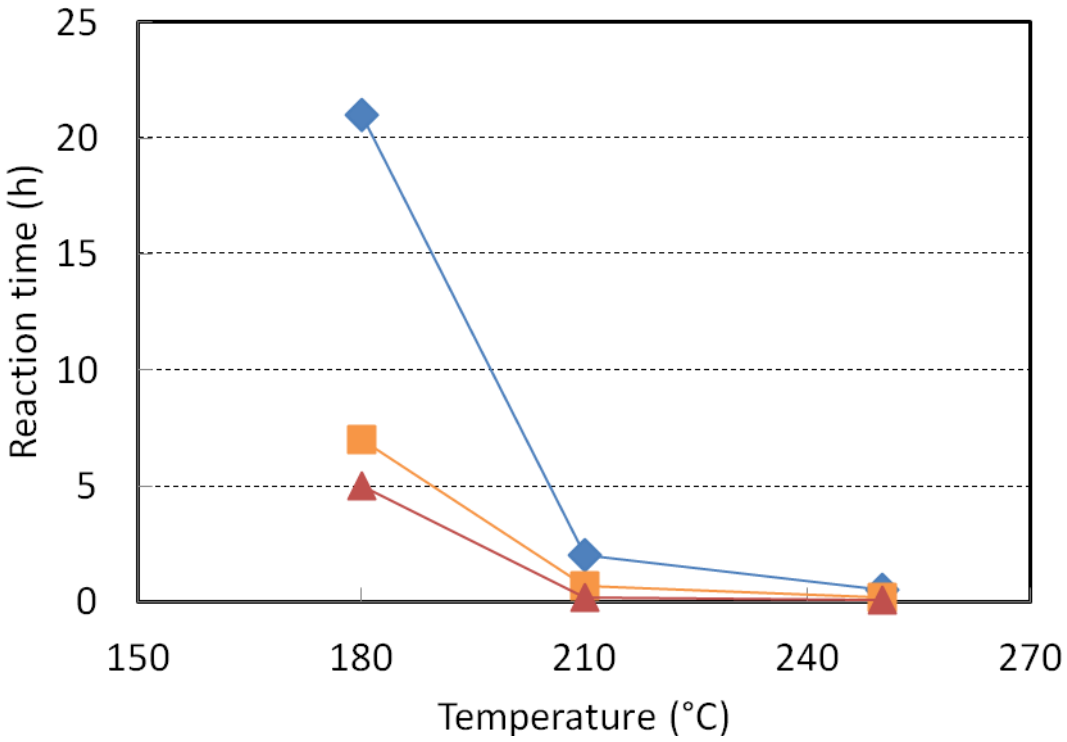


Figure 2 Reaction time needed to obtain the overall yield to PE + BPEC equal to 95% (◆), 50% (■) and 30% (▲), in function of the reaction temperature used. Reaction conditions: Phenol/ethylene carbonate 1/4 (molar ratio), catalyst/phenol 1/2 (wt ratio). Catalyst Na-mordenite SAR 13.

In Figure 2 we compare the time necessary to reach given values of PE yield (95%, 50% and 30%) for different reaction temperatures. At 150 °C

(not shown in the Figure), there was a 10% yield to PE only after 35 h reaction time, so we decided to use higher temperatures. From 180 °C to 210 °C a remarkable decrease in the reaction time occurred. By pushing the temperature further (250 °C), the reaction time was even shorter, but at a higher conversion the extent of consecutive reactions increased also while selectivity started to decrease. For example, at 210 °C the selectivity to PE was close to 97-98% even at a very high conversion of phenol, but when the reaction temperature was 250 °C it dropped to less than 95%. Therefore, we decided to carry out the experiments at the optimal temperature of 210 °C, which was the best compromise between an acceptable reaction rate (even from an industrial process point of view) and the lower formation of by-products.

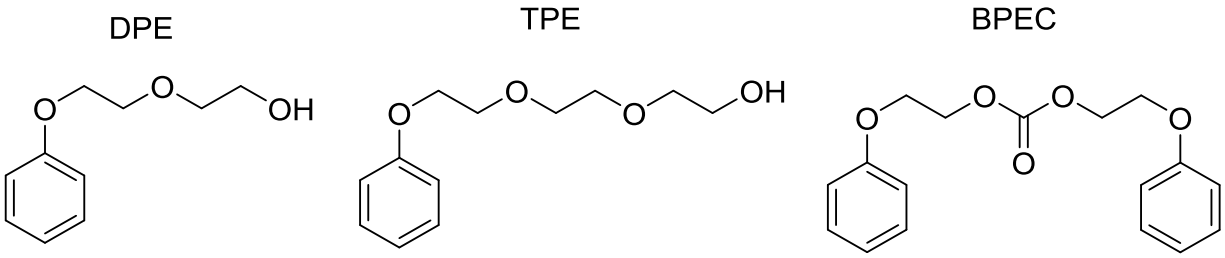


Figure 3 By-products in the reaction between phenol and EC.

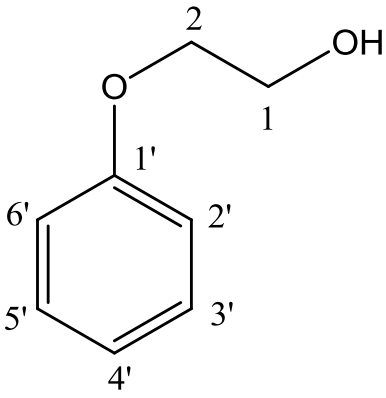
All the reaction products were isolated from the mixture by means of flash chromatography (230-400 mesh) by using as eluent a petroleum ether/ethyl acetate mixture (vol ratios from 8/2 to 7/3). Then the products (PE, DPE and BPEC, see Figure 3) were identified by means of ESI-MS and NMR. The exception was 2-[2-(2-phenoxyethoxy)-ethoxy]ethanol (TPE), because the signals due to C14 and C15 triplets overlapped the signals of other CH_2 moieties in other by-products (DPE). With this compound, identification was achieved by means of ESI-MS and GC-MS.

ESI-MS spectra (positive or negative), were recorded using a Waters Micromass ZQ4000, equipped with a capillary probe (3.54 kV), with 20 Volts cone voltage, and direct injection (20 μL/min).

^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform at 25 °C on a Varian Inova 300, at 300 MHz and 75 MHz respectively.

Here I report the NMR spectra of all the products. Chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signal of the solvent (7.26 ppm and 77.0 ppm respectivley). The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal.

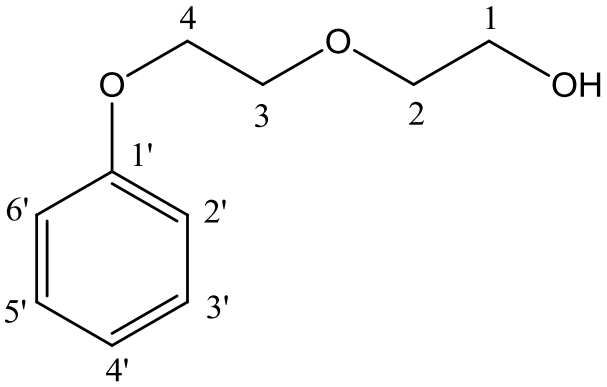
2-phenoxy-1-ethanol (PE)



^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34-6.89 (5H, m, Ar), 4.09 (2H, m, C 2), 3.96 (2H m, C 1), 2.04 (1H, bs, OH).

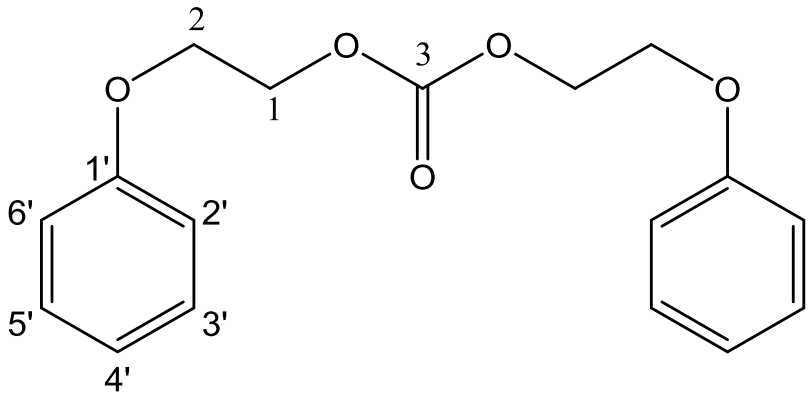
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 158.7 (C 1'), 129.7 (C 3-5'), 121.3 (C 4'), 114.7 (C 2'-6'), 69.2 (C 2), 61.7 (C 1).

2-(2-phenoxyethoxy)ethanol (DPE)



^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34-6.89 (5H, m, Ar), 4.09 (2H, m, C 4), 3.96 (2H, m, C 3), 3.69 (2H, m, C 2), 3.59 (2H, m, C 1), 2.04 (1H, bs, OH).

bis(2-phenoxyethyl)carbonate (BPEC)

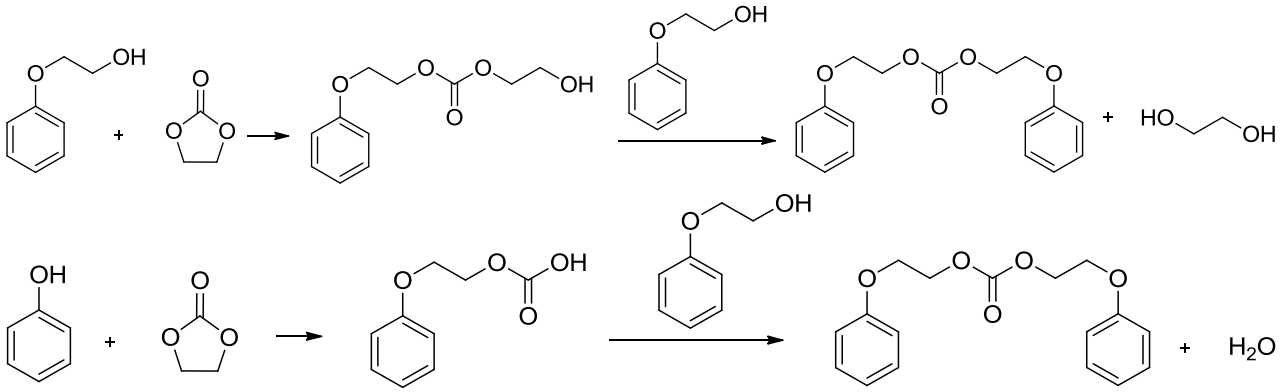


^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32-6.89 (10H, m, Ar), 4.52 (4H, m, C 2), 4.21 (4H, m, C 1).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 158.5 (C 1'), 155.2 (CO 3), 129.6 (C 3'-5'), 121.4 (C 4'), 114.7 (C 2'-6'), 66.5 (C 2), 65.6 (C 1).

The assignment of the structure to BPEC was based on the fact that (i) its 1H NMR spectrum did not show a signal attributable to a hydroxyl moiety, (ii) the two CH_2 moieties are strongly deshielded, (iii) its ^{13}C NMR showed a quaternary C atom at 155.2 ppm, and (iv) the ESI spectrum showed a peak at m/z = 302. All this strongly suggested the structure of a symmetrical carbonate such as BPEC.

The two by-products DPE and TPE usually formed in low amounts (overall yield less than 2%), with the exception of experiments carried out with a large excess of ethylene carbonate. On the contrary, BPEC could reach 10-15% of yield at complete phenol conversion; we hypothesized two different reaction pathways of formation (Scheme 3).



Scheme 3 Plausible mechanisms for the formation of BPEC by-product during the reaction between phenol and EC. Top: mechanism (a); bottom: mechanism (b).

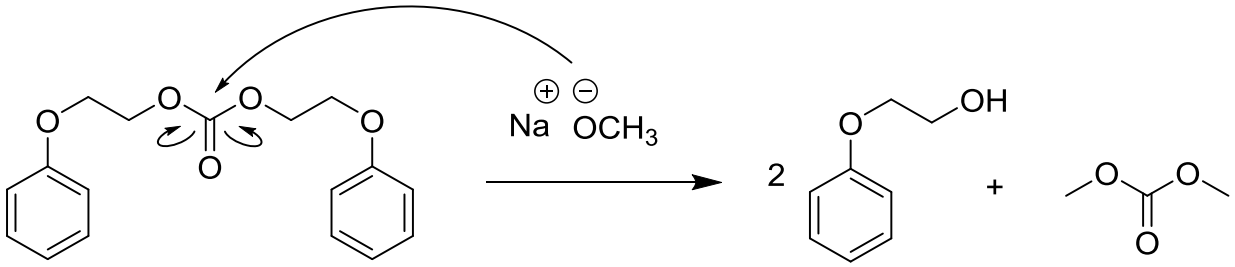
(a) Transesterification mechanism: by successive reactions between PE and the unconverted EC, and then again with another molecule of PE, with the release of ethylene glycol;

(b) carboxylation-esterification: by the formation of the intermediate obtained by reacting phenol with EC; the latter either eliminates CO_2 to form PE, or may be transformed further by esterification with PE.

We did not notice the formation of diphenyl carbonate, which might be the product of the parallel reaction of transesterification of phenol with EC. This could be due to the fact that the softer nucleophile phenol reacts preferably with the soft electrophile, namely the alkylydene C atom in the carbonate, to produce glycol ether.[30] Regarding PE, instead, the aliphatic alcohol probably reacts with the hard C atom of the carbonyl forming the transesterification product; for this reason, the (a) mechanism still is possible. In the case of (b) mechanism, the intermediate compound reacts preferably with PE, instead of releasing CO_2 and forming PE, under conditions leading to PE accumulation. Therefore, both mechanisms are more encouraged at conditions of high

phenol conversion, and they are in any case favored at high EC concentration.

A fundamental point regarding BPEC is that it could be easily and completely hydrolyzed to PE (Scheme 4). After separation by flash chromatography, BPEC was converted into PE (reaching 100% yield) within 5 h reaction time, using 2% $NaOCH_3$ catalyst in refluxing methanol. In acidic conditions the same reaction also occurred, but it was much slower compared to the previous one. Therefore, BPEC is not a waste compound of the process, but an intermediate for PE synthesis.



Scheme 4 The reaction of BPEC transformation into PE.

Figure 4 shows the effect of the reaction time on phenol and EC conversion, and on the yield to PE (the desired product) + BPEC (the by-product which could be converted to PE in a separate vessel), as well as on by-products DPE and TPE, at the temperature of 210 °C, for three different phenol/EC molar ratios, equal to 1/1, 1/2, and 1/4. The catalyst used was Na-mordenite SAR13 (50 wt% with respect to phenol, which corresponds to 10% mol Na).

We noticed that decreasing the phenol/EC molar ratio, a progressive increase of the reaction rate occurred; in fact, complete conversion of the limiting reactant (i.e. EC with the 1/1 phenol/EC molar ratio, but phenol with 1/2 and 1/4 phenol/EC molar ratios) was achieved in 28 h in the first case, while in 6-8 h with the 1/2 ratio, and in less than 3 h with the 1/4 ratio.

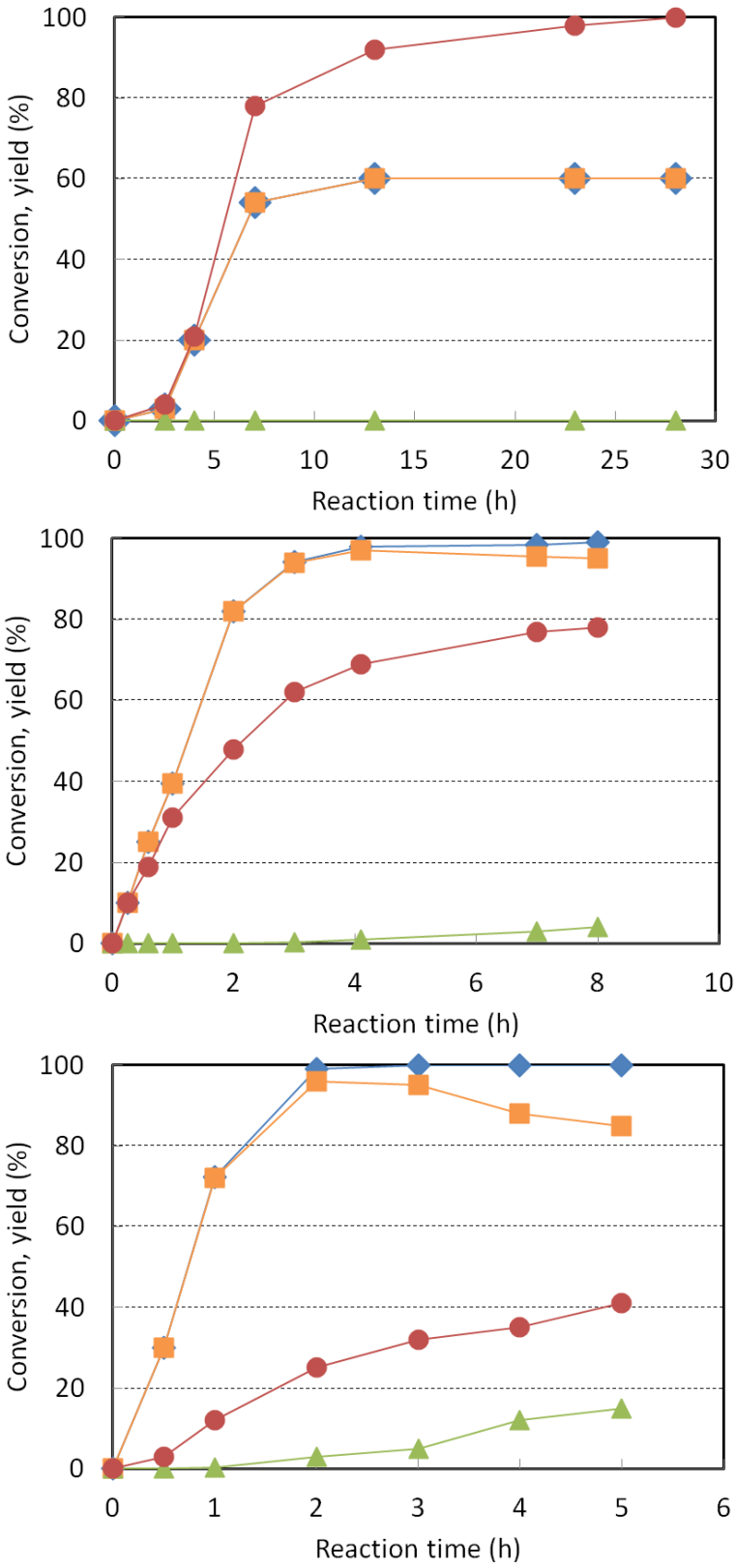


Figure 4 Effect of reaction time on phenol conversion (◆), EC conversion (●), and yield to PE + BPEC (■), and DPE + TPE (▲). Reaction conditions: T 210 °C; catalyst/phenol 1/2 wt ratio; Na-mordenite catalyst; Phenol/EC molar ratios 1/1 (top), 1/2 (middle) and 1/4 (bottom).

Moreover, in the experiment of 1/1 phenol/EC feed ratio, the maximum conversion of phenol was just 60% (note that the curves of phenol

conversion and PE yield are overlapped). Despite the use of a stoichiometric feed, EC was clearly the limiting reactant because it underwent the parallel decomposition via decarboxylation and successive oligomerization of ethylene glycol. We demonstrated this carrying out an experiments with only EC, under the same reaction conditions.

In this case, the selectivity to PE was very high (substantially 100%), because of the defect of EC which did not allow the formation of the by-products.

When we increased the EC fed, its conversion was less than 100%, but it still went on reacting even after complete conversion of phenol, because of the formation of DPE, TPE (by-products which further consume EC), and ethylene glycol oligomers. The selectivity to PE was total only for phenol conversion lower than 100%; then, the longer reaction times led to a rapid increase in by-product formation, especially with the phenol/EC feed ratio equal to 1/4. In general, we noticed that when the reaction approached the complete conversion of phenol, the selectivity declined, mainly because of the formation of BPEC. Then, also the formation of the more undesired by-products started (DPE and TPE), although it remained very low, especially if higher phenol/EC ratios were used.

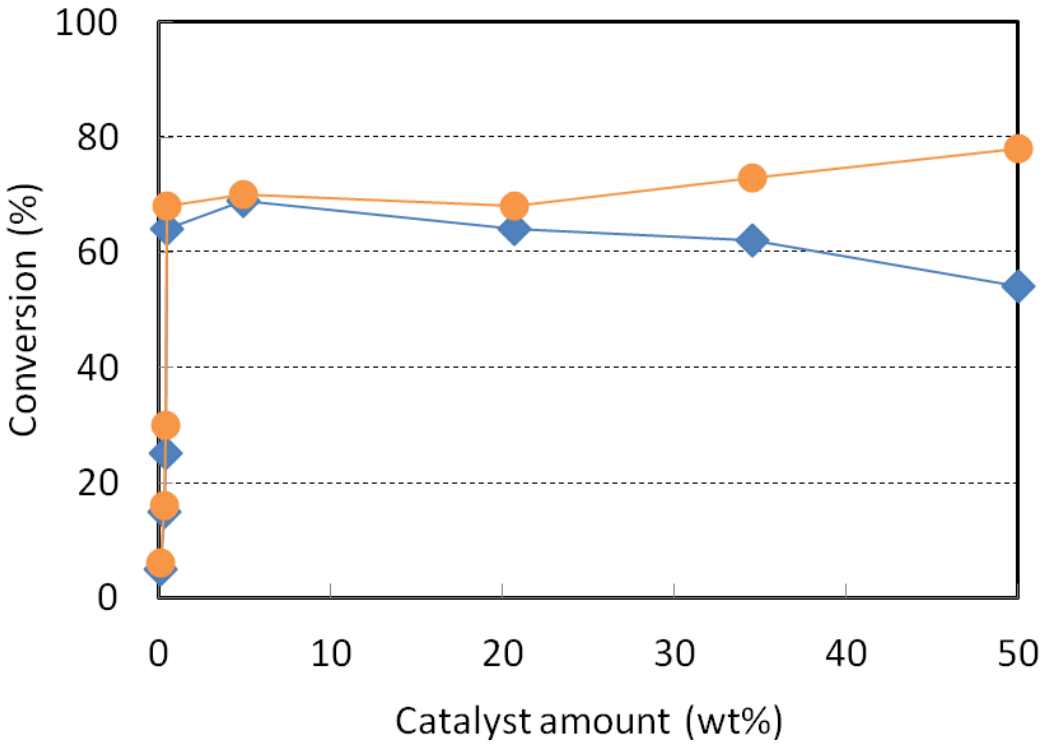


Figure 5 Effect of the catalyst amount (weight in respect to the phenol) on phenol conversion (◆) and EC conversion (●). Reaction conditions: T 210 °C, reaction time 7 h, feed ratio phenol/EC 1/1; catalyst Na-mordenite.

After the screening of the molar feed ratios, we investigated the effect of the catalyst amount on catalytic behaviour, at fixed reaction conditions (Figure 5). In the catalyst/phenol wt ratio interval ranging between 0 and 0.5% we noticed that the conversion of phenol and EC were proportional to the catalyst amount. Increasing the amount of catalyst, the conversion of phenol decreased while that of EC increased; as shown in the previous test with an equimolar phenol/EC ratio (Figure 4, top)), instead of reaching the complete conversion of phenol, the latter was less than 100% because of EC transformation into non-useful products. In other words, the decrease of the phenol conversion for increasing

catalysts amount (Figure 5) was due to the increased contribution of EC decomposition.

Therefore, the greater was the catalyst amount used, the more facilitated the decomposition of EC became with respect to its reaction with phenol, causing a decline in both yield to PE and phenol conversion. On the other hand, when the amount of catalyst was increased from 0.5 to 5 wt%, the phenol conversion increased only a few percentage points, although the EC conversion was still similar to that of phenol, thus keeping very low the amount of decomposed EC. Thus, we cannot assert that, for catalyst loadings higher than 0.5 wt%, a poorer contact between reactants (because of the absence of solvent) and catalyst might have made the reaction slower compared to the experiments carried out with lower catalyst amount.

Moreover, it is also worth noting that at such conditions (with an equimolar ratio between phenol and EC, and a phenol conversion lower than 70%) the selectivity to PE was always close to 99%, with less than 1% BPEC, and no formation of DPE and TPE at all.

Finally, this preliminary investigation allowed us to define the best reaction conditions, those which allow a compromise between almost total conversion of phenol within a few hours reaction time, while maintaining both high selectivity (≥ 98%) to PE+BPEC and minimal EC transformation into by-products. The conditions found were: T = 210 °C, molar feed ratio phenol/EC 1/2, and catalyst/phenol wt ratio 1/200 (0.5 wt% catalyst).

In Figure 6 is shown the catalyst performance under optimized reaction conditions; the total conversion of phenols was achieved within 9 h reaction time and the selectivity to PE was total up to more than 70% conversion. At total phenol conversion the selectivity to the more

undesired DPE (with traces of TPE) was 4%, while the selectivity to BPEC was 17-18%.

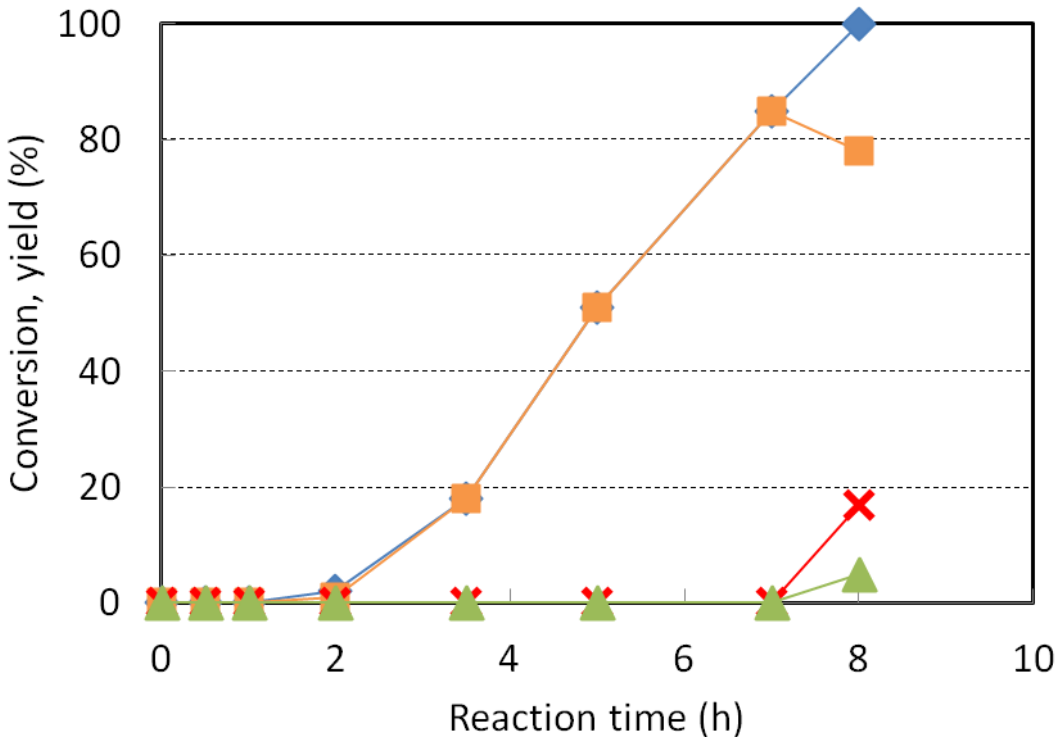


Figure 6 Effect of reaction time on phenol conversion (◆), and on yield to PE (■), BPEC (×), and DPE + TPE (▲).Reaction conditions: T 210 °C, phenol/EC molar ratio 1/2, catalyst amount 0.5 wt% with respect to phenol.

