Understanding glycidylation reaction for the formation of pure mono, diglycidyl and dual monomers as glycidyl methacrylate of vanillyl alcohol

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Keywords: epoxy; glycidyl ether; vanillin, biobased polymers; vanillyl alcohol; glycidylation

Abstract

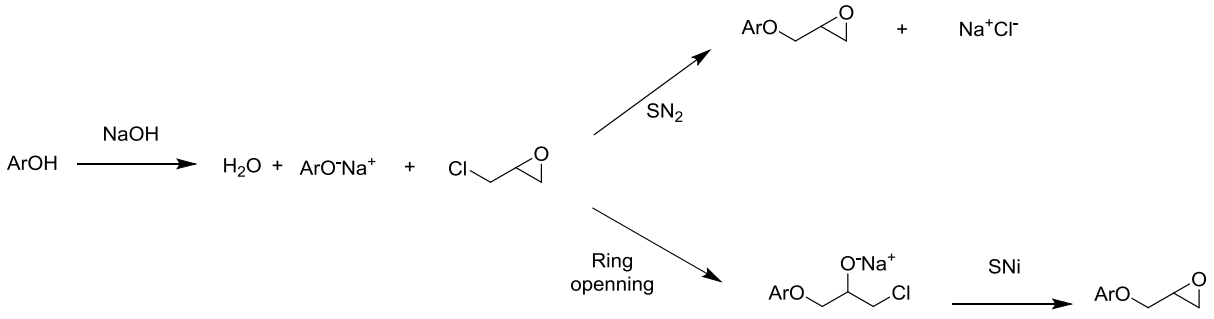
The mono epoxy methacrylate and the diepoxy of vanillyl alcohol (DGEVA) are products already known and reported in literature. However, their respective synthesis processes lead to mixtures of products and side-products. Hence, the final reaction yields are low, mainly due to the purification steps. The mixture of by-products obtained is due to the presence of phenol and methylol in raw vanillin. In this article we have proposed selective synthesis methods avoiding the formation of these by-products, which allows to consider the industrialization of these synthetic routes. Thanks to the difference in reactivity and the basicity of the catalysts used, we were able either to propose a two-step synthesis of the mono-epoxy vanilin , or to epoxidize the two hydroxyl groups to obtain the diepoxy in a single step. Finally, a toxicology study of pure vanillyl alcohol and pure DGEVA was carried out to demonstrate the interest of vanillyl alcohol as a potential substituent of BPA

1. Introduction

Bisphenol A is the aromatic alcohol mainly used in polycarbonate and epoxy thermosets. In epoxy thermosets, Bisphenol A (BPA) is used to synthesize Diglycidylether of Bisphenol A (DGEBA) which represents 75% of commercial epoxy resin, i.e. 2.5 Mt/y.

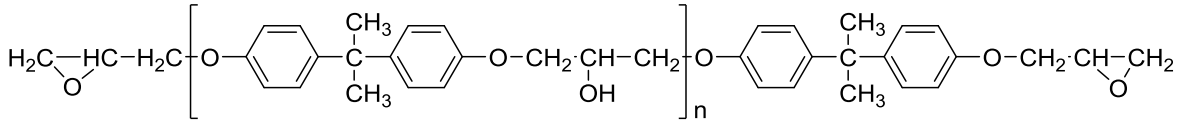
Generally, DGEBA is synthesized by the reaction between bis (4-hydroxyphenylene)-2,2-propane (called bisphenol A) and epichlorohydrin in the presence of NaOH. The mechanism of the reaction between phenols and epichlorohydrin has been reported in literature.[1-3] In the procedure, epichlorohydrin is used in significant excess and reaction is carried out in an

aqueous sodium hydroxide solution. It is clearly reported that the reaction between the phenate ion (ArO^-) and epichlorohydrin follows two competitive mechanisms. A one-step mechanism corresponding to nucleophilic substitution (SN_2 mechanism) with cleavage of the C−Cl bond; and a two-step mechanism based on ring opening of epichlorohydrin with ArO^- followed by intramolecular cyclization (SNi) of the corresponding alcoholate **(Scheme 1).**



Scheme 1: mechanism of glycidylation reaction between phenols and epichlorohydrin

Concerning the synthesis of DGEBA, the main product strongly depends on the stoichiometry of the reactants. Generally, DGEBA **(Scheme 2)** is commercialized with n between 0.03 and 10 to cover all applications, from coating to composites. At room temperature these pre-polymers are crystalline solids for n values close to 0, viscous liquids for n ∼ 0.5, and vitreous (Tg ∼ 40−80°C) for higher values.



Scheme 2: Commercial DGEBA

The glycidylation reaction of BPA and others diphenols is easily carried out in a single step in the presence of a catalytic phase transfer agent, a strong base and an excess of epichlorohydrin at the beginning of the reaction. In theory, an excess of epichlorohydrin allows to limit oligomerization. Low oligomerization represents an advantage for obtaining a fluid product while adjusting the viscosity, compared to pure diglycidyl (n=0), which is solid. This excess allows to limit the oligomerization. A recent patent claimed a process for the glycidylation reaction of numerous diphenols, which permits to obtain pure diglycidylated products (>97% yield) without any purification step, like column chromatography generally used in academic studies.[4] The authors proceeded in two steps, using phase transfer catalysts for the first step of synthesis yielding the chlorohydrin. A wide variety of phase transfer catalysts can be used, for example quaternary ammonium salts, quaternary phosphonium salts, sulphoxydes, sulphonates, guanidinium salts and imidazolium salts. Then, in a second step,

after the elimination of the epichlorohydrin excess by distillation, the addition of basic soda solution allowed to form the diglycidyl ether.

However, BPA is classified as an endocrine- disrupting substance (EDC) due to its potential to mimic estrogen and human health risks.[5] The potential health hazards of EDCs include various cancers, brain and behavioral changes in fetuses or infants, and female reproductive issues.[6-7]

Among biobased products[8], which are non-hazardous and available in large quantities to replace BPA, there are plant oils, furan derivatives, tannins and lignin. To achieve the physico-chemical properties of DGEBA, oils and to a lesser extent furans, cannot be considered. Concerning oils, the literature is abundant with many derivatives reported. However, the Tg of materials thereof are still below ambient temperature, which is not acceptable for composite applications. Regarding furan, the materials obtained from the diepoxy derivative, eg 2,5-bis [(2-oxiranylmethoxy) methyl] furan (BOF), have Tgs around 100°C, much lower than those of DGEBA based materials with equivalent hardeners.[9-10]

Regarding lignin and tannins, these substances are available in very large quantities in biomass. However, they are very complex (poly-) phenols. Their polymeric nature, the difficulty of the extraction process and the variability depending on the plant and the extraction methods and the difficulty of epoxidation process, prevent them from becoming an industrial reality for replacing DGEBA. Hence, to replace DGEBA it is necessary to use molecular natural phenols such as vanillin, eugenol, isoeugenol or ferulic acid obtained from lignin fragmentation or cardanol produced from cashew nut shell liquid (CNSL).[11-12] Concerning cardanol-based materials, the presence of an alkyl chain of 15 carbons reduces the aromatic density, which entails a decrease in mechanical properties compared to DGEBA-based materials.

Only the materials obtained from vanillin, [13-14] eugenol, [15] isoeugenol[16] and ferulic