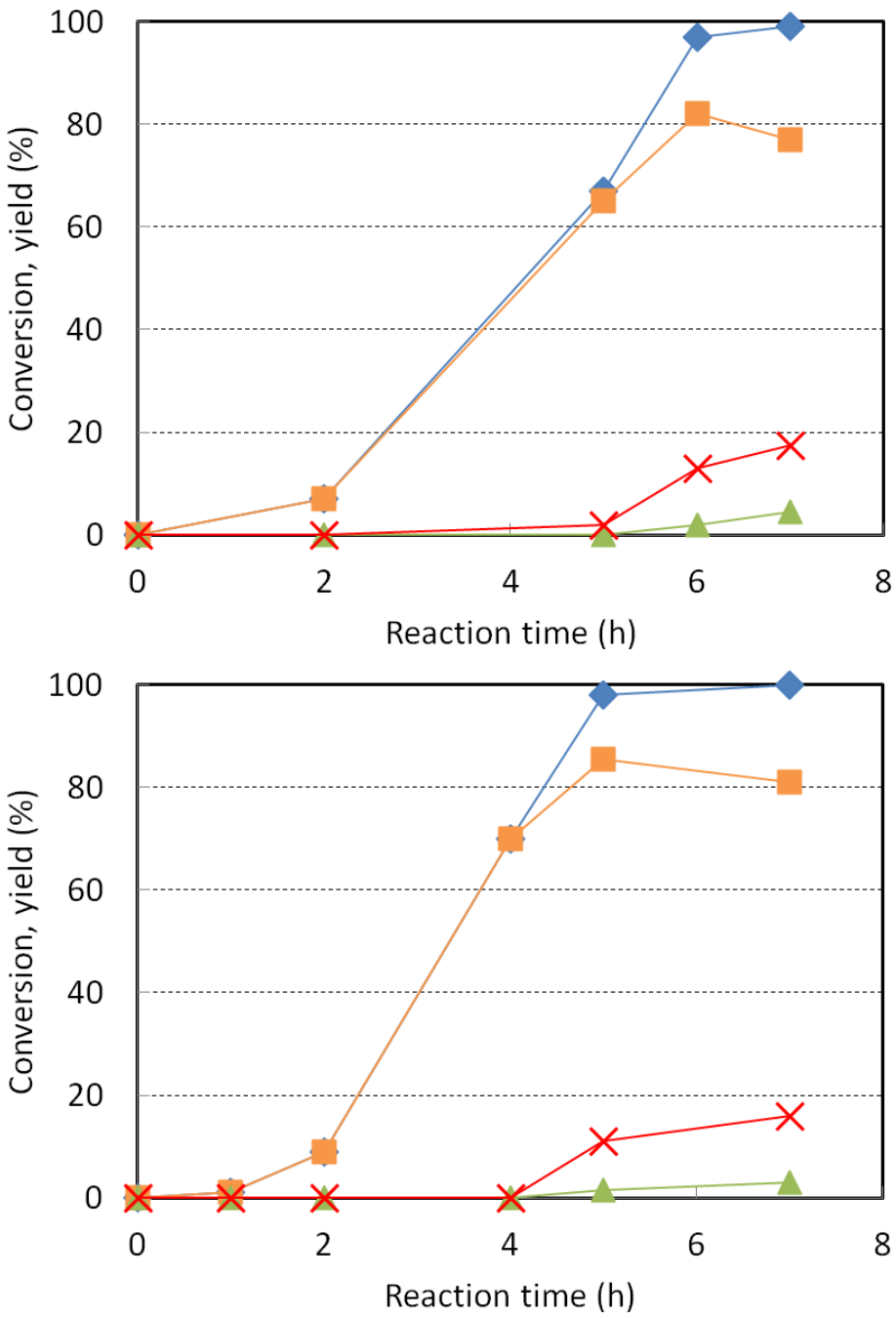


Figure 7 Effect of reaction time on phenol conversion (◆), and yield to PE (■), DPE+TPE (▲), and BPEC (×). Reaction conditions: catalyst amount 0.5 wt% (top), and 5 wt% (bottom); T 210 °C, phenol/EC feed ratio 1/2, catalyst treated Na-mordenite.

Under these conditions we noticed the presence of an induction period (see Figure 7), which led to negligible yield to PE in up to 2 h; such effect was not registered under conditions of high catalyst loading with the same 1/2 phenol/EC feed ratio, while, it was apparently seen when the equimolar feed ratio was used. So we thought that the induction period might be related to the use of a low catalyst amount, and might be due to problems related to the scarce access of reactants to the basic active sites located in zeolites pores, a problem which may be overcome by using large catalyst amounts (probably because of the contribution of external sites).

Moreover, the induction period was followed at first by a slow increase in conversion, but later on by an acceleration with a rapid increase in the conversion within a short reaction time and this phenomenon is clearly unexpected under catalytic conditions. One possible explanation is the presence of an autocatalytic effect due to the PE itself.

The induction period, and the autocatalytic effect

In order to confirm our hypothesis, we planned experiments without any catalyst.

The tests shown in Figure 8 (top) were carried out by adding increasing amounts of PE (from 4% to 126%) in the reaction medium, at 210°C (no reaction was observed in the absence of catalyst at 180°C, even after 24 h), with a phenol/EC ratio equal to 1/2. We first treated the commercial PE with silica plug in order to remove any traces of alkali metal cations which could influence the reaction (the possible contamination of the reactants used because of alkali metals was ruled out, based on the negligible Na content analytically found).

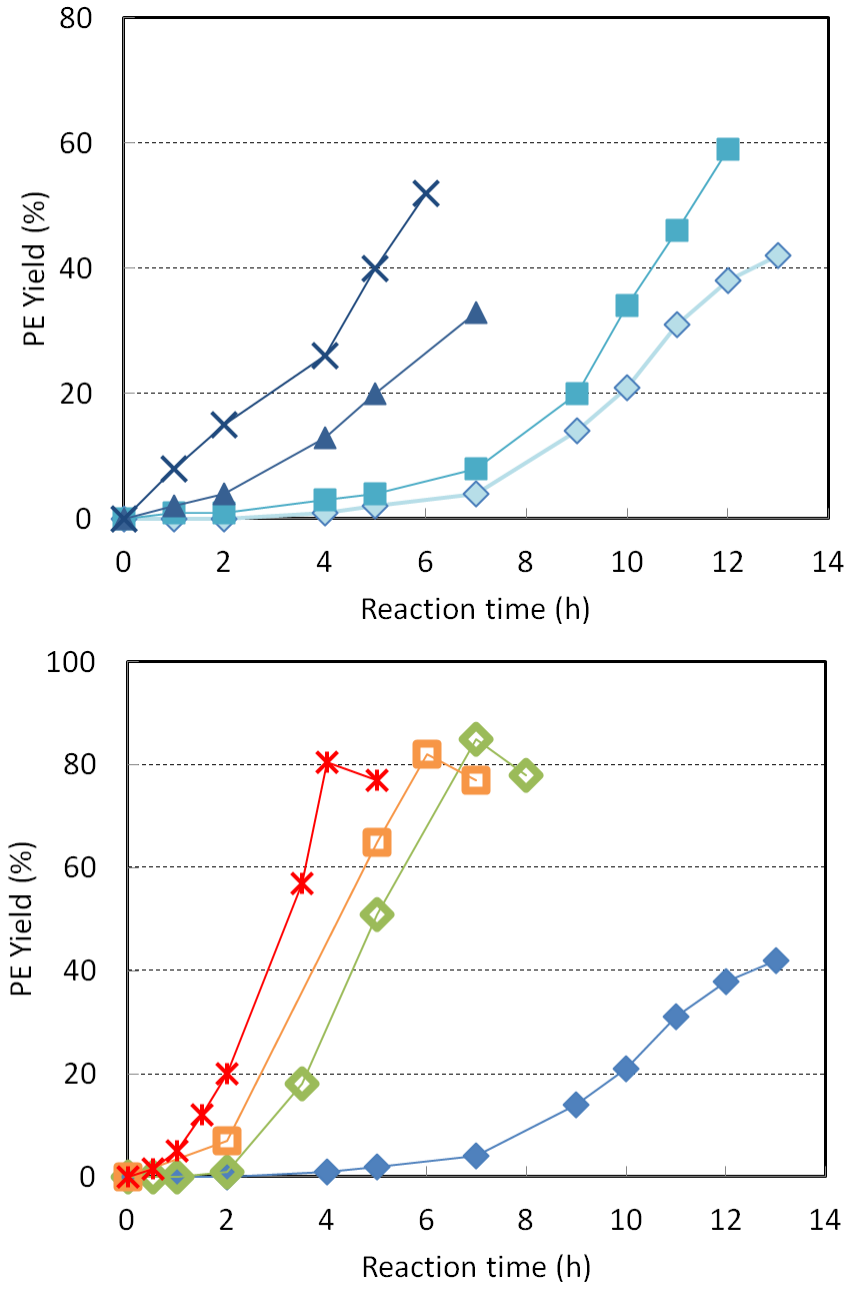
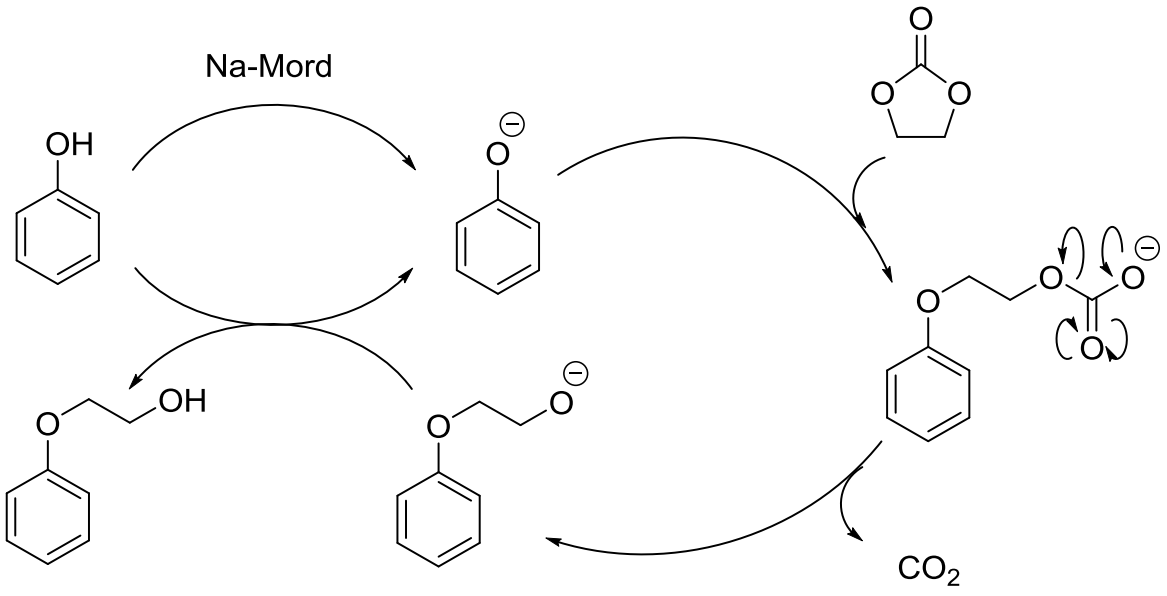


Figure 8 Effect of reaction time on yield to PE. Top: experiments without any catalyst, with increasing amounts of PE added from the beginning (wt% with respect to phenol): 0% (◆), 4% (■), 17% (▲), and 126% (×). Yields were calculated after subtraction of the PE amount added. Bottom: comparison between PE yields without catalyst (◆), with 0.5 wt% (with respect to phenol) Na-mordenite catalyst (◇), or 0.5 wt% treated Na-mordenite (□), and with 3±1 ppm NaOH (×). Reaction conditions: T = 210 °C, phenol/EC ratio 1/2.

Figure 8 (bottom) compares the yield to PE shown in function of time, both in the absence of any catalyst (and without preliminary addition of PE), and in the presence of the catalyst (0.5 wt% Na-mordenite, in respect to phenol fed).

We noticed that the reaction proceeded even in the absence of any catalyst, but was clearly slower than in the presence of the catalyst (Figure 8 bottom). After 7 h reaction time yield to PE was about 4% (as also shown in Figure 5, for a phenol/EC ratio equal to 1/1). There was an induction period of a few hours, after which the reaction started. It is possible that the reaction took some time (i.e. the induction period) to show a non-negligible reaction rate in the absence of added catalysts, because of the slow formation of the phenate anion (although accelerated at 210 °C, compared to lower temperatures). Then the reaction rate was accelerated because of the formation of PE; to this regard we hypothesized an autocatalytic effect (see Scheme 5).



Scheme 5 The autocatalytic effect of PE on the reaction rate.

We can also notice that adding an increasing amounts of PE from the beginning of the reaction, the induction period was shorter until it

became negligible when the reaction was carried out in the presence of a rather high amount of PE. Moreover, addition of PE accelerated the reaction rate: a rapid increase of the yield in function of time was observed in the presence of the greater amounts of added PE.

In all cases, the selectivity to PE was 100%, because of the relatively low phenol conversion observed. Only in the case of the experiment carried out with the highest amount of PE did we notice the formation of BPEC (however, with only 1.2% selectivity).

In Figure 8 (bottom) it is also shown the catalytic behaviour seen with the addition of 3±1 ppm NaOH. The homogeneous catalyst was the most efficient, with no induction period but still with evidence of the autocatalysis effect.

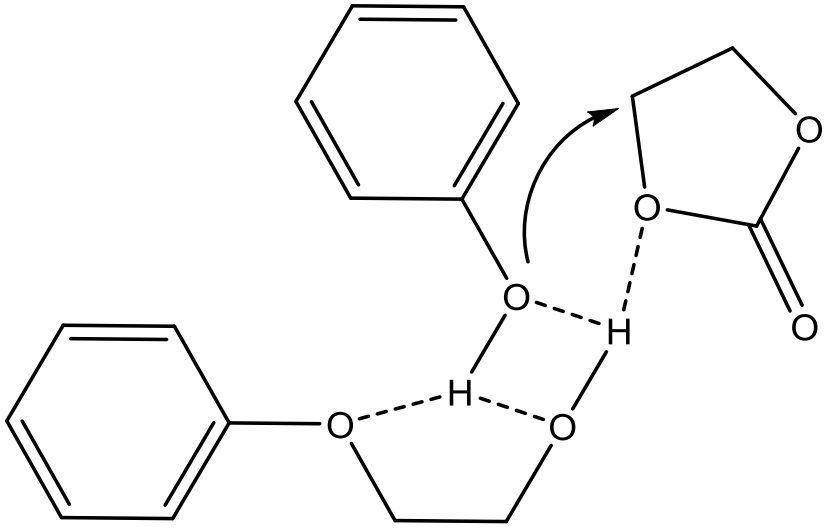
Assuming that the phenate formation is the rate-determining step (which is accelerated by the basic catalyst), and because of the stronger basicity of the deprotonated PE compared to the phenate, the generation of the former species within the catalytic cycle (Scheme 5) leads to a rapid deprotonation of phenol. At this point, the phenate is again available for a further transformation into PE, originating the autocatalytic effect. In other words, as long as phenol is present in the reaction medium, the deprotonated form of PE will readily react generating the phenate species. When the amount of phenol is lowering at the end of the reaction, the deprotonated PE will pick up the proton initially released by phenol to the Na-mordenite catalyst.

Moreover, also the release of CO_2 is a strong driving factor for the generation of the strong base, the deprotonated form of PE; the latter species, however, is soon converted into PE, because of its basic character.

Some experimental evidences support our hypothesis. The by-product BPEC forms only when the conversion of phenol is very high; despite

this compound is formed by a consecutive reaction, a small (but non-negligible) amount of it could start to form at intermediate values of phenol conversion. This occurs because under conditions of phenol starvation the PE alkoxide may attack the carbonyl bond of EC, starting the reaction sequence which forms BPEC (Scheme 3). In this regard, the basic catalyst (either the ppm of Na^+ or the Na-mordenite) acts as an initiator, more than as a true catalyst, whereas the main role of increasing the reaction rate is played by the deprotonated form of PE (Scheme 5). This led us to hypothesize about the presence of a heterogeneously-initiated and heterogeneously-terminated reaction (in the presence of the zeolite), but with a crucial contribution of the proton-exchange between phenol and PE alkoxide acting a homogeneous catalysis. However, the zeolite may play an important role in improving the reaction selectivity, which confirms that the reaction occurs, at least in part, within the confined environment of the mordenite pores.

With regard to the induction period, and to the role shown by the added PE (Figure 8, top), it must be underlined that we operated in the absence of any solvent; for this reason, there is a favoured interaction between the nucleophilic O atoms of PE and the proton of phenol. This might lead to the development of a concerted weakening of the O-H bond in phenol, facilitating the interaction with EC (Scheme 6), thus finally leading to a considerably shortened induction period. Moreover, we experimentally observed that PE makes the solution less viscous, playing itself a solvent which may facilitate the diffusion in the presence of the zeolite catalyst.



Scheme 6 A hypothesis of a concerted H-bonding interaction between phenol, PE, and EC under solventless conditions, facilitating the attack of the Ph-$O^{\delta-}$ species onto EC.

On the other hand, the efficiency of the catalyst determines the duration of the induction period. For example, the use of high amounts of catalyst (Figure 7) permitted an important shortening of the induction time, but this is clearly not very sustainable from the Green Chemistry standpoint, besides the fact that it also accelerated the decomposition of EC. Data obtained also evidence that diffusion in zeolite pores can play a role in the reaction; therefore, in order to investigate the effect of a modification of porosity on catalytic behavior, we carried out a post-treatment on the Na-mordenite.

Post-treatment of the Na-mordenite: a comparison of catalytic performance

The silanization procedure on unidimensional and aluminum-rich zeolites, such as mordenite, showed a pore mouth narrowing effect more significant than with other zeolites, such as ZSM-5.[37] In order to reduce the microporosity through pore mouth blocking, a post-treatment on the industrial mordenite was carried out using a chemical liquid deposition with TEOS as silanization agent.

The liquid-phase post-treatment was carried out using a 20 mL mixture of 5 vol% TEOS in *n*-hexane mixed with 2.5 g zeolite at room temperature for 15 h. The system was filtered, dried at 120 °C and calcined at 450 °C for 3 h. The procedure was repeated twice.

The characteristics of the two samples, the original Na-mordenite and the treated one, are summarized in Table 1. The treatment did not lead to any change in the XRD pattern of the sample. Indications of textural changes are given from the surface area and porosity, where the surface area of parent mordenite was high (452 m^2/g), and after post-treatment decreased down to 109 m^2/g. Finally, both the total pore volume and micropore volume showed a dramatic decrease, thus indicating a clogging in the microporosity, while the mesopore volume and area were left substantially unchanged.

Table 1 Main features of the Na-mordenites used for reactivity experiments.

	Original Na-mordenite	Treated Na-mordenite
Total pore volume (cc/g)	0.189	0.069
Micropore volume (cc/g)	0.151	0.030
Surface area (m^2/g)	452	109
Micropore area (m^2/g)	418	77
Mesopore area (m^2/g)	34	32
Average pore diameter (Å)	17	23
Maximum pore diameter DFT (Å)	5.9	5.9
Na content (wt % Na_2O)	6.5	6.0

The catalytic behaviour of the two zeolites is compared in Figure 8 (bottom). It can be noticed that the induction period was considerably shorter with the treated zeolite; however, the overall amount of Na available was probably decreased in the treated zeolite because of the less pore volume accessible to reactants. The autocatalytic effect cannot be the only one responsible for the different initial behaviour shown by the two zeolites, because the amount of PE formed during the first 1-2 h reaction time was too low to have any effect on the initial behaviour. This evidences that the delay in starting the reaction is affected by the accessibility of reactants to the Na sites, a phenomenon which does not play an important role only when a large amount of catalyst is used.

The post-treated catalyst evidenced also a different behaviour on its reusability, as shown in Figure 9, by comparing the conversion of phenol at 210 °C and after 5 h reaction time, with the untreated and post-treated Na-mordenites. After each run, the catalysts were separated from the

reaction medium by filtration, washed with acetone, dried in an oven at 100 °C overnight, and then reloaded again for the successive. Tests were carried out using both low (0.5 wt% in respect to phenol) and high (25 wt%) catalyst loading.

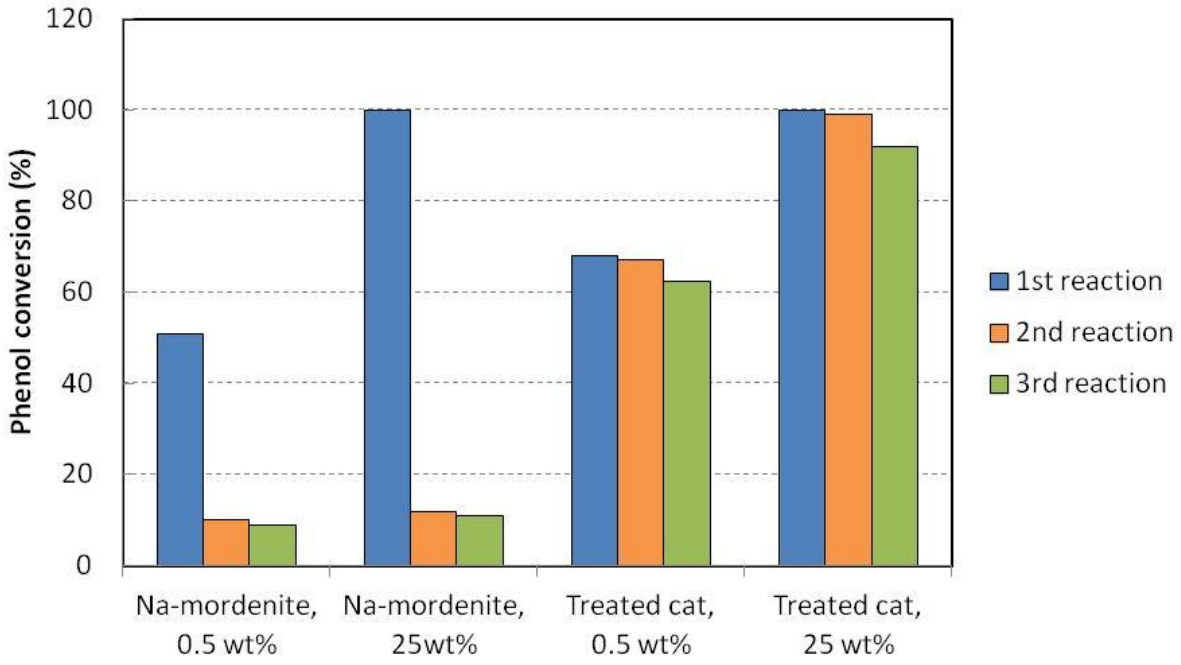


Figure 9 Phenol conversion after 5 h reaction time at 210 °C, phenol/EC ratio 1/2, with both untreated and treated Na-mordenite catalyst, for the fresh catalyst, and after recovery and reuse in a 2nd and 3rd reaction. Tests carried out using either 0.5 or 25 wt% catalyst (with respect to phenol).

We found that the untreated catalyst showed a drastic deactivation effect already after the first use, while the post-treated Na-mordenite showed negligible deactivation. We think that the deactivation of the untreated Na-mordenite was mainly due to the accumulation of organic residues inside catalyst pores, as evident from the brownish colour of the zeolite. On the contrary, the same effect was less relevant in the post-treated catalyst, which substantially kept its activity. In fact, the IR spectrum of the used untreated catalyst showed bands at 1775 and 1800 cm^{-1}, which

are attributable to C=O moiety-containing organics. We tried to regenerate the catalyst treating it at 400 °C for 3 h in flowing air but it did not lead to a complete recovery of the catalytic activity. The accumulation of organic compounds with the untreated catalyst may once again be attributed to difficulties in the diffusion of reactants, a phenomenon which might facilitate consecutive reactions to heavier compounds.

However, we thought also that another possible reason for deactivation is a small (but non-negligible) leaching of Na, which was investigated by AAS. Both in solvents used for the analytical measurement and in solutions after reactions, atomic absorption analyses were carefully performed to determine the Na concentration in reactants, with the aim of determining the amount of Na leached during the catalytic reaction. The different Na concentration between the initial solution and the post-reaction one was very low (few ppm), thus close to the analytical error. In fact, Na can be considered an ubiquitous contaminant because traces of this element are always present; thus, we took extreme care to minimize occasional errors.

Due to the insolubility of PE in water, we dissolved our samples in 2-propanol (Sigma-Aldrich), because of both its chemical-physical characteristics and its very low Na content. The procedure for the analysis was the following: (a) 50 µL of sample (either the reactant, or the reaction mixture after reaction) were brought to 5 mL volume with 2-propanol; (b) the sample was then analysed with a SpectraA-100 Varian instrument, equipped with graphite furnace GTA 110, radiation source Na/K. The line at 330.3 nm was used, instead of the main one at 589.6 nm, because the analysis of the organic solution led to an out-of-range absorption; a further dilution of the solution would have led to a major error in the measurement, and therefore the weaker line was used. A 10 µL sample was injected. The furnace temperature ranged from 75 °C up to 2000°C, with intermediate steps at 85, 95, 120 (solvent removal), and 700 °C

(pyrolysis and incineration of organics). The analysis was carried out using an Ar flow of 3 mL/min. (c) The final Na concentration was obtained after subtracting the Na content from the solvent. For each sample, the analysis was repeated 6 times. Finally, because of the insolubility of Na salts in organic medium, the calibration curve was made by means of an aqueous solution of $NaNO_3$ (500 ppb Na), obtained by dilution of a standard solution (1000 ppm Na); the volume of standard solution injected was 10 µL.

The analysis showed for the untreated zeolite after the first use a residual Na content loss of ca 1.6±0.4 % (relative amount) of the overall Na content, which would correspond to ca 3±1 ppm Na concentration in the reaction medium. The leaching of Na was found to be lower in the case of the treated zeolite, after analysis of Na in the solution; however, due to the difficulties encountered in the analysis for the previous reasons mentioned, and to the experimental error dealt with during these measurements, we cannot assert that the treated catalyst gave no leaching at all.

In order to verify a possible contribution of Na ions leached from the catalyst, we stopped the reaction with the untreated Na-mordenite at about 10% phenol conversion (reaction conditions: T = 210 °C, 0.5 wt% catalyst, phenol/EC 1/2) and filtered off the catalyst, and then went on with the reaction in the absence of catalyst. In Figure 10 are shown the overlapped curves of the PE yield of the two mordenites (after filtration) and the NaOH.

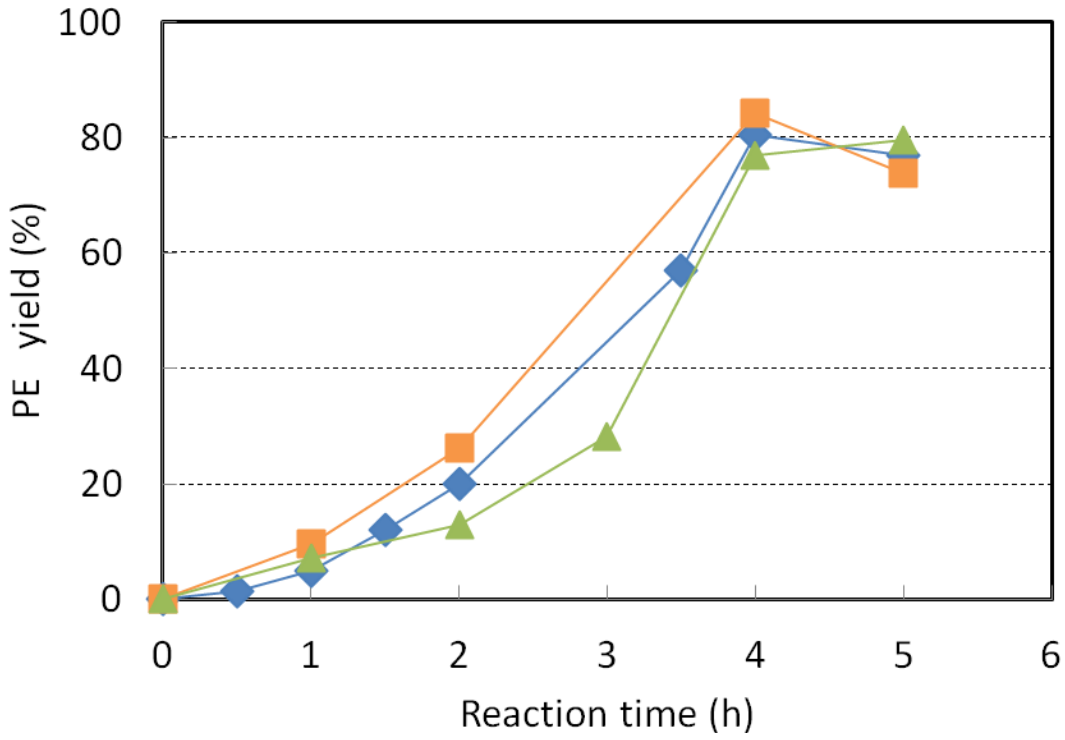


Figure 10 Comparison between PE yields with 3±1 ppm NaOH (◆), after-filtration of untreated Na-mordenite (■), and after-filtration of treated Na-mordenite (▲).

In the case of untreated Na-mordenite, the PE yield in relation to time showed a trend very similar to that obtained when using NaOH (a few ppm) as the catalyst, shown in Figure 8 (bottom). Although the interpretation of data was also conditioned by the autocatalytic effect of the PE (which was present in the filtered solutions, although with a yield of just 10%), this result demonstrated that also the leached Na may contribute to the catalytic behaviour seen.

When the same experiment was carried out with the treated catalyst, the reaction rate after catalyst filtration was slower than that shown both by the Na (3 ppm) catalyst and after filtering off the untreated Na-mordenite; after 2 h reaction time, the rank for PE yield was the following: solution after filter-off of the untreated Na-mordenite, 26% > fresh solution with 3 ppm Na, 20% > solution after filter-off of the

treated Na-mordenite, 12%. However, the difference between the three solutions was decreased after 4-5 hours reaction time, because of the autocatalytic effect due to PE. The lower leaching of Na shown with the treated catalyst may again be related to a quicker diffusion of reactants which limits the chemical interaction between acidic molecules and basic sites.

The better performance of the treated catalyst evidenced that Na-mordenite with controlled porosity may overcome problems related to hindered diffusion, with reduced induction time, less deactivation, and improved catalyst recyclability. As shown in Figure 5, the amount of catalyst affected the catalytic behaviour. Therefore, we repeated some experiments by using increasing amounts of the treated catalyst (0.5 wt% and 5 wt% in respect to the phenol fed), in order to optimise both the conversion rate and the yield to PE. The reaction conditions were again a phenol/EC ratio equal to 1/2, and a reaction temperature of 210 °C. The results (see Figure 7) show that the conversion and yields to products depend on the reaction time with 0.5 and 5 wt% of the treated catalyst. With the latter catalyst, and in conditions where phenol is the limiting reactant, 98% conversion of phenol was obtained after 5 h reaction time, while, employing only 0.5 wt% catalyst, 7 h were required. Remarkably, in the first case the yield to PE was 86% (with 12% BPEC and 2% DPE), while in the latter one the yield to PE was 82% (14 % BPEC, 2% DPE). The experiment with 25 wt% catalyst led to complete phenol conversion in 5 h reaction time, but selectivity to PE was only 75%, with 6% BPEC and a high yield to DPE+TPE (19%). Regarding the conversion of EC, in the two cases with low amount of catalyst, it was close to 50% (which means that a negligible amount of EC was wasted into by-products), whereas in the case with 50 wt% catalyst the conversion was 90%, evidencing an important contribution of EC decomposition. Overall, the

optimized conditions with the best catalyst were T= 210 °C, 5 wt% catalyst and phenol/EC molar ratio 1/2; with these reaction conditions, the induction period shown was 1 h only.

We think that the microporosity affects the start-up of the reaction, and considering that the mesopores are also present in the untreated Na-mordenite, we can hypothesize that in the presence of the smaller pores a higher degree of reactants retention, both phenol and EC, leads to a greater transformation of EC into heavy compounds, which may partially block both smaller and larger pores, thus retarding diffusion and counterdiffusion. Finally, the obstruction may delay the initiation of the reaction between the reactants. This hypothesis was also confirmed by the experimental evidence that the untreated Na-mordenite soon became brown even in the presence of EC only, because of the formation of polymeric compounds.[38] Conversely, this phenomenon was much less relevant in the case of the treated zeolite.

Homogeneous vs heterogeneous catalysis

Under our reaction conditions, the use of a heterogeneous catalyst evidenced problems such as a much lower TOF (3 ppm NaOH are enough to catalyse the reaction more efficiently than 5 wt% Na-mordenite), and diffusional limitations which, however, can be solved by a proper catalyst modification. Overcoming these problems leads to better activity, with shorter induction time (not observed with the homogeneous catalyst), increasing catalyst reusability, and negligible Na leaching. On the other hand, Figure 11 shows that the most important improvement concerned the selectivity to PE achieved with the optimal heterogeneous catalyst, under conditions which make it possible to minimize the parallel EC decomposition.

The Figure shows the selectivity to both PE and PE + BPEC for the treated Na-mordenite (at 0.5 and 5 wt% catalyst loading), and for the homogeneous NaOH catalyst. The best selectivity was achieved with the zeolite. This difference is lower if the comparison is made with the untreated Na-mordenite catalyst, probably because of the contribution of the homogeneous reaction due to Na leached. This also demonstrates that with the treated catalyst the reaction occurred, at least in part, within the zeolite mesoporosity, limiting the formation of bulk by-products and providing a higher selectivity to PE at very high phenol conversion.

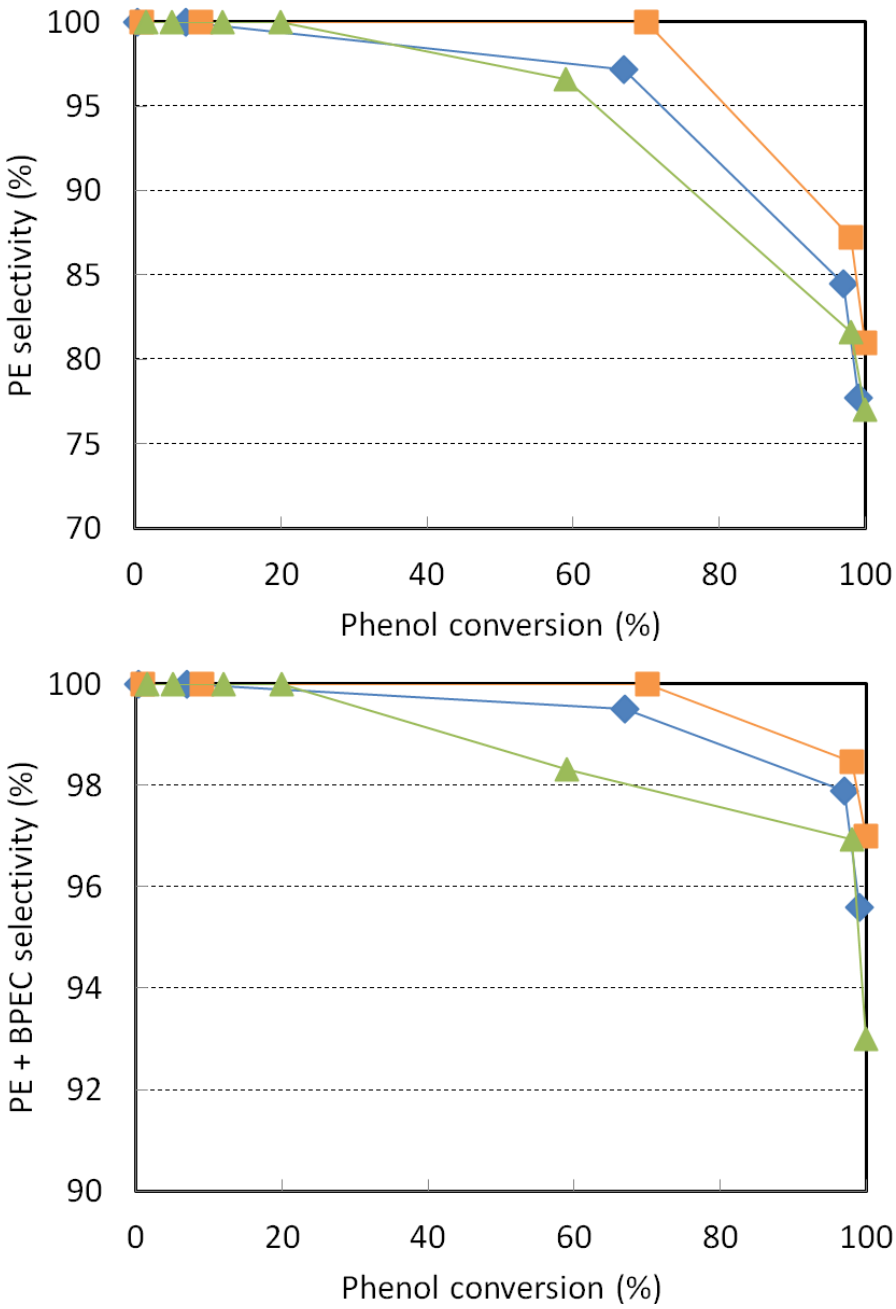


Figure 11 Selectivity to PE (top) and to PE + BPEC (bottom) in relation to phenol conversion at 210 °C, phenol/EC molar ratio 1/2, and variation of reaction time. Catalysts: treated Na-mordenite 0.5 wt% in respect to phenol (◆), 5 wt% in respect to phenol, (■), and NaOH 3±1 ppm (▲).

CONCLUSIONS

We investigated the synthesis of PE by reacting phenol and EC, under both homogeneous (NaOH) and heterogeneous (Na-mordenite) catalytic conditions, without any solvent, as an alternative to the current industrial process, which employs ethylene oxide. We also found that an outstanding selectivity to PE and BPEC of over than 98% could be achieved at 98% phenol conversion. Total selectivity was shown only under conditions at which phenol conversion was about 60%, because ethylene carbonate was the limiting reactant. By the way, BPEC could be easily separated and transformed with 100% yield to phenoxyethanol.

The Na-mordenite heterogeneous catalyst proved to be reusable and to cause a negligible Na leaching; however, in order to do that it had to undergo a post-synthesis treatment which decreased the micropore volume.

Unfortunately, few ppm of Na were enough to catalyse the reaction, so a contribution to reactivity derived from a minimal amount of Na released (although below the detection limit of the analytical method used), even with the treated catalyst cannot be completely ruled out. Even so, the heterogeneous catalyst provided a higher selectivity than that achieved with the homogeneous NaOH catalyst. Moreover, the post-treated Na-moredenite showed a shorter induction period with respect to the untreated one.

An autocatalytic effect was observed; it was explained by considering the stronger basicity of the deprotonated form of 2-phenoxyethanol compared to the phenate.

Finally, even though our process requires an additional step (the production of EC by reaction between ethylene oxide and carbon dioxide), a very similar technology is also employed in the new Omega

process for the production of ethylene glycol (MEG), developed by Shell. Indeed, MEG is produced by first reacting ethylene oxide with CO_2 to produce EC, which is then hydrolyzed to MEG. The advantage of this process, compared to conventional ethylene oxide hydrolysis, is the final better selectivity to MEG. The same occurs in our process, which reaches a higher final selectivity to PE achieved using EC compared to that achieved employing ethylene oxide as co-reactant for phenol.

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SYNTHESIS OF HYDROXYTYROSOL

INTRODUCTION

Hydroxytyrosol (3,4-dihydroxyphenylethanol, DOPET) is the most powerful natural antioxidant currently known. It can be found in leaves and fruits of olive, extra virgin olive oil and it is particularly abundant in olive oil mill wastewaters from where it can be recovered. Hydroxytyrosol is a metabolite of oleuropein (Figure 1), another major phenolic component of olive products; they both give to extra-virgin olive oil its bitter and pungent taste. Well-documented studies confirm its anti-inflammatory, antibacterial, antioxidant health benefits, its anticancer (fat-related) activity, it improves the quality of life for osteoporosis patients and, mainly, it reduces heart disease pathogenesis.[1]

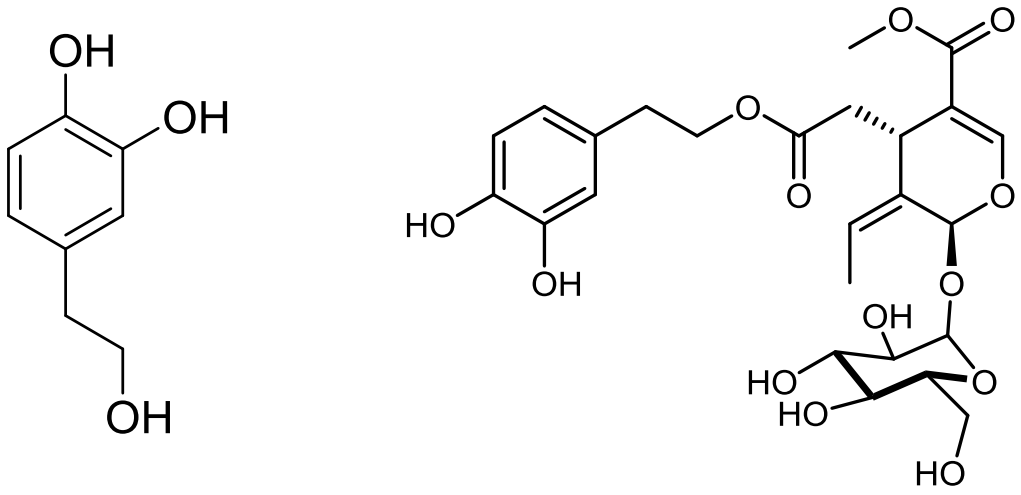
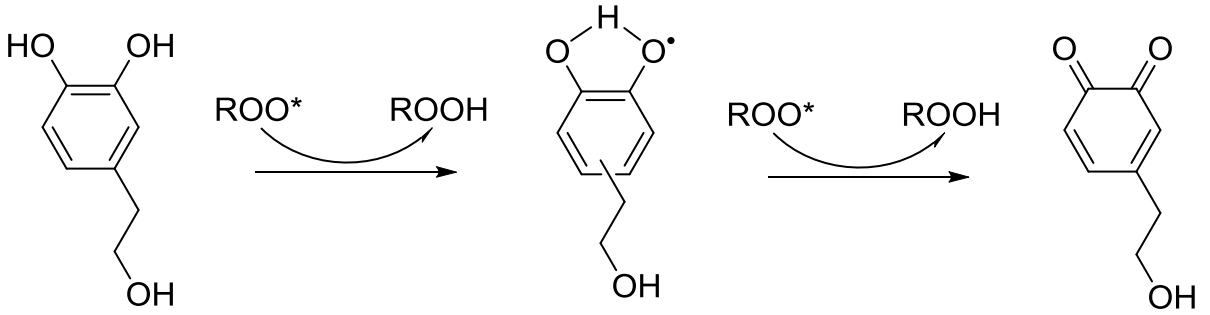


Figure 1 Structures of hydroxytyrosol and oleuropein.

Although still relatively new to most people, hydroxytyrosol promises to soon become a staple in natural health care.

More active than antioxidant vitamins and synthetic antioxidants, hydroxytyrosol exerts its antioxidant activity by transforming into catechol. The antioxidant properties of the *o*-diphenols are associated to their ability to form intramolecular hydrogen bonds between the hydroxyl group and the phenoxy radical; therefore, the catechol avoids the chain propagation by donating a hydrogen radical to alkylperoxyl radicals (ROO·) formed in the initiation step of lipid oxidation (Scheme 1).[1]



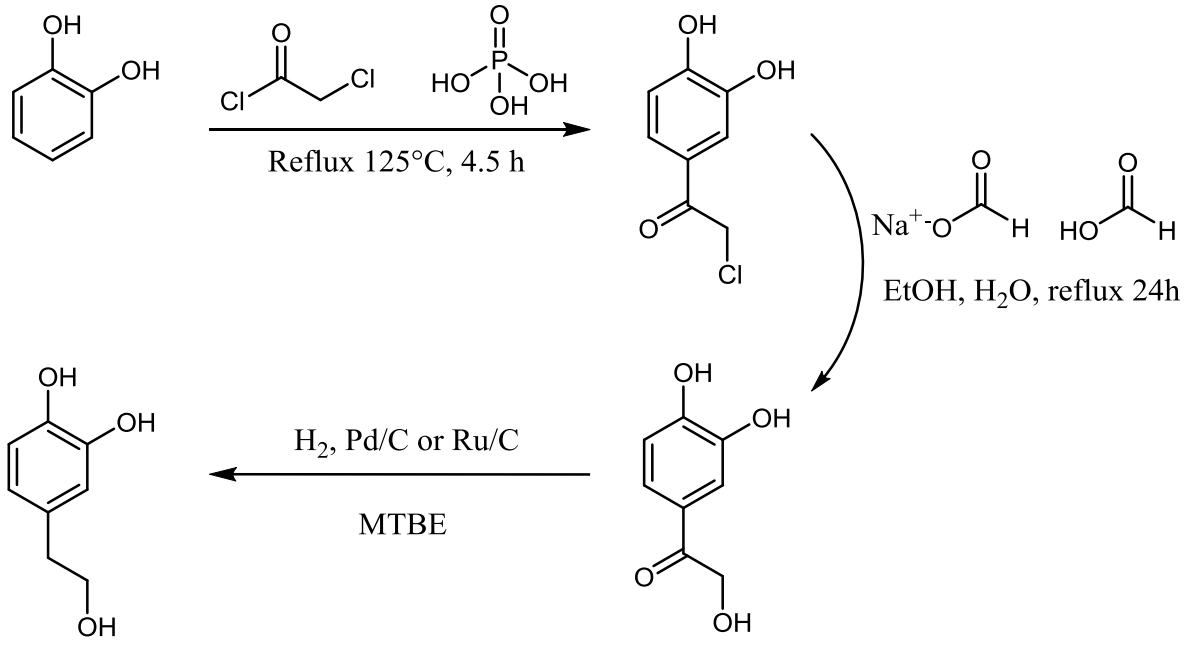
Scheme 1 Antioxidant mechanism of hydroxytyrosol.

Moreover, hydroxytyrosol is an amphiphilic molecule (log *P*= 0.02), so it is rapidly absorbed into the bloodstream and tissues, where it can perform its free radical scavenging duties. It is the only phenolic compound that is able to cross the blood-brain barrier, which allows it to also absorb free radicals throughout the central nervous system. It is also a metabolite of the neurotransmitter dopamine, which means it may play a role in neuroprotection. Therefore, hydroxytyrosol is employed in food (stabilizer for vegetable oils, beverages, margarines, yogurts, etc.), pharmaceutical (supplements) and cosmetic industries (sun screens, lotions, shampoos, deodorizers etc). It is not surprising that many chemical efforts have been made to collect pure hydroxytyrosol, either by synthesis or from natural sources.[2]

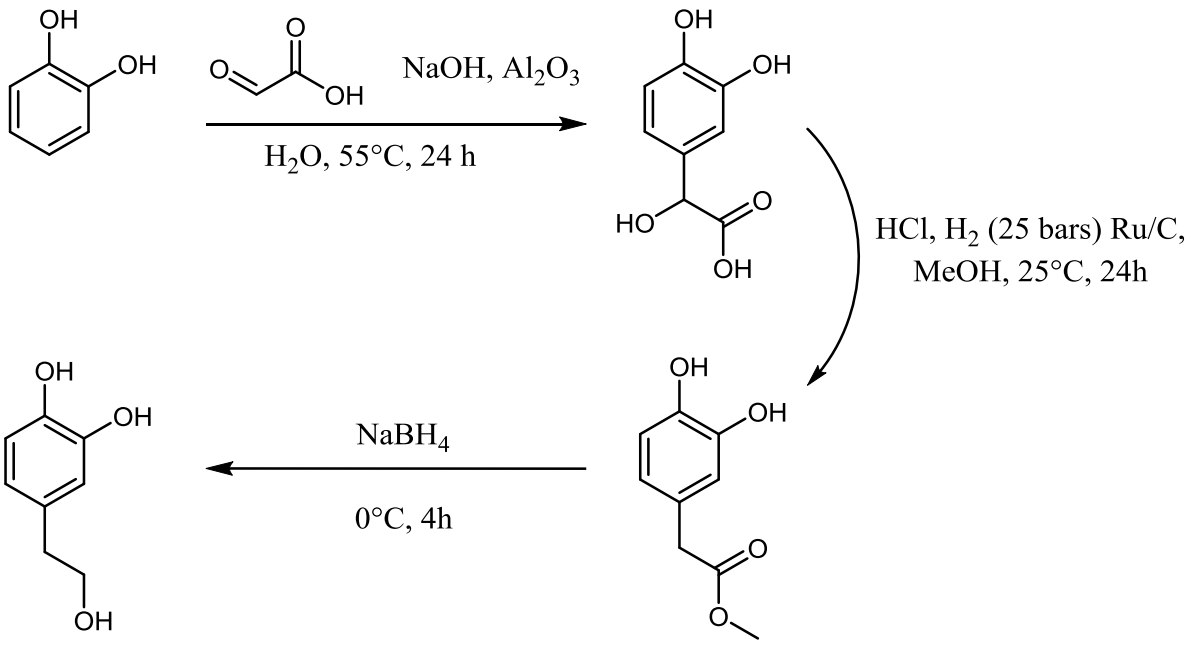
There are several synthetic approaches but they have important disadvantages because they are generally based on simple reduction of commercial 3,4-dihydroxyphenylacetic acid (or the corresponding methyl ester, or the mono/bis methoxylated catechol derivatives) using halogenated reactants and stoichiometric reductants ($NaBH_4$ or $LiAlH_4$). Other examples starts from tyrosol (or derivatives such as homovanillyl alcohol) but this is a highly costly reactant and a two step IBX-oxidation/$Na_2S_2O_4$-reduction is necessary. More recently, commercially available 3,4-dihydroxybenzaldehyde was used as starting material, but again it is not a cheap reactant and a multi-step reaction is required, employing also halogenated reactants/solvents.[3]

There are several patents: some use expensive starting materials (such as tyrosol and derivatives)[4] or carcinogenic reactants (such as epoxides derivatives,[5] safrole[6]). There are examples of total synthesis of hydroxytyrosol starting from cheaper materials (such as catechol), but again the problems are related to multi-step reactions, the use of halogenated reactants (which release HCl) and stoichiometric reductants.[6,7,8]

Here two examples taken from DSM patents are shown.[7,8]



Scheme 2 DSM patent for the synthesis of hydroxytyrosol.



Scheme 3 DSM patent for the synthesis of hydroxytyrosol.

Of course they employ cathecol which is a cheap reactant, but, in the first case, they use also halogenated reactants while, in the latter one, homogeneous catalysts (NaOH and HCl) and stoichiometric reductants were used. In both cases, the process needs three steps and purifications after each step.

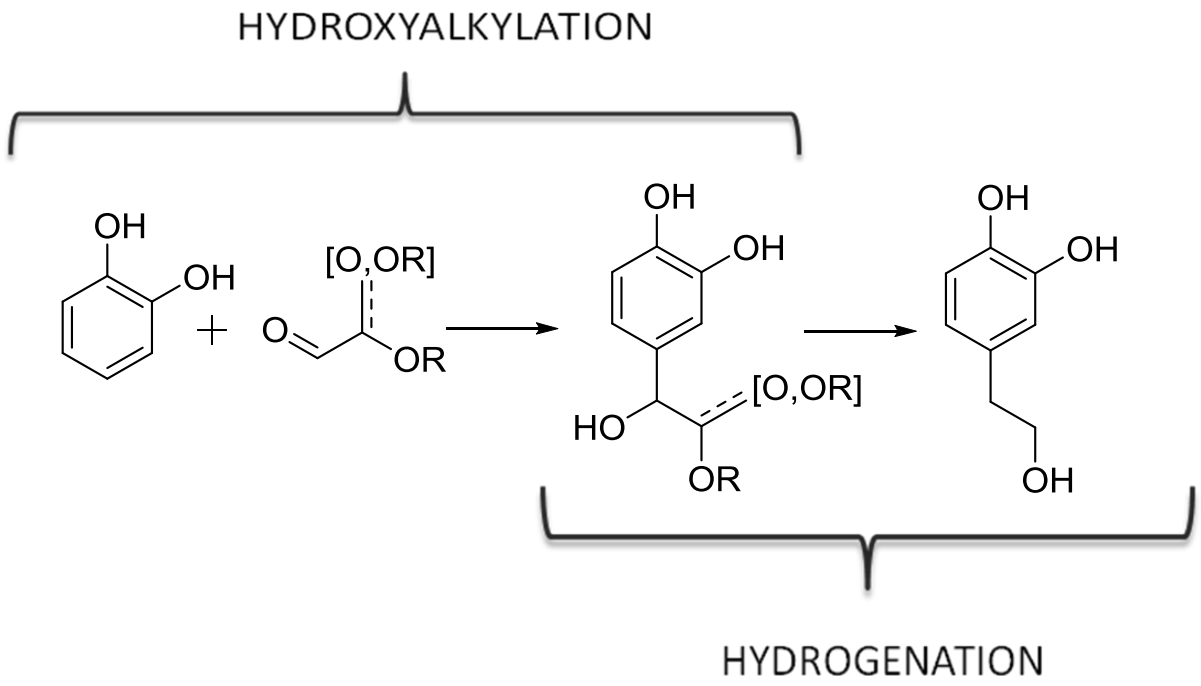
At last, there are examples based on enzymatic treatments of natural sources, such as oleuropein or tyrosol-containing wastewaters originated from olive processing.[9,10]

Nowadays the only way to obtain hydroxytyrosol at an industrial scale is by means of extraction (or in some cases by membrane filtration) from wastewater of olive oil production. The more relevant issues are the low extraction yield, the use of large amounts of organic solvents (such as hexane, ethyl acetate) and the several (and expensive) steps of purification.[11,12]

However, none of the above-mentioned processes provides hydroxytyrosol in high amount and purity or the processes are very expensive.

OUR AIM

Our aim was to develop a two-step reaction starting from cheap reactants, avoiding halogenated or stoichiometric reductants, and using only water as solvent.



Scheme 4 Design of our two-step process.

The idea behind the new process is to hydroxyalkylate the catechol with an oxygenated C2 compound to obtain the corresponding para-substituted product. The second step is the one-pot hydrogenation of this intermediate to hydroxytyrosol using H_2 as reductant and a metal supported catalyst.

RESULTS

PRELIMINARY TESTS: HYDROXYALKYLATION

The hydroxyalkylation is a well-known reaction: this is also the first step for the industrial production of vanillin. As described in literature,[13] the reaction of guaiacol and sodium glyoxylate is carried out in presence of NaOH (0.5 equivalents respect to the guaiacol) in water. So we took this example as the starting point for our study.

Initially, instead of using catechol, we decided to start with guaiacol because it facilitated the reaction work-up and the chromatographic purification of the products.

We carried out several qualitative tests in order to screen which reactants and reaction conditions were the most promising. The reactions were usually followed by TLC and NMR.

The first issue was the choice of the oxygenated C2 compound for the hydroxyalkylation and we tested the reactivity of glyoxylic acid, glyoxal and 2,2-dimethoxyacetaldehyde (Figure 2).

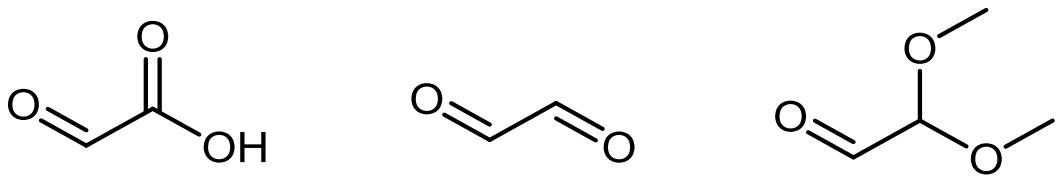
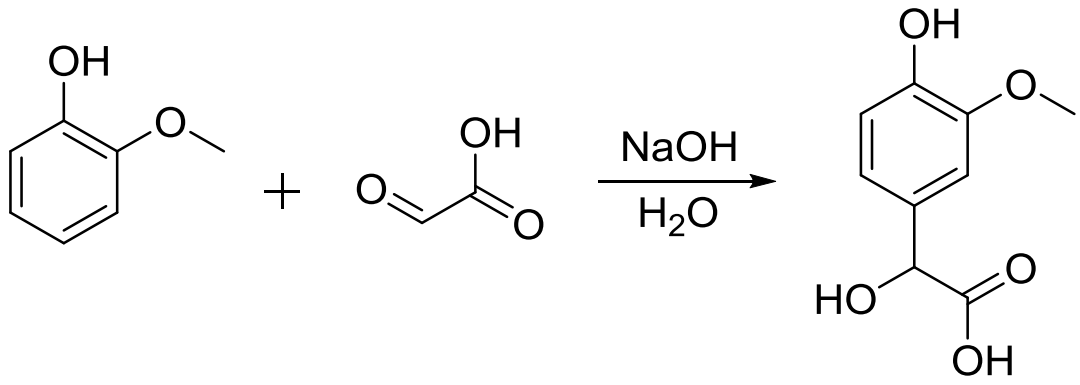


Figure 2 Structures of glyoxylic acid, glyoxal and 2,2-dimethoxyacetaldehyde.

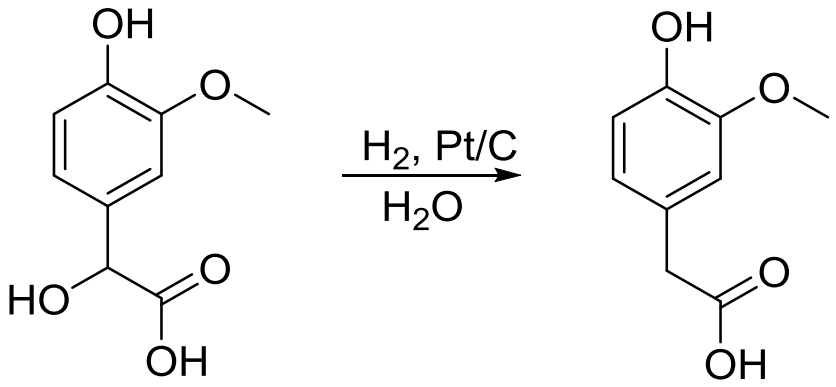
Glyoxylic acid

We followed the previously mentioned patent for the synthesis of the mandelic derivative: global molar feed ratio of guaiacol : glyoxylic acid : NaOH = 1 : 0.5 : 1, in water at 40 °C for about 5 h. We obtained the desired product with good yield (48% by NMR) and we purified it by means of a chromatographic column.



Scheme 5 Reaction between guaiacol and glyoxylic acid.

The problem was the hydrogenation step: we loaded the mandelic derivative in the autoclave carrying out the reduction in water at 150 °C, 5 bar H_2, in presence of Pt catalyst (10%w/w carbon supported) for 7 hours, but this was not enough to reduce the carboxyl group. We only obtained the hydrogenolysis of the benzylic hydroxy group (almost 100% yield by ^{1}H-NMR), even carrying out the reaction in acetic acid for 3 days.

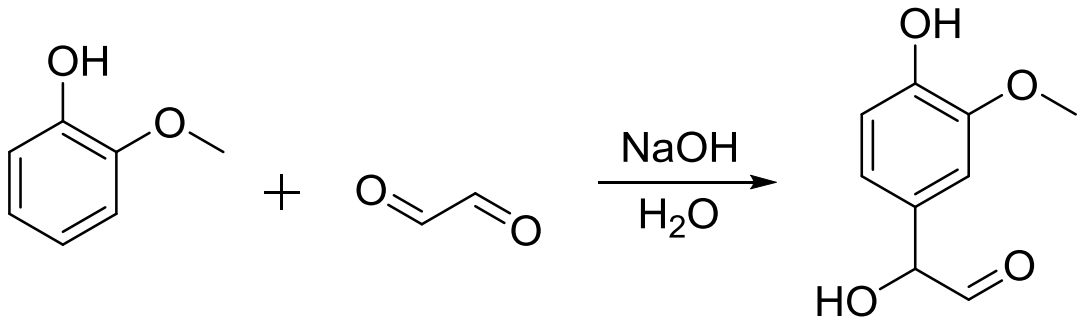


Scheme 6 Reduction of the guaiacol mandelic derivative.

This allowed us to understand that very drastic reduction conditions are necessary and we decided to continue testing the other reactants.

Glyoxal

Amongst the oxygenated C2 compounds used, glyoxal is the cheapest one and the product that should form is the closest to hydroxytyrosol.

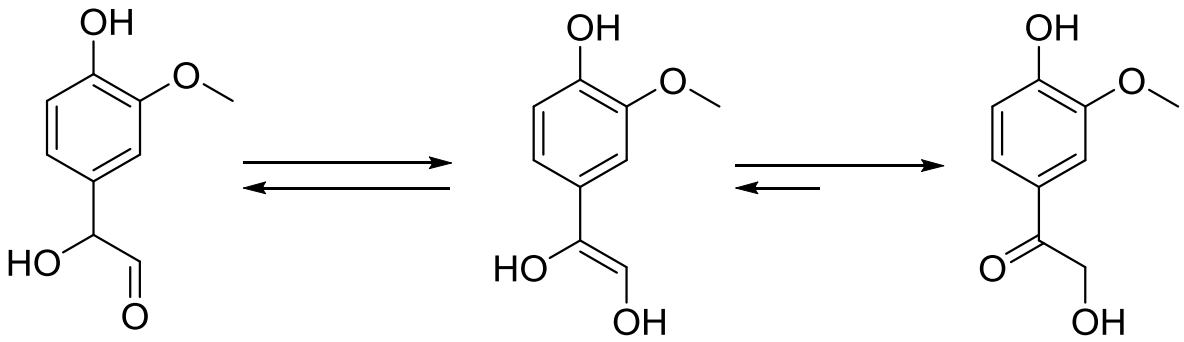


Scheme 7 Reaction between guaiacol and glyoxal.

For these reasons, we investigated this reactant more in depth. We tested several reaction conditions, chancing the guaiacol : glyoxal molar feed ratio

(1:1 – 1.5:1 – 2:1 – 4:1 – 1:10 – 1:8), the temperature (from room temp to 100 °C), the reaction time, and the amount of NaOH. We also tested other catalysts such as Na-mordenite, H_2SO_4, H-mordenite, but in all cases we did not exceed the 4% yield to the desired product.

The major product obtained was the hydroxyketone derivative (see Scheme 8) and a little amount of the desired product. We hypothesized the formation mechanism of this new product (confirmed only at a later stage).



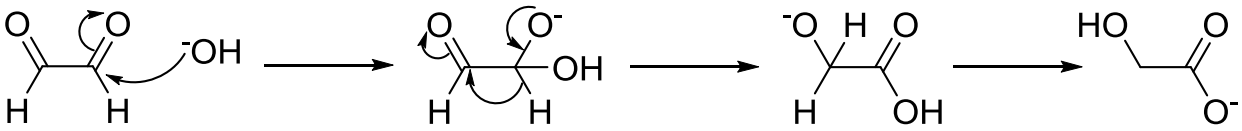
Scheme 8 Tautomeric equilibrium between hydroxyketone and hydroxyaldehyde derivatives.

A double tautomeric equilibrium occurred switching the aldehyde to the ene diol and finally to the ketone. This ketone derivative is a molecule more stable with respect to the starting aldehyde because the carbonyl group is now conjugated to the aromatic ring, making it the more favored product. It could form during the reaction, but since the tautomeric equilibrium is better catalyzed by acids, it might form even during the work-up (to extract the products in chloroform we usually acidified the reaction mixture to pH=5), moreover the silica used for the chromatographic purification could push the equilibrium towards the ketone derivative.

By the way, obtaining either the ketone or the aldehyde did not make much difference; the most important problem is that we usually obtained 2-4% of

lumped yield to the two compounds (in any case, not higher than 10%), although the (normalized) conversion of guaiacol generally spanned from 30 to 50%. This means that heavy products were formed; for example, we found by GC-MS a compound with m/z = 304 which could be a dimer made of two molecules of guaiacol linked by one molecule of glyoxal.

One further problem is that the glyoxal underwent an intramolecular Cannizzaro reaction (Scheme 9).



Scheme 9 Intramolecular Cannizzaro reaction mechanism in basic aqueous solution of glyoxal.

As reported in literature,[14,1516] this reaction occurs very quickly in aqueous medium at 40 °C adding NaOH, like an acid-base titration. This side reaction was confirmed monitoring the pH of the reaction mixture, which, in 3 h, decreased from 9.5 down to 6.5. We tried also to add the glyoxal during time (generally 4 hours and then one hour of digestion) to minimize the glyoxal disproportion, but also this did not work.

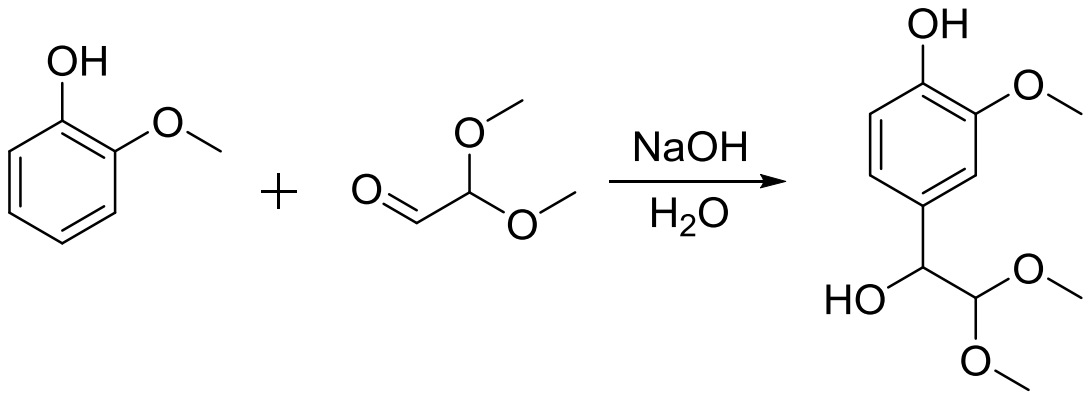
In order to avoid the Cannizzaro reaction, we decided to use acid catalysts, such as H_2SO_4 and H-mordenite SAR 15, but in this way we obtained several products (most of them not identifiable) and the glyoxal also formed oligomers (in some cases the reaction mixture became slightly gelatinous).

2,2-dimethoxyacetaldehyde

The 2,2-dimethoxyacetal (DMA) was chosen because it has the aldehydic group which is suitable for the hydroxyalkylation, while, in basic aqueous solution, the acetal group is stable and cannot react forming by-products. Another important advantage is that the intramolecular Cannizzaro cannot occur.

This reactant can also be easily prepared by reacting glyoxal dissolved in alcohol (in this case methanol) in the presence of an acid catalyst (which could be either homogeneous or heterogeneous). The major product obtained is the mono-acetal (about 70% yield) which is distilled from the crude of reaction;**Errore. Il segnalibro non è definito.** the other product is the bis-acetal (30% yield) which can be recycled and reacted with a stoichiometric amount of glyoxal for the transacetalization in order to form again the mono-acetal.

The first reaction was carried out with a molar feed ratio guaiacol : DMA : NaOH = 1 : 0.5 : 0.5 (concentration of guaiacol 0.4 M), 10 mL of water; the DMA was added dropwise in two hours, while the temperature went from 20 to 45 °C. After 15 hours reaction, the results were very satisfactory: we obtained only two products (the para and the ortho isomers, see Scheme 10), the conversion of guaiacol was about 50% (almost complete with respect to the theoretical value) and the sum of yields to the products was about 45% (almost the maximum achievable). Conversion and yields were calculated after separation with a chromatographic column. We also noticed that the pH decreased from 10.05 to 9.65 only.



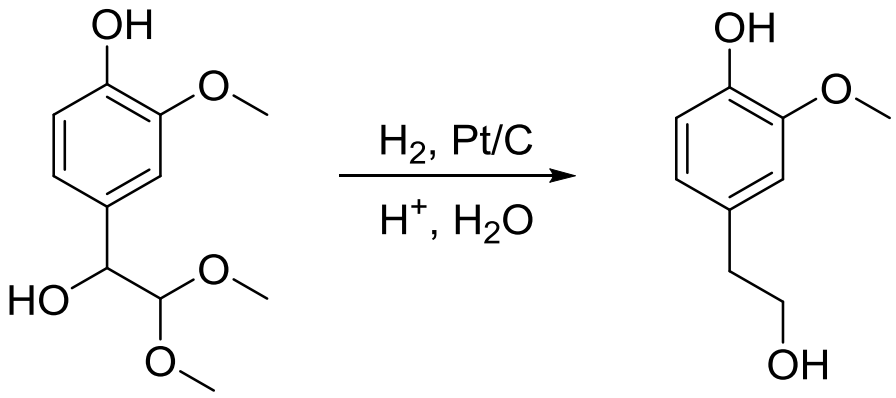
Scheme 10 Reaction between guaiacol and 2,2-dimethoxyacetaldehyde.

After a brief qualitative optimization of the reaction conditions (reaction temperature increased up to 80 °C and reaction time reduced down to 6-7 h), we started with some reduction tests of the *p*-hydroxyacetal guaiacol derivative.

PRELIMINARY TESTS: HYDROGENATION

Before starting with detailed kinetic and optimization studies for the hydroxyalkylation, it was necessary to carry out some preliminary hydrogenation tests in order to have some evidences that the catechol hydroxyacetal could be reduced to hydroxytyrosol.

The reactions were generally carried out loading in an autoclave 75 mg of para-hydroxyacetal guaiacol derivative, 25 mg of Pt (5% w/w carbon supported), 30 mg of acetic acid, 10 mL of water. The temperature was set at 150 °C and the hydrogen pressure at 6 bars for 7 h reaction.



Scheme 11 Reduction of the guaiacol acetal derivative to homovanillyl alcohol.

The products were purified by chromatographic column and analyzed by NMR: the major product was the desired one, the guaiacol derivative of the hydroxytyrosol (Scheme 11); the second product was the hydroxyketone derivative (see Scheme 8) and, finally, we also found a little amount of unreacted starting material.

This first result was very satisfactory and we decided to transfer the accumulated knowledge from the guaiacol to the catechol and to carry out a

brief screening of reaction conditions. With these tests we found and identified a by-product, the 4-ethylcatechol (EC, see Figure 3), probably due to over reduction of the hydroxytyrosol.

We also found that increasing the temperature from 90 °C to 150 °C it was possible to push the equilibrium from the hydroxyketone derivative to the hydroxytyrosol, even if we decreased the hydrogen pressure from 3.3 to 1 bar. Moreover, replacing platinum with palladium, while using the same reaction conditions (150 °C, 1 bar H_2, 7 hours), there were no traces of the hydroxyketone, which was converted to hydroxytyrosol (and a minor amount of 4-ethylcatechol).

All these qualitative tests and data allowed us to start with an intense quantitative work for both reaction steps. Therefore we developed an HPLC method (the instrument was equipped with Kinetex 5µm EVO C18 100A column, 100x4,6 mm, with UV detector set at λ=270 nm) which, moreover, allowed us to notice other reaction products (Figure 3) and, cross-checking data from HPLC and NMR analysis, we outlined all the products of the reduction step.

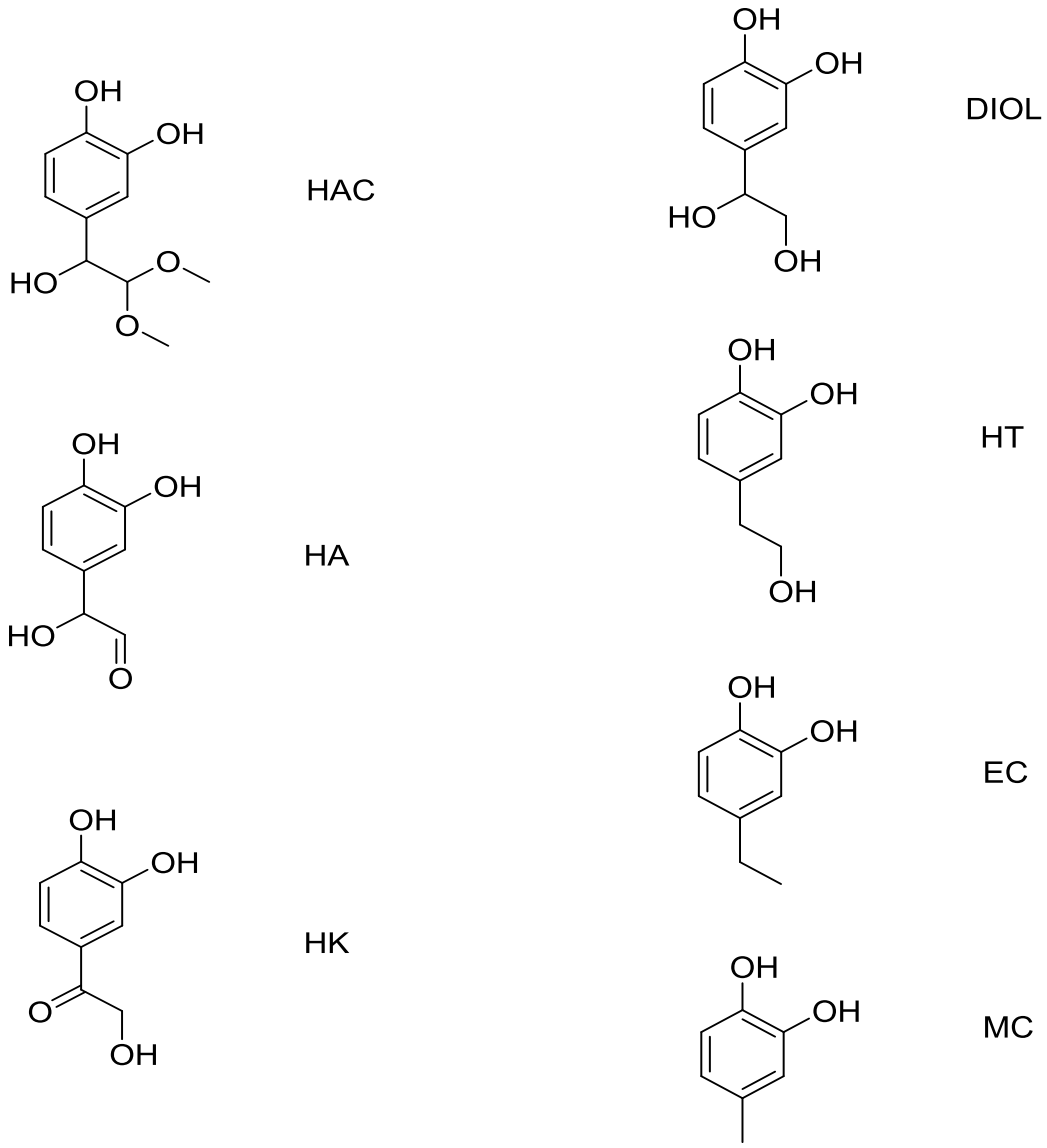


Figure 3 Structures of catechol derivative (HAC) and reaction products (HA, HK,DIOL, HT, EC, MC).

PROCESS OPTMISATION

HYDROXYALKYLATION: *catechol to catechol hydroxyacetal derivative*

In this chapter I report a study on the hydroxyalkylation of catechol with DMA. Generally, the reaction solvent was water, but also employing organic solvents we obtained very interesting results.

The reactions were carried out in 5 mL close cap vials and generally the amount of reactants were 130 mg of catechol, 98 mg of DMA solution (60% w/w in water), 23 mg of NaOH, 1.8 mL of water.

In some cases we had a lack in mass balance, but this was due to problems during the sampling of the "time zero"; in fact we did not notice any by-products (except for the ortho-hydroxyacetal) during and at the end of the reaction (despite the crude reaction was analyzed by both HPLC and NMR). For this reason, the selectivity reported is calculated based on yields sum and not on conversion.

We started the screening at low temperature, reacting for 2.5 hours at 40 °C and then 60 °C (or directly at 60 °C for a total of 23.5 hours). The selectivity was consistent with the previous tests (or even better with a molar feed ratio of catechol : DMA : NaOH = 1: 0.5: 0.5), but even at 23.5 h the reaction was not complete. We decided to move to 80 °C and study the influence of the ratio between reactants (Table 1); at this temperature the reaction was complete in 5-6 hours (except for experiment D110) which is an acceptable reaction time from an industrial point of view.

We noticed that the amount of NaOH influences the products distribution: independently from the amount of DMA used, feeding 0.5 equivalent (or less) of NaOH (with respect to the catechol fed), the selectivity to the para-hydroxyacetal was constant at 70%. When we fed one equivalent of the base, the selectivity decreased down to 53-60%.

The amount of DMA used, instead, influenced the DMA efficiency, which is the molar percentage of DMA (calculated with respect to the initial amount) which is transformed into the two reaction products. In particular, in order to keep the efficiency high, we had to operate with a defect of DMA; the best compromise between efficiency and an hypothetical industrial production, forced us to work with 0.5 equivalent of DMA (with respect to the catechol fed).

In order to keep the concentration of DMA low during the reaction and to increase the productivity, we decided to feed one equivalent of DMA dropwise in 4 hours and let the crude "digest" for overall 22 h (see experiment D114). Contrary to what expected, the efficiency was 70% only and moreover the reaction time became longer and the reaction was not complete, even after 22 h.

Table 1 List of hydroxyalkylation experiments between catechol and DMA; molar feed ratio, temperature, conversion and theoretical maximum conversion of catechol, yields sum, product selectivity, and DMA efficiency are reported.

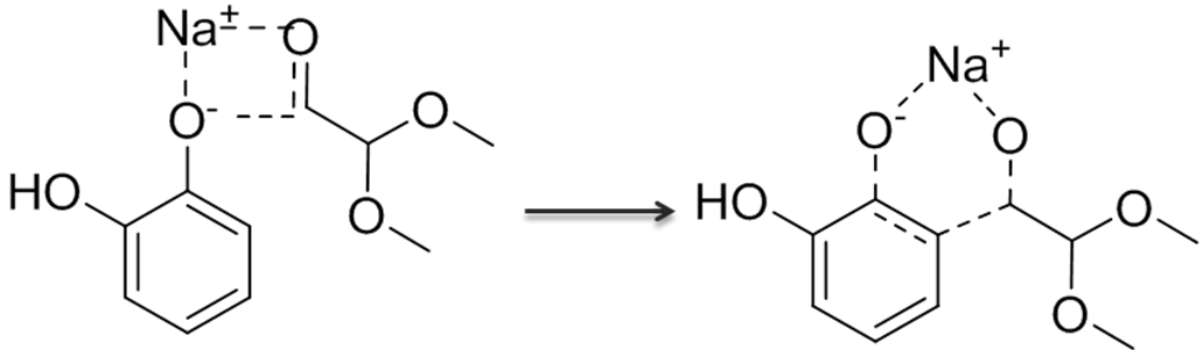
	MOLAR FEED RATIO						**Selectivity (%)**		**Efficency DMA**
	CATECHOL	DMA	NaOH	T (°C)	X	**Σ Y** %	HAC	iso-HAC	%
105	1	1	1	80	75	69	60	40	79
106	1	1	0.5	80	62	52	69	31	65
107	1	0.5	1	80	45	40	53	47	96
108	1	0.5	0.5	80	44	33	69	31	96
109	1	1	1	room	60	40	66	34	65
110	1	0.5	0.25	80	37	27	70	30	79
114	1	1	0.5	80	65	69	69	31	70
117	1	1	1	40-60	70	67	65	35	74
118	1	0.5	0.5	40-60	34	32	71	29	69
121	1	0.5	0.5	60	37	37	69	31	79

THE SOLVENT INFLUENCE

Some tests were carried out in organic solvents (Table 2) so, for solubility reasons, we replaced NaOH with NaOMe.

The results showed an opposite selectivity to the two products compared to the experiments carried out in water: using methanol the ortho hydroacetal product showed a selectivity of 82-85% (only 30% was obtained in water); this behavior was even more drastic when we used THF as solvent, reaching a selectivity of 93% to the ortho product.

Similarly to the Kolbe-Schmitt reaction,[17,18,19] we supposed that the reaction proceeded via intermediate alkali metal catechol-DMA complex (see Scheme 12). Of course, this reaction mechanism favours the ortho hydroxyalkylation but this is true in organic solvents, because they cannot solvate the catecholate salt, which can coordinate the aldehydic carbonyl of the DMA allowing the formation of the complex. On the contrary, carrying out the reaction in water, the solvent can now solvate and "isolate" the sodium catecholate, inhibiting the Kolbe-Schmitt mechanism.



Scheme 12 Hypothesis of activation of DMA to ortho hydroxyalkylation by sodium catecholate.

In order to increase the screen/isolation effect of the solvent we decided to increase the ionic strength of water; so we carried out another reaction using salty water (10% NaCl), but the result was worse than the corresponding one realized in pure water (only 60% of selectivity to the para product).

Table 2 List of hydroxyalkylation experiments between catechol and DMA; molar feed ratio, temperature, conversion of catechol, theoretical maximum conversion of catechol, yield sum, product selectivity, and DMA efficiency are reported. The reaction solvent is methanol or THF and the catalyst sodium methoxyde; the solvent of experiment 125 is water with 10 w% of NaCl and the catalyst is NaOH.

	MOLAR FEED RATIO						**Selectivity (%)**		**Efficency DMA**	**Solvent**
	CATECHOL	DMA	NaOMe	T (°C)	X	**Σ Y** %	HAC	iso-HAC	%	
113	1	1	1	Reflux	68	57	18	82	73	MeOH
119	1	0.5	1	Reflux	49	34	18	82	100	MeOH
122	1	0.5	1	60	44	33	15	85	90	MeOH
123	1	0.5	1	80	47	41	9	91	96	THF
124	1	0.5	1	80	45	44	7	93	92	THF
125	1	0.5	0.5	80	43	38	59	41	93	H_2O

How to improve the selectivity?

In order to improve the selectivity to the para compound we thought that, as reported in literature for the Kolbe-Schmitt reaction,**Errore. Il segnalibro non è definito.** KOH might be used. By keeping constant the other parameters of reaction, the result showed the same product distribution as with NaOH but a lower DMA efficiency (about 55%).

Another attempt was to add 0.5 equivalents of Al_2O_3 as reported in literature for the synthesis of mandelic derivatives.[13] The selectivity (70% to para product) and DMA efficiency (100%) obtained were the same of the previously found under the best conditions with NaOH only.

Another strategy to improve the selectivity to the desired product was to form hindered salts of the catechol which do not permit the ortho hydroxyalkylation.

Hindered basic catalyst: alkylammonium hydroxides

The first idea was to employ ammonium hydroxydes, such as tetramethyl- and tetrabutyl-ammonium hydroxide (respectively TMA and TBA). In the first case we did not obtain any improvement in selectivity (still 70% to the para isomer) and moreover the conversion of catechol was not complete, even after 23 h of reaction. Moving to the TBA, we obtained a slight improvement (up to 78% of selectivity, calculated by NMR). In both cases we had problems with the solubility of the hydroxides in water (working in methanol the reactions did not take place) and, during the work up (for example, during extraction with organic solvents or separation with chromatographic column), there was no possibility to separate them from the products because of their amphiphilic feature.

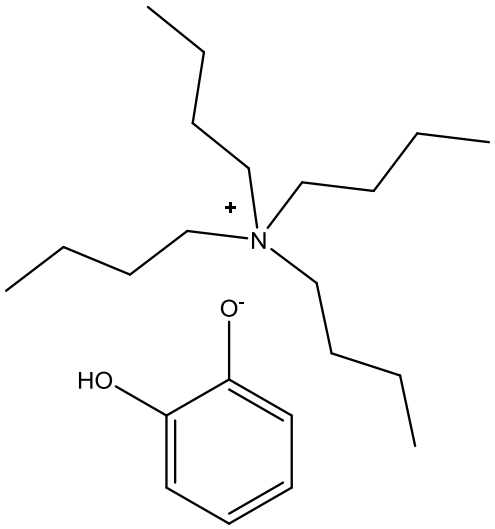
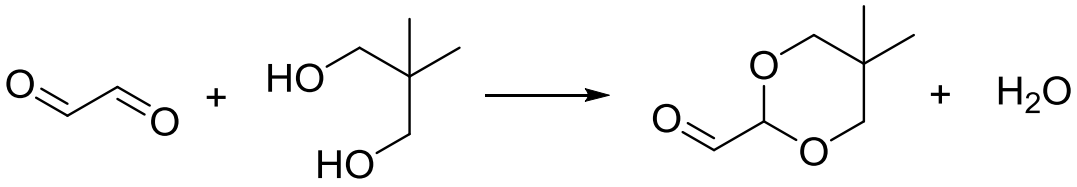


Figure 4 Representation of the tetrabutyl ammonium catecholate, which hinders the ortho position of the aromatic ring.

For these reasons this strategy was abandoned. By the way, we do not exclude that a supported ammonium hydroxide salt (over silica for example) could work well improving the selectivity and drastically simplifying the work-up.

Hindered hydroxyalkylating agent: synthesis of 5,5-dimethyl-1,3-dioxane-2-carbaldehyde from 2,2-dimethyl-1,3-propanediol

Finally we tried another approach to improve the selectivity by employing a more hindered acetal, such as 5,5-dimethyl-1,3-dioxane-2-carbaldehyde from 2,2-dimethyl-1,3-propanediol (DDC, see Scheme 13).



Scheme 13 Glyoxal acetalization with DDC.

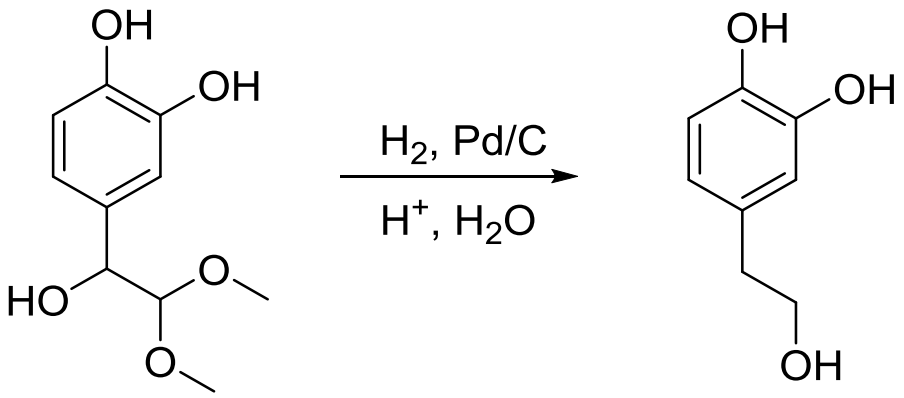
First of all we synthesized this acetal as follows (similarly to what reported in literature[Errore. Il segnalibro non è definito.]): in a 100 mL Dean-Stark system, we loaded 10 g glyoxal solution (40% w/w in water), 6.8 g 2,2-dimethyl-1,3-propanediol, 0.244 g of p-toluenesulphonic acid, 35 mL of toluene and then heated at reflux the mixture for 7 h (7.5 mL of water were collected in the graduate cylinder, about the theoretical amount calculated). After cooling the crude, we added 1.5 g of $NaHCO_3$ and left it under magnetic agitation overnight at room temperature. The day after, we filtered the crude over celite and removed the solvent by rotavapor and vacuum pump. Then we distilled it (using a vigreux column under at about 80 °C at 30 mbar) isolating 0.7 g of DDC (identified by NMR).

Once we had synthesized and purified the acetal, we carried out two reactions in the best reaction conditions found with DMA. In the first one we added 0.9 mL of methanol to facilitate the dissolution of the DDC but the reaction was quite slow and it was complete after about 26 h; we thought that this was probably due to the presence of methanol which did not allow the

temperature to rise up to 80 °C. The second experiment was carried out without methanol and the reaction rate was very similar to the tests with DMA (reaction complete in about 6 h). In both cases the final conversion of catechol was about 40% (the theoretical maximum was 49%) and the selectivity to the para isomer was 75%. These results are not totally reliable because we did not calibrate these new products at the HPLC, so we assigned them the same response factors of the corresponding isomers of the catechol hydroxyacetal (it is plausible to assume this because the two acetals do not have different chromophores). By the way, a slight improvement of selectivity was found, but not as important as we hoped for.

HYDROGENATION: *catechol hydroxylacetal derivative to hydroxytyrosol*

Here an in-depth kinetic and optimization study of the reduction of catechol hydroxyacetal to hydroxytyrosol is reported.



Scheme 14 Reduction of the catechol acetal derivative (HAC) to hydroxytyrosol (HT).

Generally the reaction was carried out in an acetic acid aqueous solution (taken as acid catalyst reference), hydrogen (up to 6 bars) and a metal catalyst supported over carbon. All reactants were loaded in a stainless steel autoclave. The first tests (Figure 5) were carried out with one equivalent of acetic acid, 3 H_2 bars, Pd (10% w/w over carbon, 2.5% mol/mol respect to HAC), at 150 °C. The graph reports the conversion of HAC and the yields of the products.

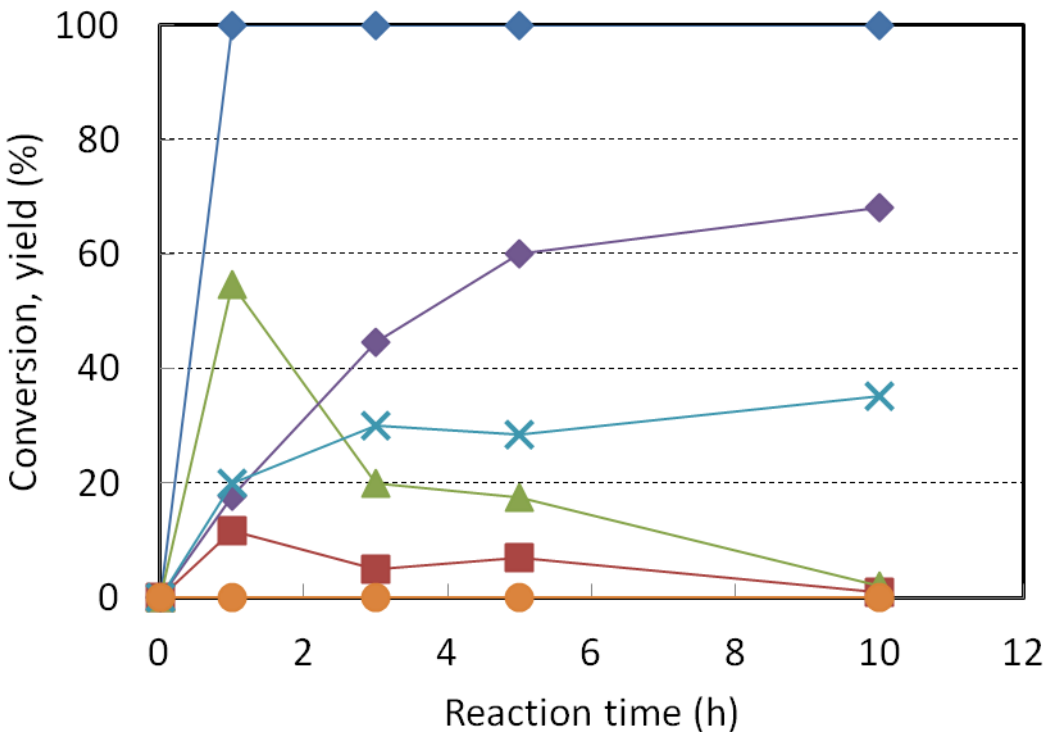


Figure 5 Effect of reaction time on HAC conversion (◆), and yield to HK (▲), DIOL (■), HT (◆), MC (×), and EC (●). Reaction conditions: T = 150 °C; HAC/Pd/acetic acid 1/0.025/1 molar ratio; 3 bars of hydrogen.

After one hour, HAC was completely converted and all the products were already formed (except the 4-ethylcatechol, EC). From the trends we could notice that HK (the major product) and DIOL were reaction intermediates which were completely converted after about 9-10 h. On the contrary, HT and MC increased during time, achieving a yield of about 68 and 35% respectively. Thanks to this first experiment, we had another indication about the reaction pathway because we demonstrated that DIOL was only a reaction intermediate, which probably was consecutive with respect to the HK and then it was reduced to HT.

There was another question open: how can the MC form and why in such high amount?

Comparing the structures of HAC and MC, we hypothesized that a decarbonylation might have occurred. Moreover we found examples from the literature[20] that support our hypothesis.

By the way, in order to demonstrate the decarbonylation, we sampled the atmosphere of the top of the autoclave at the end of the reaction and, by GC-TCD, we indeed found carbon monoxide.

To further demonstrate the decarbonylation mechanism we carried out an experiment at one bar of hydrogen (leaving the other reaction parameters constant): theoretically, decreasing the hydrogen pressure, the release of gas from the reaction mixture (in our case carbon monoxide) should be favoured.

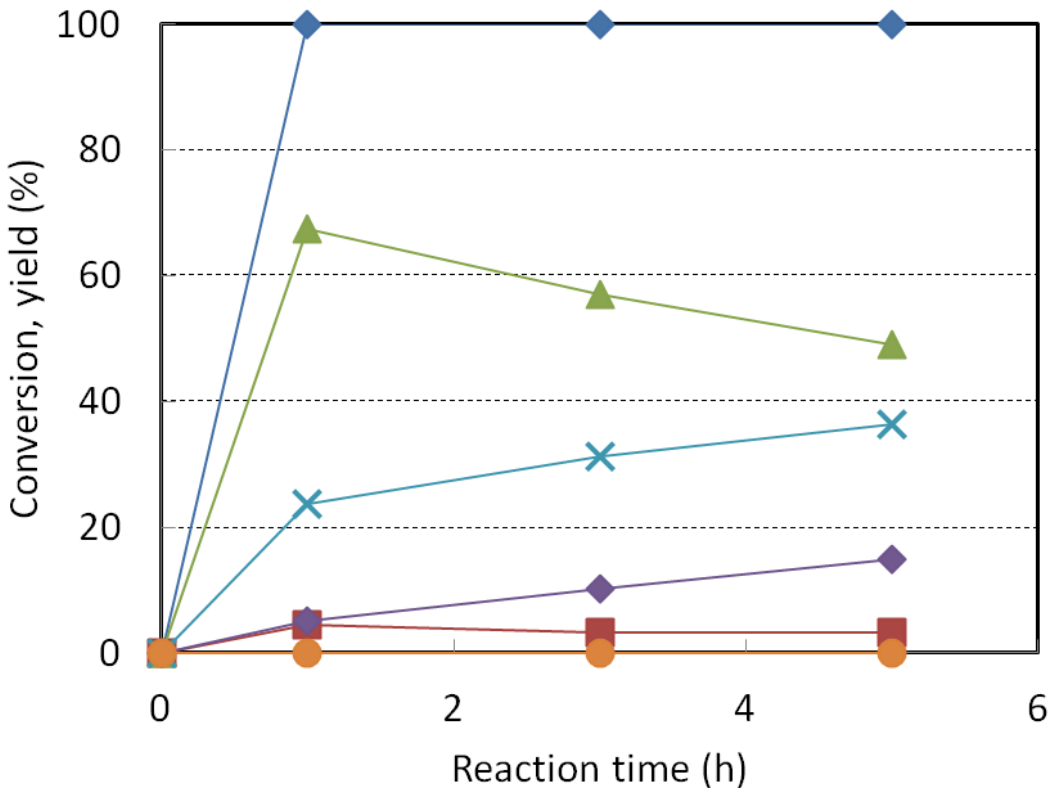


Figure 6 Effect of reaction time on HAC conversion (◆), and yield to HK (▲), DIOL (■), HT (◆), MC (×), and EC (●). Reaction conditions: T = 150 °C; HAC/Pd/acetic acid 1/0.025/1 molar ratio; 1 bar of hydrogen.

Indeed, comparing the new results (Figure 6) with the previous one, in correspondence of the same yield of HK (1 hour for the test at 3 bars H_2 and 5 h for the test at 1 bar H_2), we noticed that at low pressure the yield to MC was about 20% higher and the yield to HT was about 10% lower, with respect to the experiment carried out at 3 bars. This corresponds to very different products selectivity: decreasing the hydrogen pressure the selectivity of MC and HT changed respectively from 40% and 35% to 67% and 27%.

We also carried out the opposite test, increasing the hydrogen pressure up to 6 bars (Figure 7).

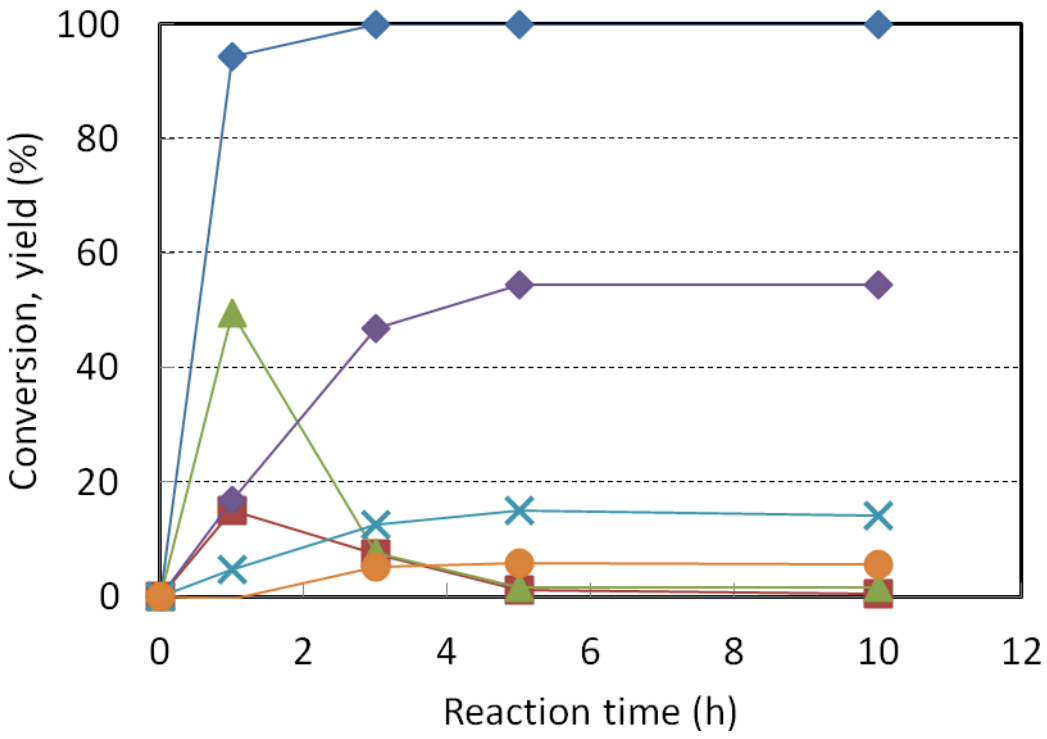


Figure 7 Effect of reaction time on HAC conversion (◆), and yield to HK (▲), DIOL (■), HT (◆), MC (×), and EC (●). Reaction conditions: T = 150 °C; HAC/Pd/acetic acid 1/0.025/1 molar ratio; 6 bars of hydrogen.

The selectivity to HT and MC were 73% and 19% respectively. This improvement was surely due to the higher pressure that disadvantaged the equilibrium towards the carbon monoxide release, but it also accelerated the reduction of the carbonyl to alcohol, removing the reactant for the decarbonylation.

We also noticed that there was a lack in the C balance (about 20%) which still is not understood. This phenomenon occurred also during other experiments at 6 bars (discussed below in this chapter).

By the way, these last tests gave us another important information: when the two reaction intermediates (HK and DIOL) were completely converted, the products distribution did not change anymore. This means that HT is stable and both MC and EC are not consecutive products of HT.

In order to better understand the reaction pathway, we decided to "slow" down the reaction rate, decreasing the temperature down to 90 °C (maintaining one equivalent of acid and 3 bars of hydrogen, Figure 8).

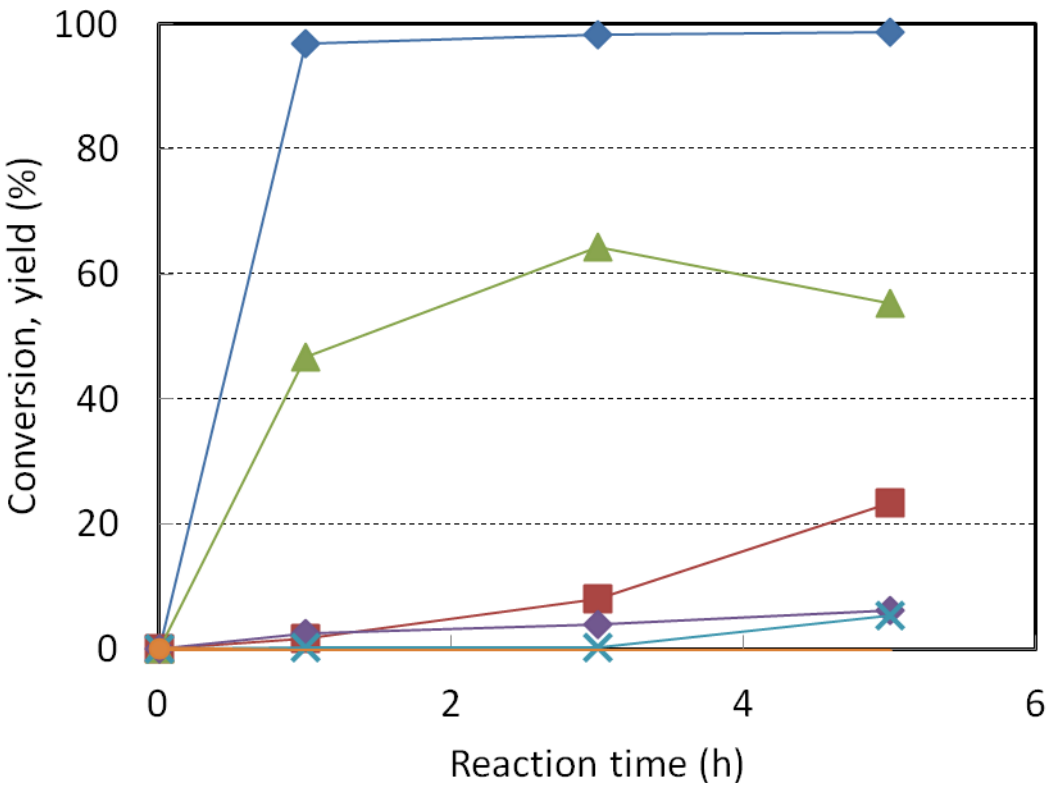


Figure 8 Effect of reaction time on HAC conversion (◆), and yield to HK (▲), DIOL (■), HT (◆), MC (×), and EC (●). Reaction conditions: T = 90 °C; HAC/Pd/acetic acid 1/0.025/1 molar ratio; 3 bars of hydrogen.

Again, HAC was quickly converted and after 1 h reaction the only product was HK; slowly also DIOL and HT started to form. Only when a significant amount of DIOL was formed (about 20% yield), also MC started to form. This could be another indication for the reaction pathway; in other words, MC could be a consecutive product of the DIOL. Moreover, we excluded that MC could form from HK because otherwise it should be present also at the beginning of the reaction, when there was only HK.

We also noticed an important lack in the C balance, particularly at the beginning of the reaction, which decreased during time. So we investigated in-depth this inconsistency and we observed that in the HPLC chromatograms there was another peak, nearly to the dead time (see Figure 9, in correspondence of the red arrow). We noticed that this product decreased

during the reaction time too, so we thought that it might correspond to the hydroxyaldehyde derivative, HA. To demonstrate this, we carried out an experiment in deuterated water, loading precise amounts of the starting HAC and the acetic acid. We left the vial at 60 °C for three days and finally we analyzed it by ^{1}H-NMR (see Figure 10, in which the corresponding products signals are indicated).

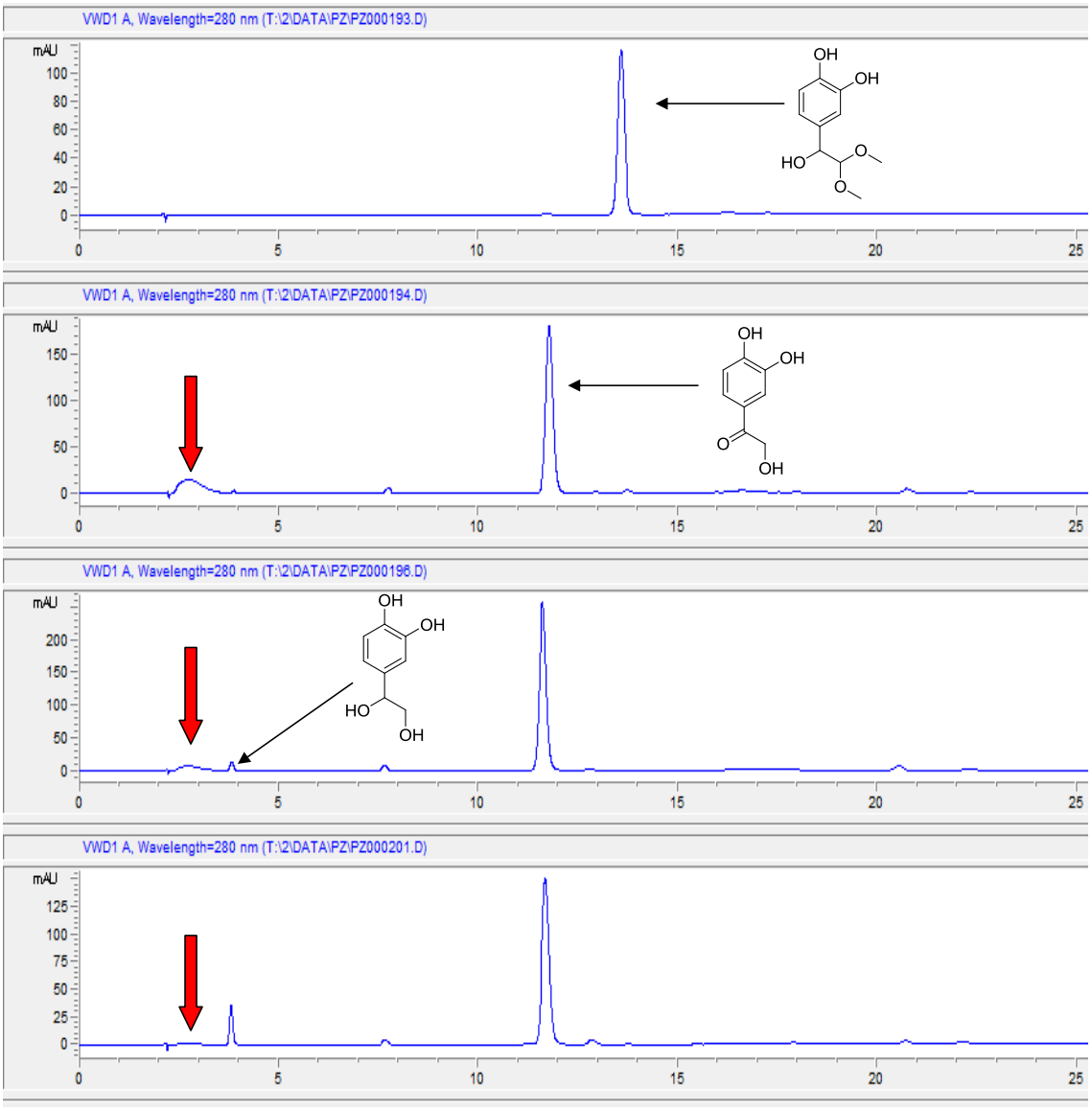


Figure 9 Screenshot of the HPLC chromatograms, from time zero (top) to 1, 3, and 5 hours reaction (bottom). The unidentified peak is indicated by the red arrow. Reaction conditions: T = 90 °C; HAC/Pd/acetic acid 1/0.025/1 molar ratio; 3 bars of hydrogen.

We found a conversion of HAC of about 55.7% with a yield to the hydrated hydroxyaldehyde of 54.7% (calculated with respect to the amount of acetic acid).

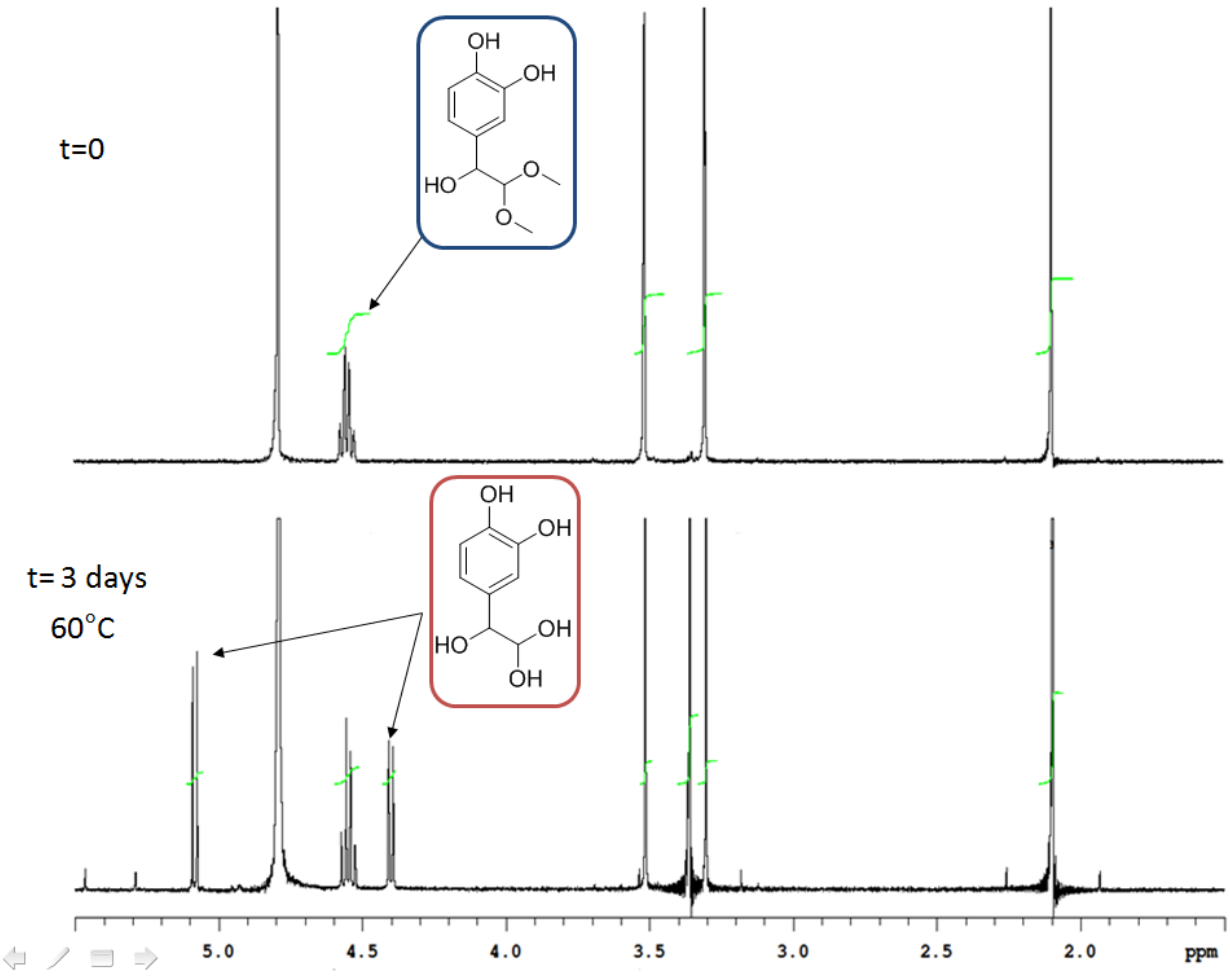
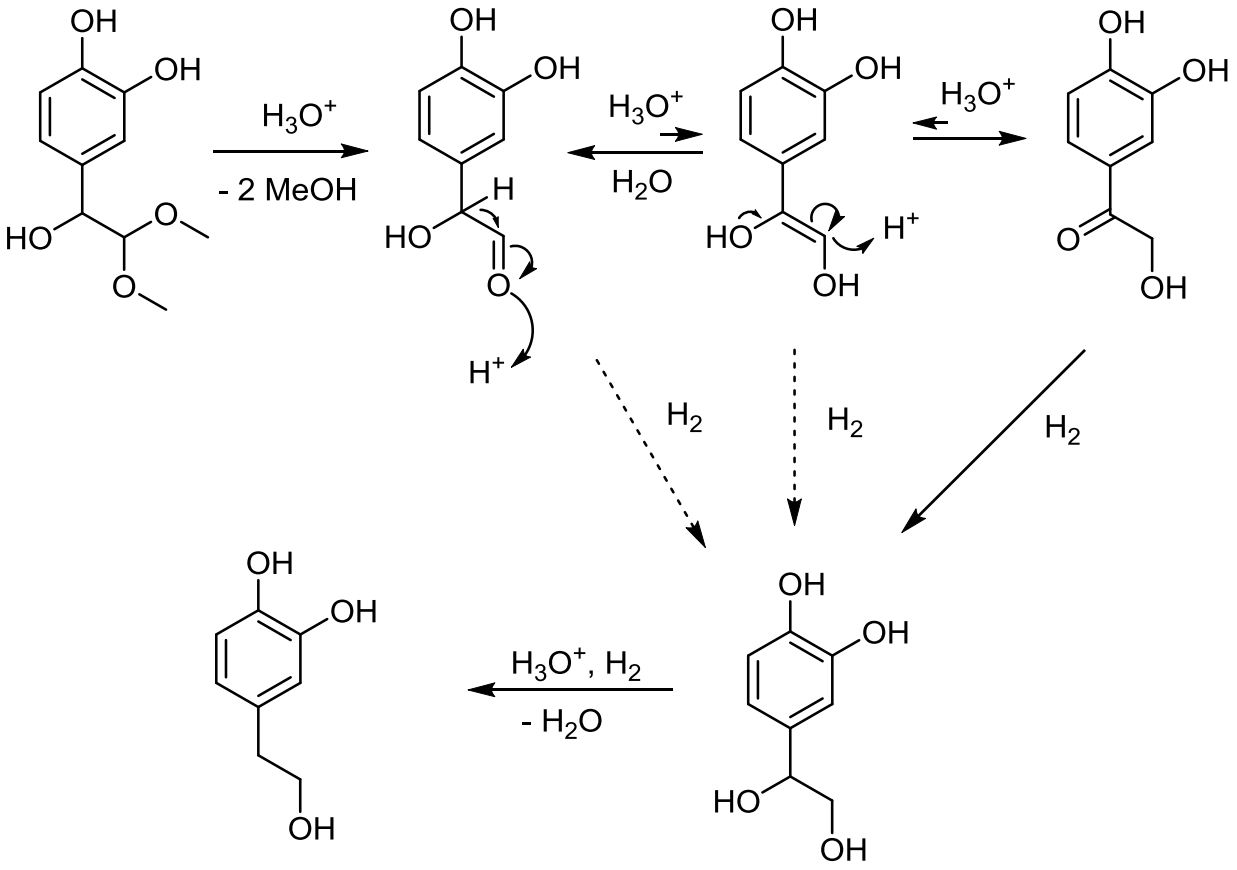


Figure 10 ^{1}H-NMR spectra of HAC (time zero, top) and reaction crude (bottom). Reaction conditions: T 60 °C; HAC/acetic acid ≈ 1/1 molar ratio, in D_2O.

At this point, we could delineate the reaction pathway starting from HAC until HT (Scheme 15).



Scheme 15 Plausible mechanisms for the formation of hydroxytyrosol.

First of all, the hydrolysis of the HAC occurs, releasing two equivalents of methanol and forming the aldehyde. Especially at high temperature, it quickly undergoes a double tautomeric equilibrium that forms first the ene-diol, then HK, which is so stable with respect to the aldehyde that we can consider it as the effective starting material (at least for the experiment at 150 °C).

Then the reduction of the ketone group to the alcohol occurs and finally the hydrogenolysis to hydroxytyrosol. Obviously the formation of DIOL could originate directly from HA, at least in part. We can even think that the reduction to DIOL does not occur via ketone, but via ene-diol, which can form at high temperature and be easily reduced by the catalyst.

What is still not completely clear is the formation pathway of the two by-products, 4-ethylcatechol and 4-methylcatechol.

In the first case, we thought that it was simply the result of the over-reduction of the hydroxytyrosol, but, as previously reported, the reduction carried out at 6 bars showed the opposite; therefore, it has to form from one of the intermediates.

For the same reason, we exclude that 4-methylcatechol is formed from hydroxytyrosol; obviously, also HK is not its direct precursor. By the way we have to consider that HK is in equilibrium with the aldehydic form HA, so it is plausible that, at 150 °C, when the aldehyde is formed, it undergoes the decarbonylation. This is a possibility because also when only HK is present in the reaction mixture, MC keeps on increasing (for example see Figure 5 and 6).

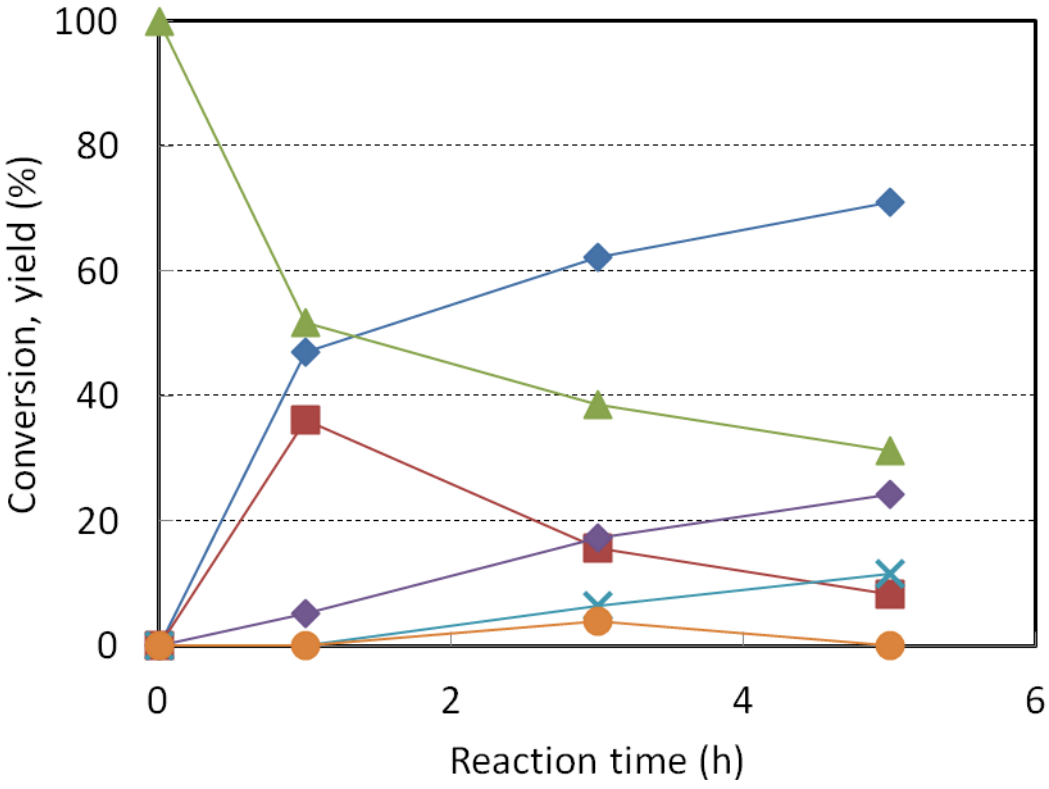


Figure 11 Effect of reaction time on HK conversion (◆), and yield to HK (▲), DIOL (■), HT (◆), MC (×), and EC (●). Reaction conditions: T = 150 °C; HK/Pd 1/0.025 molar ratio, with no acetic acid; 3 bars of hydrogen.

The experiment shown in Figure 11 (the reaction was carried out without acid in order to "slow down" the reaction rate) further supports the previously hypothesis: the starting material loaded was HK (earlier prepared and purified) and not HAC which could hydrolyze to aldehyde. As shown, MC was formed anyway. But if we observe carefully the figure, it seems that MC starts to form only after 1 h, when quite a lot of DIOL is already formed (as it happened also in the test of Figure 8).

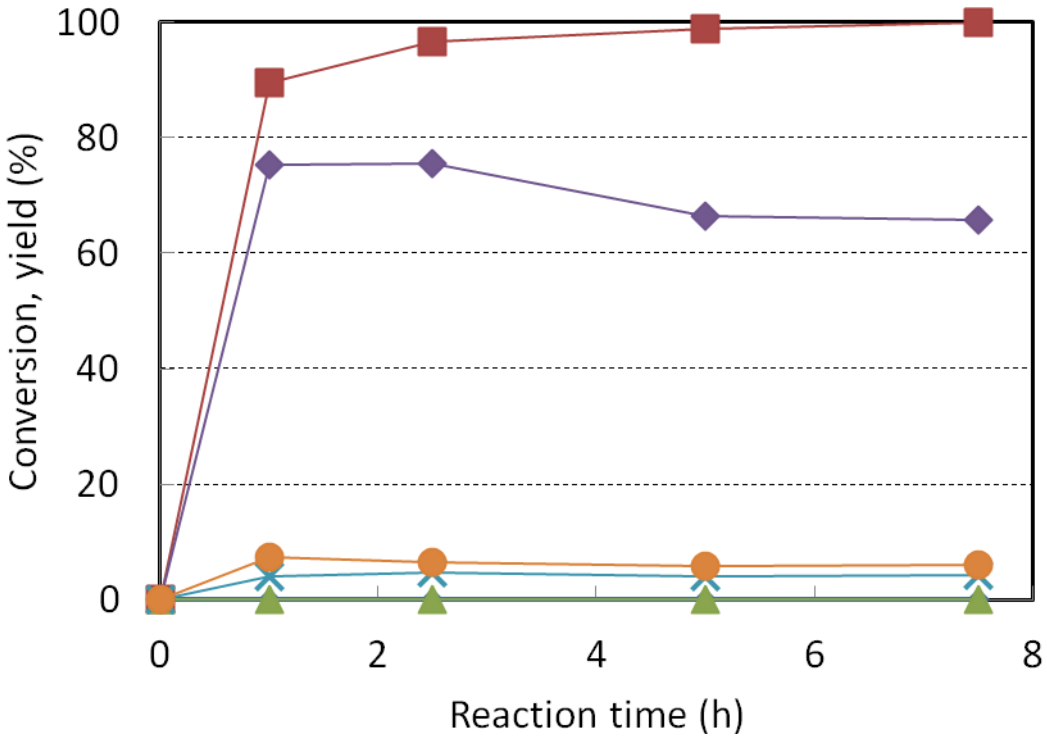


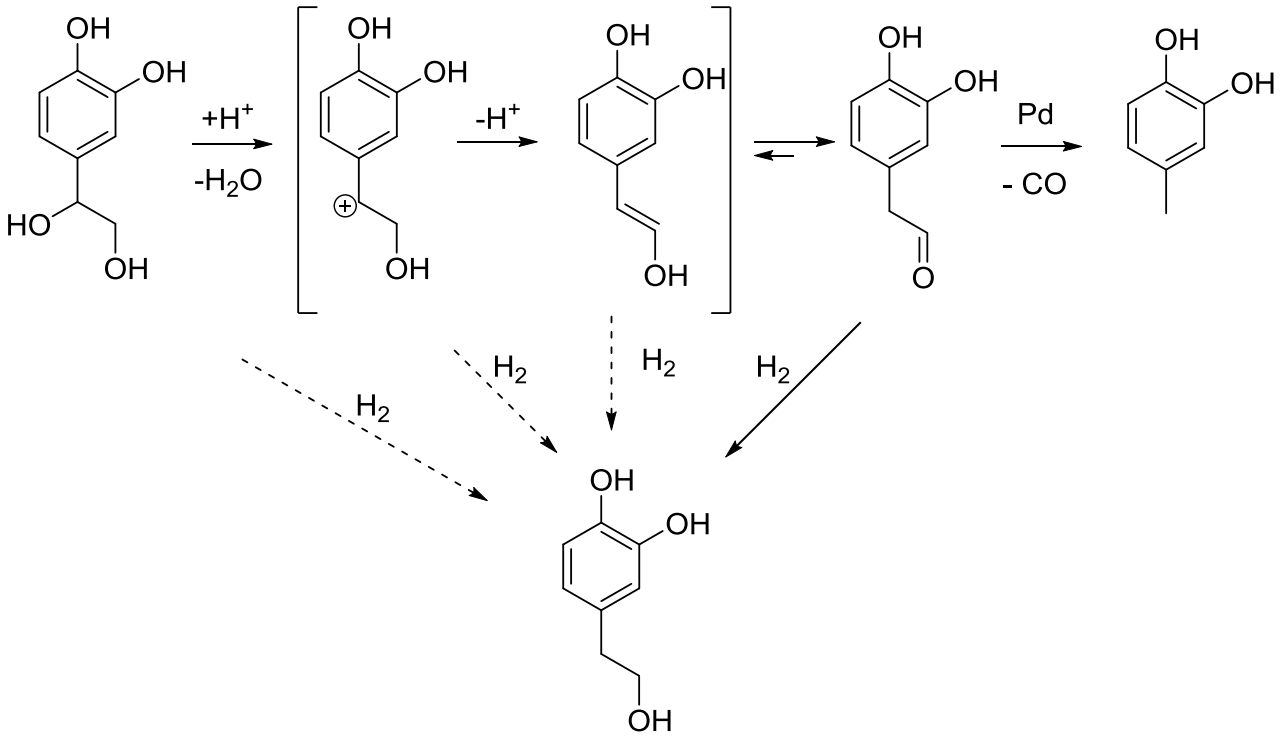
Figure 12 Effect of reaction time on DIOL conversion (■), and yield to HK (▲), HT (◆), MC (×), and EC (●). Reaction conditions: T 150 °C; DIOL/Pd/acetic acid 1/0.025/1 molar ratio; 3 bars of hydrogen.

At last, we carried out a reduction test starting from the DIOL. Although it was less than 5%, as we expected, we found that also in this case MC was formed. We also noticed that it slightly increased but only until there was

unconverted DIOL; then it stopped, suggesting, for example, that it was not formed somehow from HT.

All these tests demonstrated that MC was formed from DIOL, and in our opinion this is the most plausible way. Nevertheless, this does not mean that MC could form from other intermediates.

Finally, we hypothesized the formation pathway of MC as illustrated in Scheme 16.



Scheme 16 Plausible mechanisms for the formation of MC starting from DIOL.

First, the dehydration of the benzylic hydroxyl group occurs forming a carbocation which releases a proton forming the enol; then it undergoes a tautomeric equilibrium forming the aldehyde. Obviously each of these intermediates can be directly and quickly reduced to hydroxytyrosol, but, at last, the aldehyde formed could undergo decarbonylation (as previously demonstrated).

The investigation of the reduction continued and we decreased the amount of acid down to 0.05 equivalents.

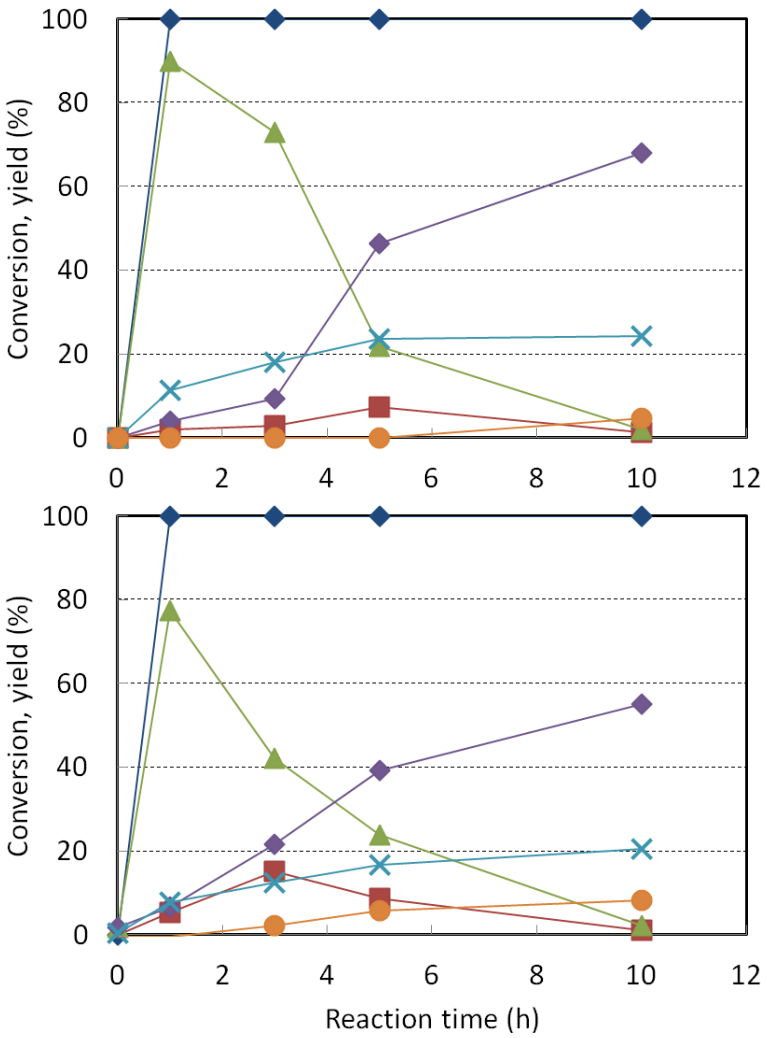


Figure 13 Effect of reaction time on HAC conversion (◆), and yield to HK (▲), DIOL (■), HT (◆), MC (×), and EC (●). Reaction conditions (top): T 150 °C; HAC/Pd/acetic acid 1/0.025/0.05 molar ratio, 3 bars of hydrogen. Reaction conditions (bottom): T = 150 °C; HAC/Pd 1/0.025 molar ratio, with no acetic acid, 3 bars of hydrogen.

As shown in Figure 13 (top), the reaction was complete in 10 h (like in the experiment with one equivalent of acetic acid). The major difference was an important accumulation of HK at the beginning of the reaction, which meant that the acid catalyst had a relevant influence also on the conversion of the ketone to the products. This let us think that HK was not directly reduced, but indeed the aldehyde formed by tautomerization, a reaction which is acid catalyzed.

We also carried out an experiment without acetic acid (Figure 13, bottom). We expected very low conversion of HAC because the hydrolysis of the acetals is

acid catalyzed, but again HK was formed and it accumulated. Moreover, also the accumulation of DIOL was more relevant with respect to the other tests. This is another evidence that the acetic acid catalyzed the formation and the conversion of the two intermediates.

By the way, the reaction was complete in 10 h (even if with a lack in the C balance of about 15% at the end).

Finally we compared the reactivity of Pd, Pt and Rh (all supported over carbon) in the same reaction conditions: one equivalent of acetic acid (with respect to HAC), 6 bars H_2, 150 °C, 10.5 hours, 2.5% mol/mol of metal catalyst. The results are summarized in Table 3.

In all cases there were problems of lack in the C balance, which went from 24% to 41%. This phenomenon is still not completely clear, however some ^{1}H-NMR spectrum showed broad signals between 0.8 and 2 ppm , and between 3 and 4 ppm. These peaks can be assigned to alkanes and aliphatic alcohols; indeed, we hypothesized that the reaction conditions could allow the aromatic ring reduction forming cyclohexanediol derivatives. Moreover, if we calculated the selectivity with respect to the yields sum, the results are similar to the previous data (hydroxytyrosol selectivity was about 70%).

What was interesting was the different behavior of the catalysts, particularly in respect to the two by-products. In this table are reported the selectivity calculated with respect to the conversion of HAC. Palladium was more selective to MC, while platinum showed the opposite behavior, being more selective to EC. Rhodium was instead the less active amongst the catalysts tested and did not differentiate between MC and EC.

Table 3 Results for the hydrogenation of HAC over different catalysts. Reaction conditions: T 150 °C; HAC/Pd/acetic acid 1/0.025/1 molar ratio, 6 bars of hydrogen, 10.5 h reaction time. The conversion of HAC is always complete, while the consumption of HK is not complete in the tests with Pd at 90 °C (95%) and Rh (85%).

Catalyst	Temp (°C)	SELECTIVITY (%)				∑Y (%)
		DIOL	HT	MC	EC	
Pd 10%	150	1	55	14	6	75
Pd 10%	90	26	46	7	6	90
Pd 5%	150	0	46	11	2	59
Pt 10%	150	0	54	8	13	76
Rh 5%	150	1	41	9	9	72*

LIQUID FLOW HYDROGENATION

At last, we performed the hydrogenation under continuous flow in a fixed bed reactor (Figure 14).

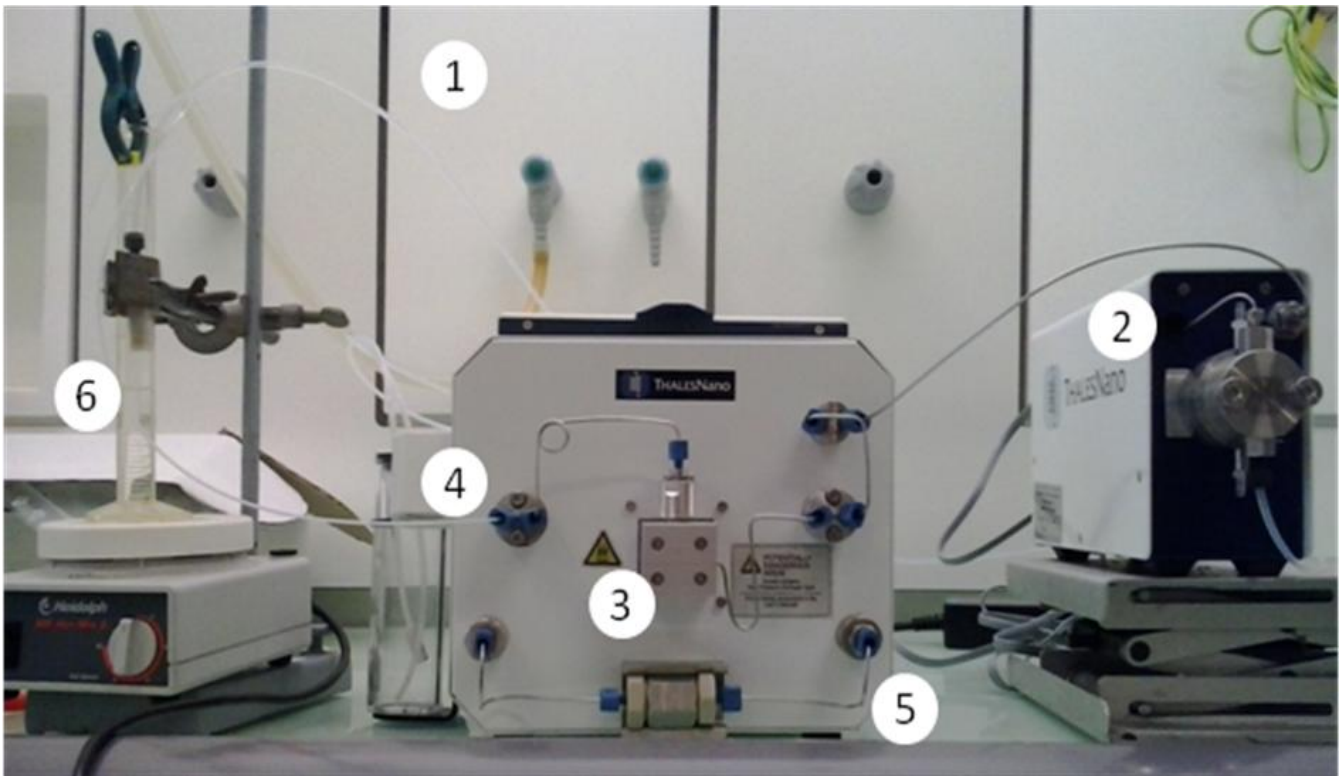


Figure 14 Picture of the flow hydrogenation system (H-CUBE mini®, ThalesNano). (1) in-line, (2) pump, (3) reactor, (4) out-line, (5) H_2 inlet, (6) reaction mixture.

Hydrogen is generated through electrolysis of water with >99.7% purity (the residual 0.3% is water). The hydrogen/compound is passed through a packed column containing solid catalyst where the reaction takes place. Then the crude is collected.

The most important advantage of this instrument is the high pressure of hydrogen reachable (100 bars). In our opinion, this could drastically limit the formation of the 4-methylcatechol because the high pressure should disfavour the decarbonylation. At the same time, it should accelerate the reduction of the aldehyde whenever it forms and, possibly, preventing the tautomeric equilibrium towards HK.

From the first tests we noticed that the reaction rate was low, even at relative high temperature (100 °C, the maximum for our instrument) and hydrogen pressure, so we decided to carry out the experiments in aqueous acetic acid solution (50% v/v), to loop the reaction mixture and take samples every one/two hours. The only problem of these reactions was that, when we changed the reaction conditions or the catalyst, we had to stop the looping and let the reactor conditioning by reducing the volume of the solution. So, each time, the mixture increased its "residence time" by decreasing the loop-time. This meant that the reaction rate increased in proportion to the decrease of volume, affecting the trends of the kinetics.

We started with Pd/C (10% w/w) at 90 °C, 90 bars of hydrogen, and a solution flow of 1 mL/min. As shown in Figure 15, unexpectedly the major product was DIOL (Selectivity of 58%, with respect to yield sum/ 32%, with respect to HAC conversion, at 1 h); also an unusual amount of HA started to form. Another important difference was that there was no HK, which probably means that the reaction pathway does not involve the tautomerization, but only the hydrolysis of the HAC to HA, its reduction to DIOL, and finally to HT.

Only increasing the temperature up to 100 °C (from 4 to 6 h reaction), both HK and MC started to form.

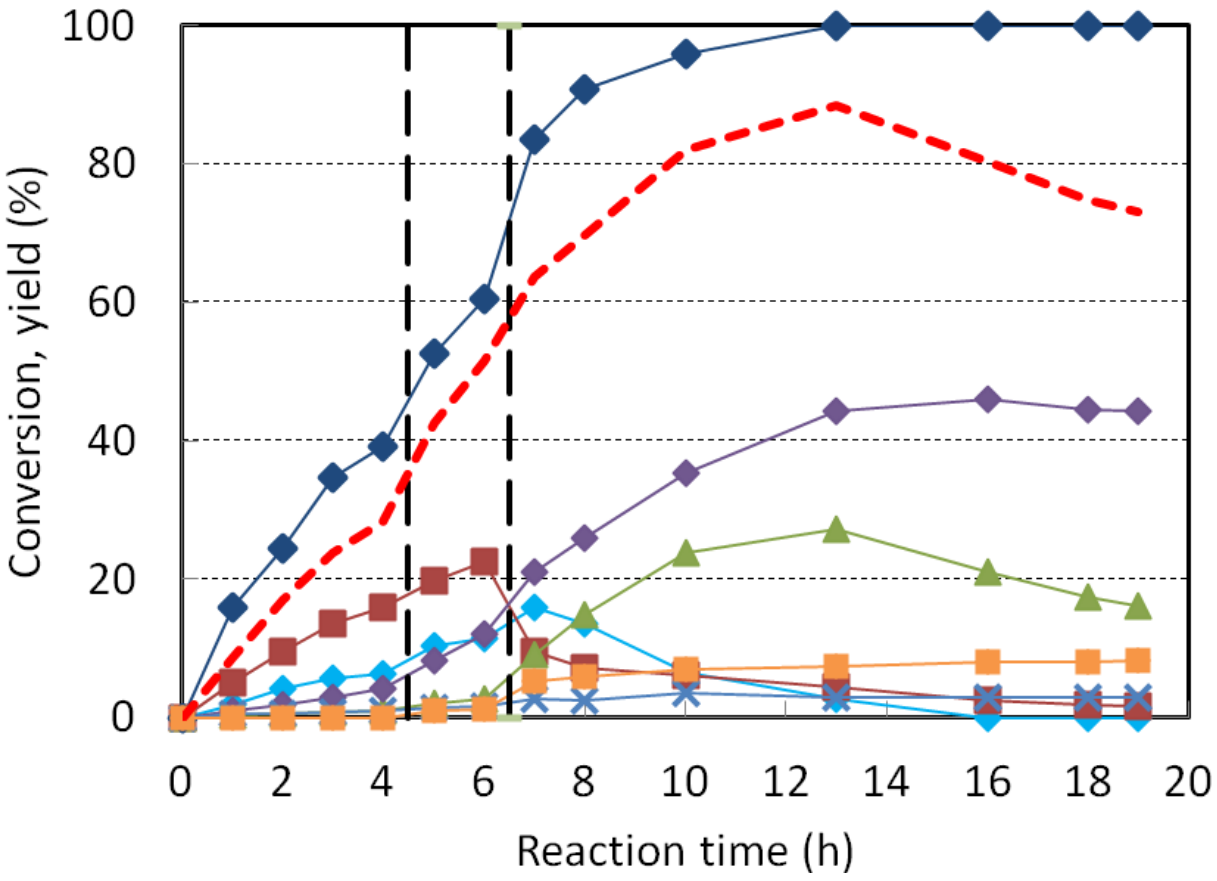


Figure 15 Effect of reaction time on HAC conversion (◆), and yield to HK (▲), HA (◆) DIOL (■), HT (◆), MC (×), and EC (■). Reaction conditions: T 90 °C, 90 bars H_2, Pd/C (up to 4 h); T 100 °C, 100 bars H_2, Pd/C (up to 6 h); T 100 °C, 100 bars H_2, Pt/C (up to 19 h). Solvent: H_2O:acetic acid 1:1 vol/vol.

After 6 h, we replaced the Pd with Pt/C (5%w/w) keeping the same reaction solution and the reaction parameters. We noticed an evident increase of the HK and HT, while HA and especially DIOL decreased.

Moreover, EC rapidly reached 5% yield after one hour, but later it increased only of 3% in 6 h. This suggested that it could form starting from either DIOL or HA because at the beginning of this latter test they were present in a consistent amount. Even if this is in contrast with the previous test at 6 bars in

autoclave (Figure 7), we could also hypothesize that EC could be formed from HT because this time the catalyst used was Pt and not Pd.

The increasing gap between conversion of HAC and yields sum was ascribable to the formation of unidentified products but also to the accumulation of water; this latter effect was due to a little amount of water present in the hydrogen flow (about 0.3 %) which accumulated during time in the reaction solution which is looping.

Concluding, Pt showed a behavior very close to the experiments carried out in autoclave facilitating the tautomerization of HA to HK; on the contrary, Pd showed a different reactivity: indeed it limited/prevented the formation of HK, favoring HA and DIOL.

At last, we carried out a reduction employing Ni-Raney catalyst at 100 °C, 100 bars of hydrogen, aqueous solution of acetic acid (50% v/v) and a solution flow of 1 mL/min in loop (Figure 16). This catalyst showed a different behavior with respect to the others: after 5.5 h the only products were DIOL (25% yield, 53% selectivity) and HT (19.7% yield, 40.6% selectivity). Only traces (1.5-3% yield) of EC were present.

After 5.5 hours, during the second day of reaction, the gap between HAC conversion and yield sum increased; maybe a degradation of the products occurred.

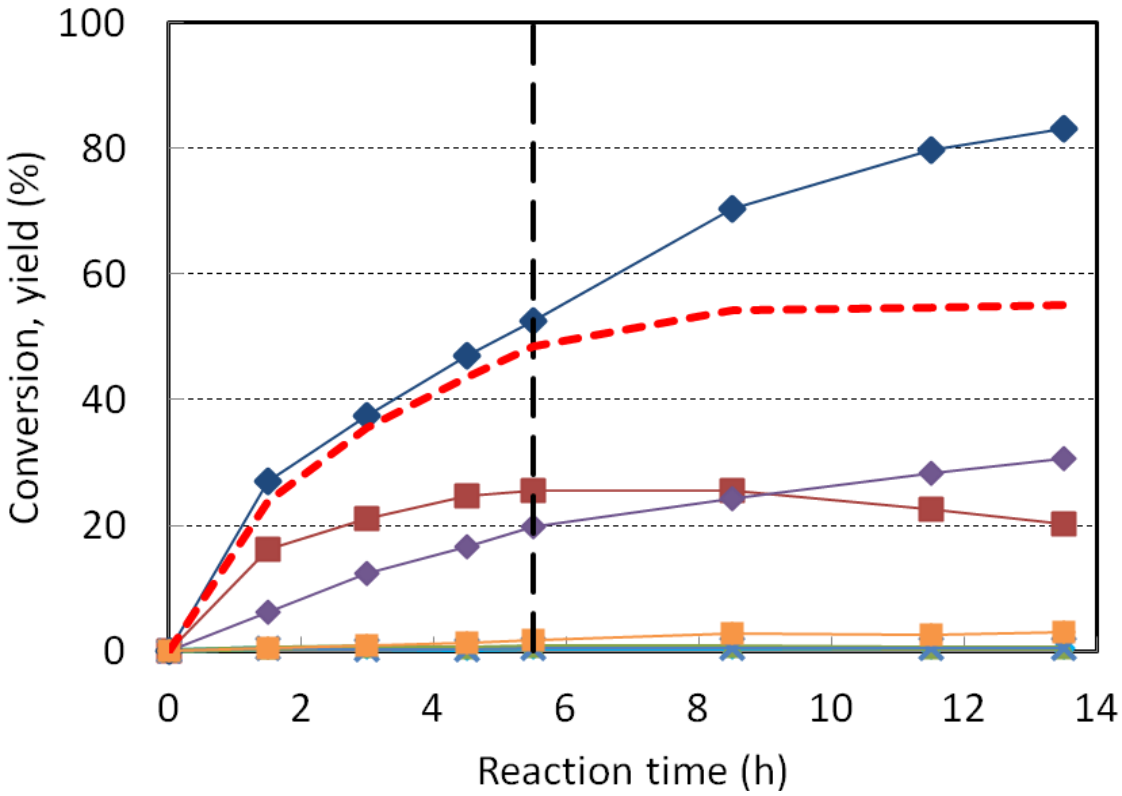


Figure 16 Effect of reaction time on HAC conversion (◆), and yield to HK (▲), HA (◆) DIOL (■), HT (◆), MC (×), and EC (■). Reaction conditions: T 100 °C, 100 bars H_2, Nichel-Raney; solvent: H_2O:acetic acid 1:1 vol/vol.

The absence of HA suggests that, whenever it formed, it was readily converted to DIOL and HT. Comparing this experiment with the previous ones, we can assert that Ni-Raney was the most selective catalyst, which strongly limited the formation of EC and prevented the formation of MC, so no decarbonylation occurred.

CONCLUSIONS

We developed a two-step reaction consisting of the hydroxyalkylation of catechol followed by the one-pot reduction to the desired product.

After a wide screening of reactants and reaction conditions, we found that best results were obtained with catechol as the starting aromatic, 2,2-dimethoxyacetaldehyde (DMA) as alkylating agent and NaOH as the catalyst with a relative molar feed ratio of 1:0.5:0.5. These reactions were carried out in water at 80 °C and they were complete in few hours. We found that an outstanding selectivity to the desired product (HAC) of 70% with respect to the DMA (limiting reagent) could be achieved at complete conversion of catechol.

We also found a very interesting influence of the solvent towards the selectivity (organic solvents strongly promote the ortho hydroxyalkylation).

Our hydroxyalkylation followed most of the Green Chemistry principles, except the use of stoichiometric NaOH. One of the future purpose is indeed to replace the homogeneous catalyst with a heterogeneous one, guaranteeing an important and elegant improvement to the process. By the way, do not forget that this first step is quite similar the other industrial examples, such as the commercial production of vanillin, which again employs NaOH.

The most interesting part of this work is the one-pot reduction of the HAC. We tested several reaction conditions and catalysts, reaching a good yield of 70% of hydroxytyrosol at complete conversion of HAC in few hours. The reaction solvent was water and we also demonstrated that the amount of acid catalyst could be reduced at least to 0.05 equivalent, or even eliminated. Anyway, we think that the acid catalyst could be replaced with a heterogeneous one (Amberlyst for example) or employing an acid support for the metal catalyst.

We deeply investigated the reaction pathway, identifying all the reaction by-products and studying in detail their formation pathways.

Finally, we can assert that this is a new approach to the synthesis of hydroxytyrosol, which, with opportune improvements, could be an alternative to the current industrial process.

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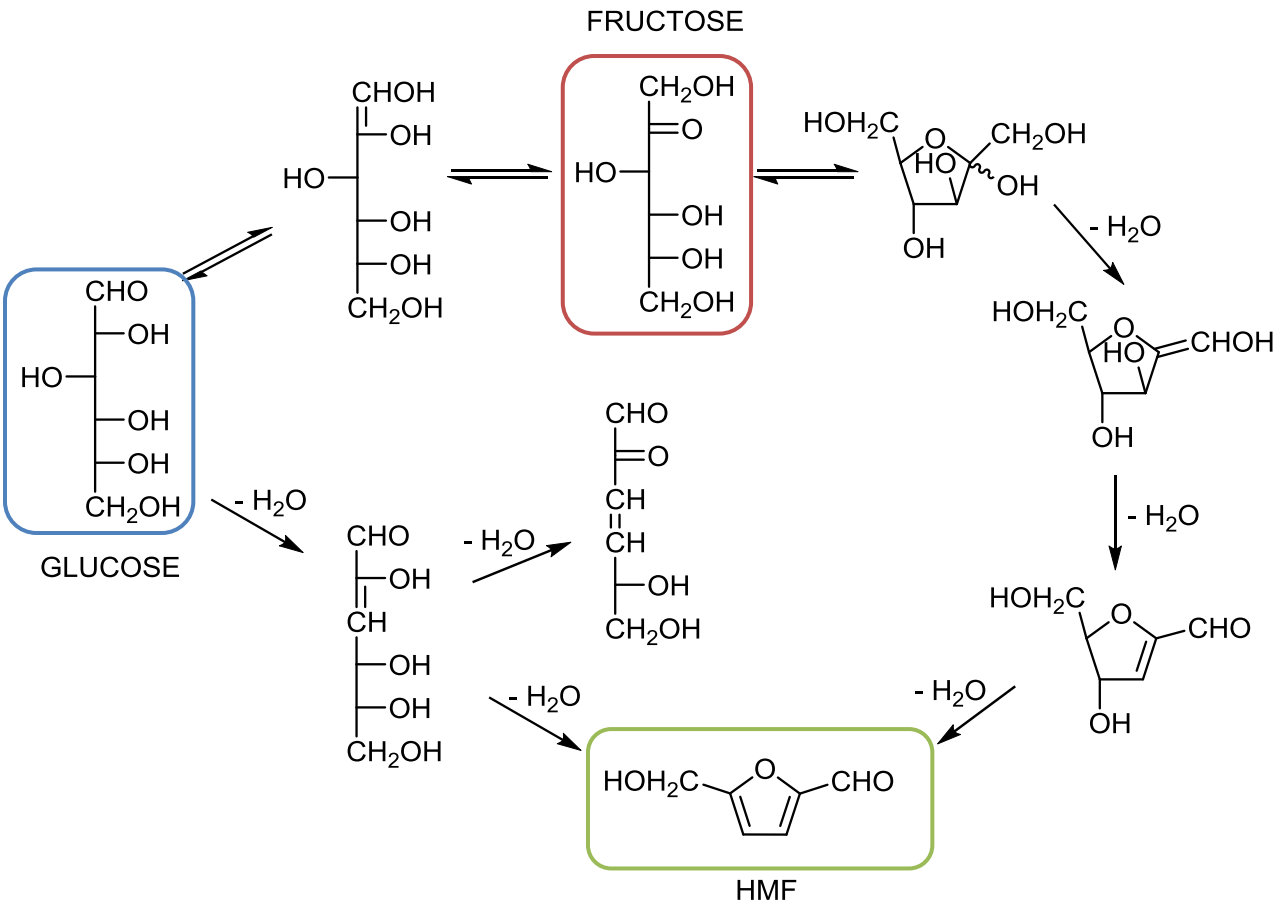
FROM FRUCTOSE TO DIESEL ADDITIVES

INTRODUCTION

Biomass and biomass-derived carbohydrates are promising carbon-based alternatives to the petroleum-based sources, both as sustainable feedstock for chemicals (because of pressing legislations regarding CO_2 emissions and environmental pollution) and as energy sources. For this reason, over the last decades, much effort has been devoted to the conversion of biomass to 5-hydroxymethylfurfural (HMF), a versatile and key intermediate in biofuel and fine chemicals production, such as polymer monomers and levulinc acid.[1]

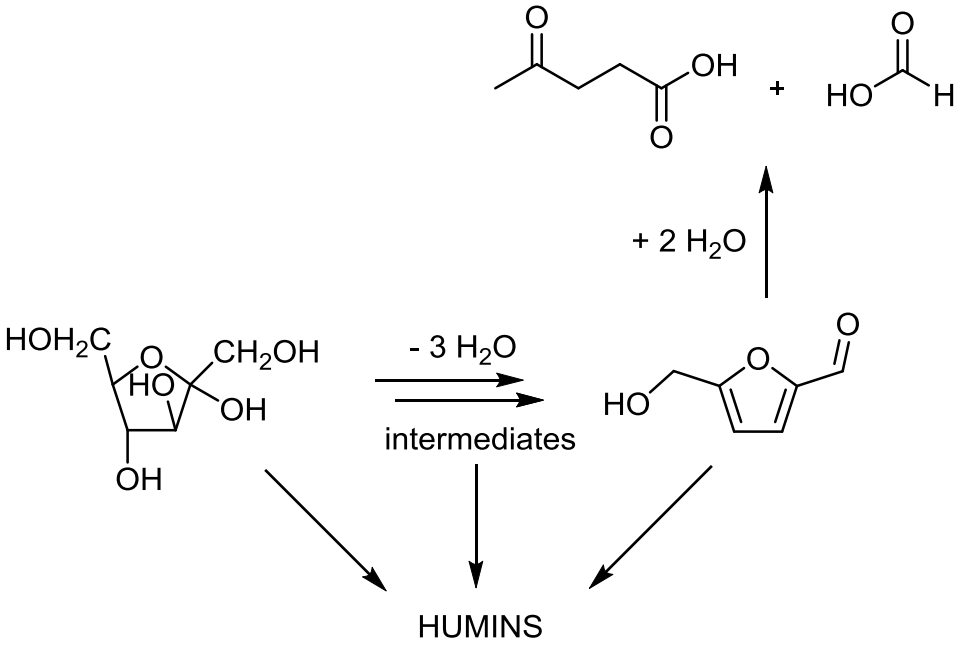
However, the large-scale application of biomass-sourced HMF is still limited due to some critical issues, such as cost, supply of the starting materials, and environmental impact. Moreover, the efficiency of the synthesis of HMF and its high solubility in water pose difficulties in large production processes, especially for isolation and purification, which require several extractions, employing large volumes of organic solvents (increasing the costs and the environmental impact).[2]

Among the carbohydrates, glucose and especially fructose are the most investigated for the dehydration to HMF (and its derivatives). Industrially, glucose is used as source of HMF because its cost is lower than that of fructose, but the dehydration process (Scheme 1) starting from fructose is more efficient and selective. This is due to the low degree of enolization of glucose, and the enolization is a determining step of HMF formation. Besides, glucose can condense to form oligosaccharides, which can react with HMF, resulting in cross-polymerized materials (humins).[3]



Scheme 1 Pathway of dehydration of glucose and fructose to HMF.[3]

This reaction has been extensively studied in different solvents in the absence and presence of catalysts. Initially, water was proposed as reaction solvent but, besides the costly work up, it can rehydrate HMF to form levulinic and formic acid (Scheme 2), which lowers the yield.



Scheme 2 Side reactions for the fructose dehydration.

In order to reduce the formation of by-products, biphasic systems were investigated, whereby an immiscible organic solvent continually extracts HMF from the aqueous phase. However, the extraction efficiency was unsatisfactory, leading to the utilization of large amounts of solvent or phase modifiers, so increasing the environmental impact and the process costs.

In addition, ionic liquids and ionic liquids diluted with water or organic solvents have been investigated, but such systems also suffer from high downstream separation costs, which limits their economic feasibility. HMF synthesis works very well in dimethyl sulfoxide, even without any catalyst, but the excellent solubility of the product and the high boiling point of the solvent make the separation very energy intensive.[4]

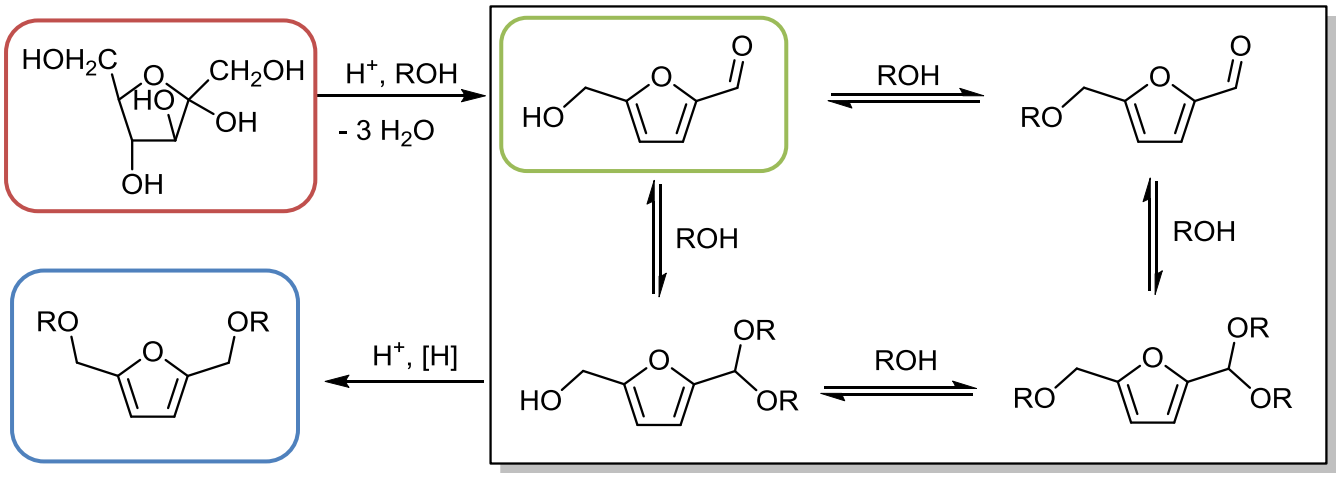
The challenge is to work under relatively mild conditions, keeping a relatively high concentration of reactant (an excess leads to consecutive and parallel reactions) and using a stable solvent that is able to dissolve the sugar, but also has a low vaporization enthalpy to minimize the energy consumption in the downstream distillation. Moreover, it is necessary to replace the homogeneous catalysts with an heterogeneous one.

OUR AIM

Our final target was a 2,5-bis-(alkoxymethyl)furan derivative, which is a diesel additive. We initially thought to a two steps process, but with the purpose to develop a one-pot one.

We decided to start from the dehydration of the fructose to obtain HMF (or its derivatives) and then convert it to the bis-alkoxylfuran. All employing commercial and heterogeneous catalyst.

The most crucial point was the choice of the reaction solvent: we opted for 1-propanol for several reason. This alcohol is environmentally friendly, it is not expensive, it can dissolve sugars very well and it is more handy. But the most important reason for choosing 1-propanol is that HMF might undergo an etherification as soon as it forms. In this way we could obtain up to four different HMF derivatives (see Scheme 3), but, anyway, they are all suitable for the second step of reduction to 2,5-bis-propoxyfuran. Moreover, the ethers could prevent side reaction (such as oligomerization, rehydration and decomposition).



Scheme 3 Reductive etherification pathway of fructose to (2,5-bis-alkoxymethyl)furan with the possible intermediate structures are also represented.[2]

Another advantage for employing 1-propanol instead of water or ionic liquid or DMSO is that the work-up of the reaction is very simple, both for the removal of the solvent itself and for the purification of the products.

RESULTS

Immediately we found out that there was not an easy method for the analysis of the reaction products. We cannot inject it into a gas-chromatograph because the fructose cannot vaporize and it could obstruct the injector or the column. The HPLC was not available. So we decided to follow the reaction by NMR, which has some advantages: it allowed us to identify (almost) all the products and, at the same time, to quantify them (although it is less reliable with respect GC or HPLC quantitative analysis). Moreover the preparation of the samples were simple: we only had to remove the 1-propanol by evaporation at reduced pressure and then, after the addition of the reference standard (acetic acid), dissolve it in the deuterated solvent.

Here I report the products of the dehydration step and the corresponding abbreviations (Figure 1). We also synthesized and purified the propyl levulinate (LEV), the 5-propoxymethylfurfural (ETH-ALD) and the 5-(propoxymethyl)-furfural-dipropylacetal (ETH-ACE).

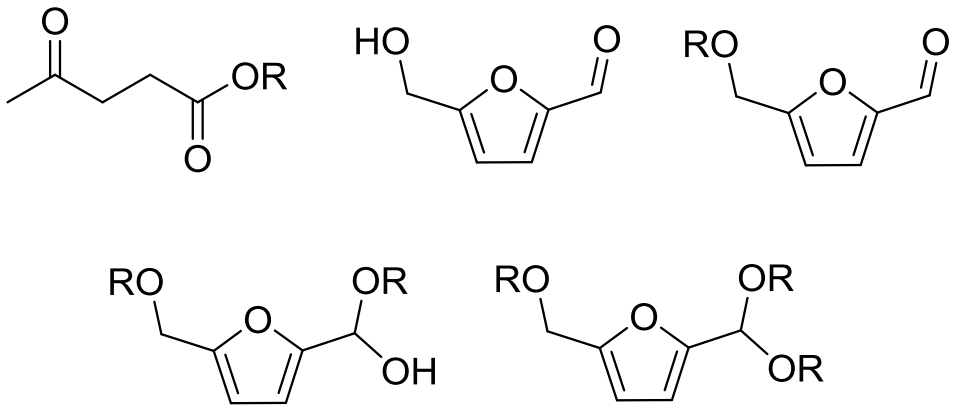
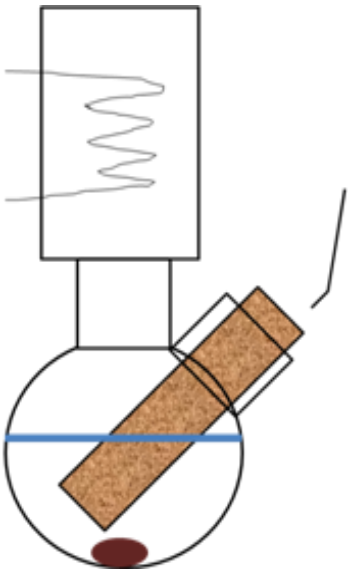


Figure 1 Structures of the products of fructose dehydration. From left to right (top): LEV, HMF, ETH-ALD; (bottom) ETH-HEM, ETH-ACE.

DEHYDRATATION TESTS WITH MOLECULAR SIEVES



Our first objective was to point out the influence of the presence of the water. So we carried out tests with and without molecular sieves. We chose sieves of 3 Å, which were pre-treated heating at 150 °C under vacuum for about one hour.

We tried to place the molecular sieves between the solution and the refrigerant as shown in figure: we loaded the sieves in a drilled cylinder in order to keep the solution in contact with the sieves without breaking them with the magnetic stirrer.

The fructose dehydrations were carried-out in a round bottom flask (25 mL), with a refrigerant and a drilled syringe filled with molecular sieves, semi-submerged in the reaction mixture. The amounts: 500 mg fructose (0.19 M), 15 mL 1-propanol, 100 mg Amberlyst-15 (17% mol/mol), in nitrogen atmosphere.

Table 1 Results for the dehydration of fructose. Product yields (calculated by ^{1}H-NMR) and reaction conditions are reported.

	YIELD (%)								
	LEV	ETH-ACE	ETH-ALD	HMF	ETH-HEM	**Σ Y** %	T (°C)	Time (min)	SIEVES
5	2	28	2	2	12	47	100	180	NO
11	3	38	2	2	10	54	100	300	NO
7	3	31	11	6	11	60	100	180	YES
8	5	28	21	5	5	65	100	300	YES
10	3	33	8	3	10	56	110	180	YES
9	4	32	8	4	10	57	90	420	YES

Comparing the results with and without molecular sieves (respectively experiments 7,8 and 5,11), we can notice a positive effect due to the sieves, that apparently do not reduce the formation of propyl levulinate but anyway improve the total yield by 10%. The most evident difference is that, using the molecular sieves, the ETH-ALD yield was higher, probably because, at least in part, they remove water from the solution pushing the equilibrium towards the dehydration.

Increasing the temperature up to 110 °C or decreasing it down to 90 °C, the total yield slightly decreases.

SCREENING OF THE REACTION CONDITIONS AND KINETICS STUDIES

In order to increase the product yields we decided to carry out the reactions in a glass autoclave (2.5 mL), which permitted to increase the reaction temperature above the boiling point of the 1-propanol.

At this stage, we started the kinetic study testing the temperature of 110 °, 120° and 130 °C. After few tests we found that at these temperatures the molecular sieves were useless, so we decided not to employ them anymore.

As shown in the graphs (see Figure 2), the trends suggest that, as expected, the HMF is the primary product starting from fructose. Then, HMF itself forms ETH-ALD and ETH-HEM; the final product is then the ETH-ACE. After a maximum total yield of about 70%, it starts to decrease, probably in favor of by-products.

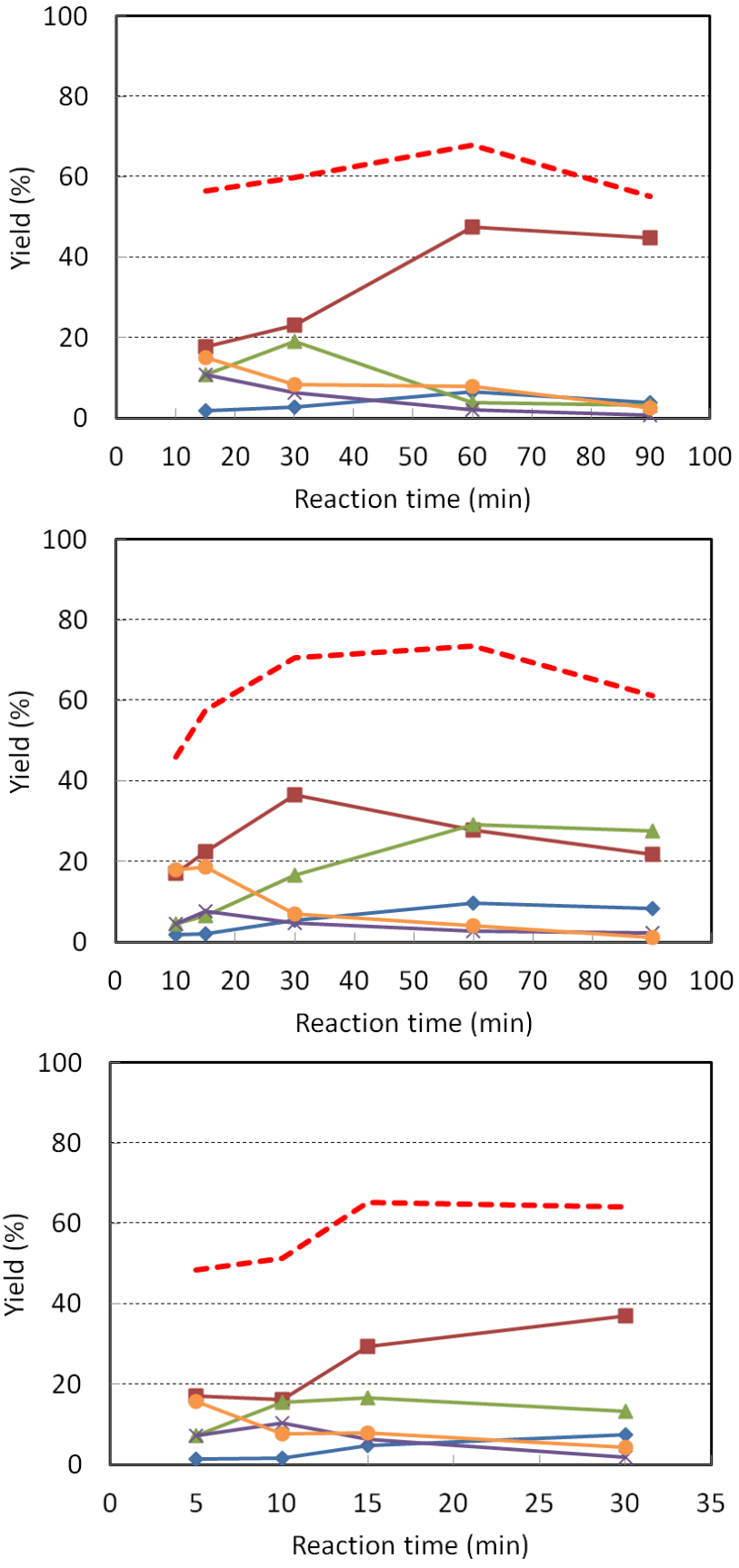


Figure 2 Effect of reaction temperature on yield to HMF (×), ETH-ALD (▲), ETH-HEM (●), ETH-ACE (■), and LEV (◆). Reaction conditions: fructose (0.21 M), 1 mL of 1-propanol, Amberlyst-15 (21% mol/mol). Temperatures: 110 °C (top), 120 °C (middle), 130°C (bottom).

The yield of propyl levulinate (maximum 10%) is not influenced by the temperature and it seems that it only depends on the extent of reaction, or rather it increases with the increase of the yield to furan derivatives (because there are more odds to hydrate them).

With respect to the tests carried out at the 1-propanol boiling point (or under), these experiments showed a very high reaction rate. For example, in the case of the experiment carried out at 110 °C, the conversion of fructose was complete in 1 hour, while, at 130 °C, it was complete already at 15 minutes.

Amongst these 3 kinetics experiments, the test at 120 °C seems to be the best one because it shows the higher sum of yields to desired products and it is needs quite a short reaction time (it is complete between 30 and 60 minutes), without being too short (as in the case at 130 °C) which makes the reaction less handy and reproducible. We still do not understand why the product distribution of ETH-ALD and ETH-ACE are quite variable.

Considering 120 °C as the best temperature, we decided to reduce the amount of amberlyst-15 (see Figure 3) and we could decrease it down to 6% mol/mol, keeping a good sum of yields of 68% and a satisfying reaction time of 90 minutes.

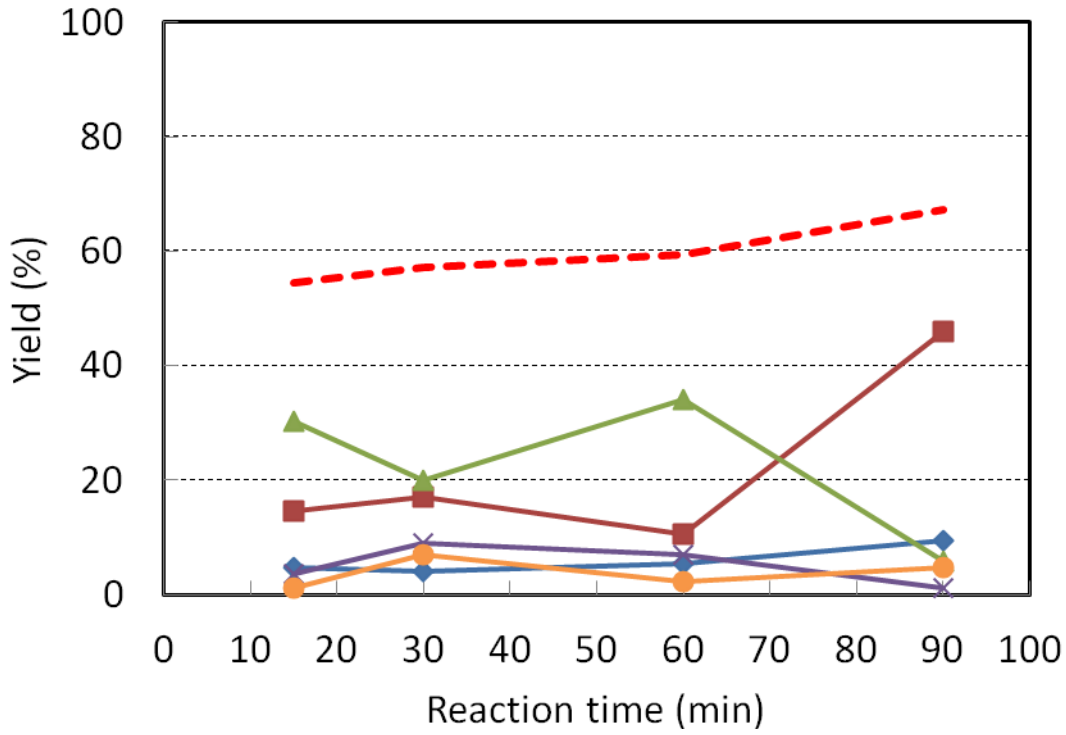


Figure 3 Effect of reaction time on yield to HMF (×), ETH-ALD (▲), ETH-HEM (●), ETH-ACE (■), and LEV (◆). Reaction conditions: fructose (0.21 M), 1 mL of 1-propanol, T 120 °C, Amberlyst-15 (6% mol/mol).

Again we can notice that the relative distribution of ETH-ACE and ETH-ALD could be very different, from an experiment to another one, but also during the same experiment (also repeating the reaction in the same conditions).

Dehydration scale-up

Table 2 Results for the dehydration of fructose. Product yields were calculated by ^{1}H-NMR.

	YIELD (%)						
	LEV	ETH-ACE	ETH-ALD	HMF	ETH-HEM	**Σ Y** %	Time (min)
71	2	22	5	3	10	40	90
72	3	28	6	2	10	46	90
73	7	39	13	0	0	52	180

Finally we scaled up the reaction up to 10 times. The reaction conditions are the same of the previous tests, but using a 1-propanol volume of 7 mL in a 10 mL stainless steel autoclave (0.22 M fructose, Amberlyst-15 18% mol/mol, T = 120 °C).

The results showed that it was not possible to reproduce the smaller scale yields; we could only reach a yields sum of 52%.

REDUCTION TO DIESEL ADDITIVES

The ideal process is the one step reductive dehydration of fructose, but we decided to start the reduction starting from pure "model" reactants (such as ETH-ACE and HMF), in order to obtain simpler crude mixtures which allowed us to study the reaction conditions and its pathway.

By the way, for this second step there were not enough time to find an appropriate analytical method and a calibration; mostly we carried out qualitative tests, just to understand if our strategies could work or not.

Moreover the products were identified, when it was possible, only by GC-MS (the NMR spectra were not useful any more), without any purification.

Tests starting from ETH-ACE

The reaction were carried-out in the glass autoclave, using the ETH-ACE (0.22 M, in 1 mL of 1-propanol) previously synthesized and purified. Pd/Al_2O_3 5%w/w (0.92% mol/mol respect to the reactant), 5 bars H_2, 80°C, 3 h, Amberlyst-15 (5% mol/mol respect to the reactant).

The GC-MS chromatogram evidenced the formation of the desired product, the 2,5-bis(propoxymethyl)furan (abbr. ETH-ETH, Figure 4).

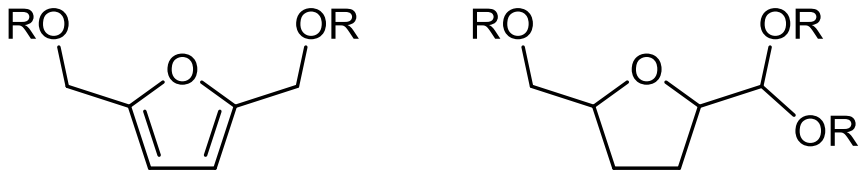


Figure 4 Structures of the products of ETH-ACE hydrogenation: on the left, the desired product (ETH-ETH), and, on the right, the acetal derivative (ETH-ACE-THF).

There was also propyl levulinate, but the main product had m/z = 215 (fragmentation: 201-155-131-113-99-89-57-43). Of course, this is not the molecular ion, so we hypothesized that it could be a fragment of the ETH-ACE with saturated ring, as shown in Figure 4, ETH-ACE-THF. Also in literature it is reported that, in these reaction conditions, it is possible the reduction of the furanic ring.[5]

Replacing the platinum with palladium, we obtained the ETH-ETH but also another product with m/z = 220 (-186-161-142-127-109-81-53) with almost the same amount. This product is still not identified, maybe it was an intermediate of reaction.

At last, we carried out a blank test without the Amberlyst-15 and we found that the ETH-ACE is stable, even at 16 bars of hydrogen and in presence of water.

Tests starting from HMF

We carried out experiments starting from HMF (0.21 M), Pd/Al_2O_3 5% w/w, 1-propanol, Amberlyst-15. The temperatures increased from 80 °C to 130 °C and the hydrogen pressure from 5 to 16 bars (Table 3).

Table 3 Reaction conditions for the reductive etherification of HMF.

	Metal Catalyst (% mol/mol)	Amberlyst-15 (% mol/mol)	Temp (°C)	H_2 pressure (bar)	Time (h)
51	0.9	4	80	5	4
57	0.9	5	100	14	8
60	1.1	7	100	16	7
70	1.1	8	130	16	7
75	1.1	7	100	16	5

In Figure 5 some new products found are shown with their corresponding abbreviations.

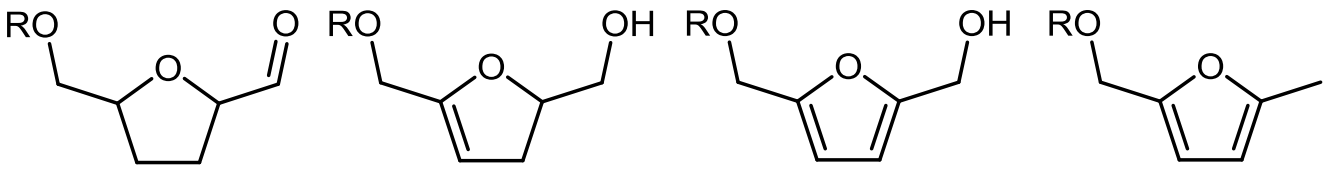


Figure 5 Some structures of the products of HMF reductive etherification; from left to right: ETH-ALD-THF, ETH-ALC-DHF, ETH-ALC, ETH-MET.

The first reaction was carried-out in 1 mL of 1-propanol (glass autoclave), 5 bars of H_2, 80 °C. NMR spectrum and GC-MS chromatogram showed the presence of little amount of LEV, HMF, ETH-ALD, ETH-ACE and, as main product, the ETH-ETH.

Other products (not identifiable by NMR) have m/z = 172 and their fragmentations suggest that they could be products (or isomers) as drawn in Figure 5.

Then we carried out three kinetics studies (but only the last one was quantified by GC-FID); the only difference is the reaction temperature: 100 °C for experiments F60 and F75, 130 °C for F70.

In the first case, at 100 °C, after one hour reaction, the main product was ETH-ETH, but there were also ETH-ALD, HMF, the product with m/z = 172 and one with m/z = 170 (probably the 2-hydroxymethyl-5-propoxymethyl furan, ETH-ALC, see Figure 5). At 2 and 4 h reaction the products increased, while ETH-ALC and HMF seemed to decrease until they disappeared. At 2 h reaction a new product also appeared (with m/z = 154, maybe the ETH-MET, see Figure 5) that continuously increased during time.

In the second experiment, increasing the temperature up to 130 °C, the reaction was faster but the product distribution was changed: at one hour the main product was still the ETH-ETH but also two products with m/z = 172 were present in a significant amount (both with about the same amount); ETH-ALD and ETH-ACE were still present but they decreased in favor of ETH-ETH. After 5 h they disappeared and other products started to form, particularly the ETH-MET. After 7 h the ETH-ETH was further consumed forming undefined by-products.

For the last experiment, carried out at 100 °C, we report also the results analyzed by GC-FID; the yields were calculated as explained previously giving the same response factor at all the products. The Figure 6 shows that the major product is ETH-ETH but also the two products with m/z = 172 were formed in a remarkable amount.

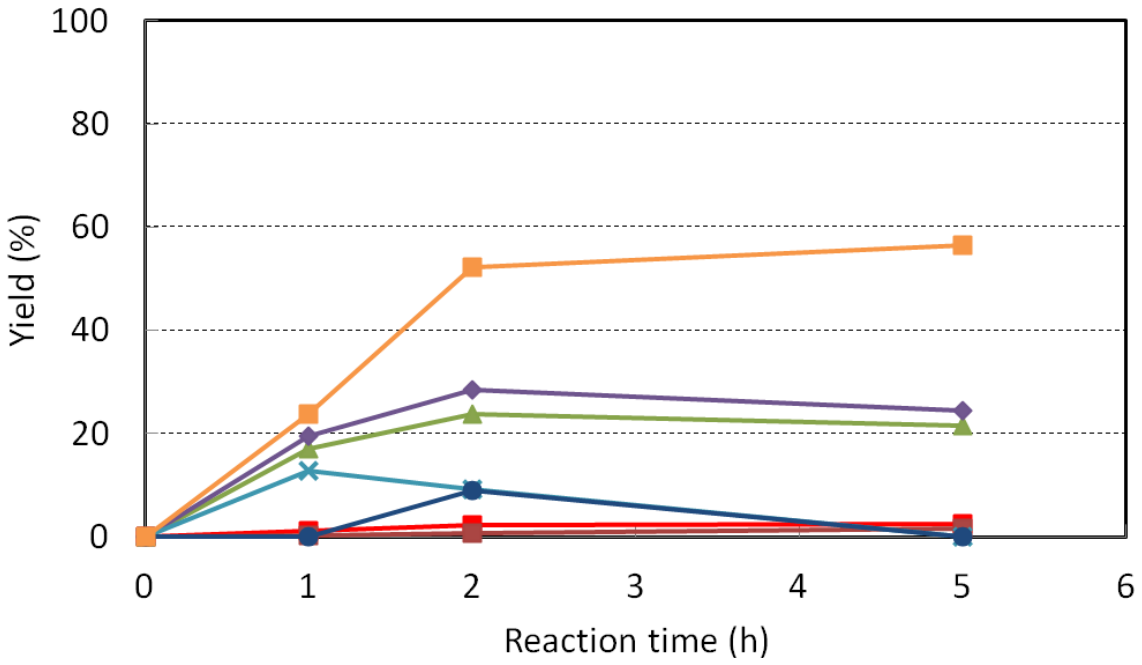


Figure 6 Reductive etherification of HMF: effect of reaction time on yield to ETH-ETH (■), ETH-ALD-THF (◆), ETH-ALC-DHF (▲), ETH-ALD (×), ETH-ALC (■), LEV (■), ETH-MET (■). Reaction conditions: HMF in 1-propanol (0.27 M), T 100 °C, Pd/Al_2O_3 (1% mol/mol), Amberlyst-15 (7% mol/mol), 16 bars H_2.

Tests with Pt/Al2O3 (5%w/w) were also carried-out, but generally it was less active then Palladium.

Tests starting from FRUCTOSE

Carrying out one-pot experiments (dehydration and then reductive etherification) starting from fructose, the results were incomprehensible, probably all the water and by-products of the dehydration led to several side reactions.

For this reason we decided to perform these tests in two steps. The first was the dehydration of fructose in 1-propanol, in nitrogen atmosphere (5 bars), at 120 °C in the presence of Amberlyst-15 for 2 hours. At the end of the reaction, Pd/Al_2O_3 was loaded and set at 16 bars of hydrogen at 120 °C.

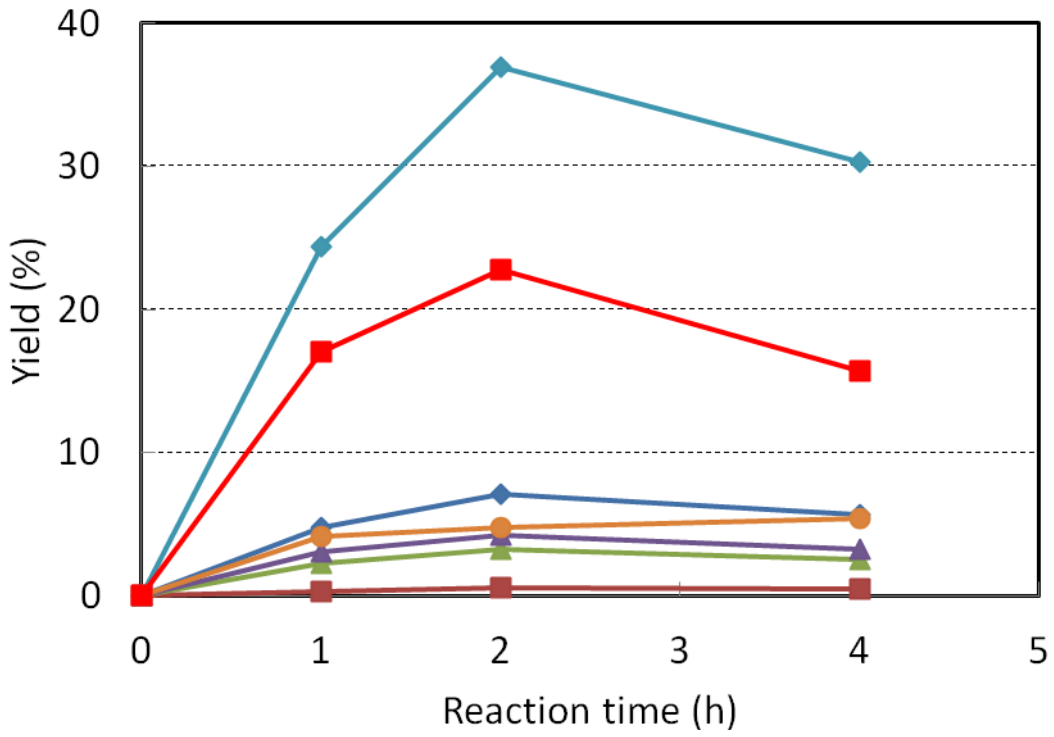


Figure 7 Reductive etherification starting from fructose: effect of reaction time on yield to product m/z = 183 (◆), ETH-ACE-THF (■), ETH-MET (◆), ETH-ETH (●), ETH-ALC-DHF (▲), ETH-ALD-THF (▲), LEV (■). Reaction conditions for the reductive etherification: crude after dehydration in 1-propanol (0.21 M), T 120 °C, Amberlyst-15 (18% mol/mol), Pd/Al_2O_3 (1.33% mol/mol), 16 bars H_2.

The results show that the major product has m/z = 183-166-143-101 and we still do not know what might be; the second product has m/z = 215 (maybe ETH-ACE-THF). For the calculation of the yield we assigned the same response factor to all the products found.

CONCLUSIONS

The production of 2,5-bis-(propoxymethyl)furan as fuel additive has been investigated starting from fructose and using heterogeneous catalysts. In particular, we studied a two-step process: first the reaction of fructose dehydration to HMF (and its ether derivatives), then the reduction to 2,5-bis-(propoxymethyl)furan.

After a wide screening of reaction conditions and kinetic studies, the dehydration of fructose, in small scale, gave us good results (64% yield to desired products and 10% yield to propyl levulinate) using commercial Amberlyst-15; unfortunately, moving to a larger scale, we could not reach the same yields.

For the reductive etherification step, before using fructose, we explored the reaction using "model reactant" (the 2-propoxymethyl-5-dipropoxyacetal-furan, ETH-ACE, and HMF). In this way we obtained simpler crude mixtures that allowed us to screen the reaction conditions more easily and, at the same time, it gave us a better understanding about the reaction pathway. The major product was always the desired 2,5-bis-propoxymethylfuran (almost 60% yield at complete conversion of HMF); other products were present and some still are not identified (as the one with m/z = 172).

Starting from fructose, the results were not so clear: the major product has m/z=183-166-143-101; the second product has m/z = 215 (probably the ETH-ACE-THF). Of course purification and identification of all the reaction products are needed, but due to time restrictions it could not be done.

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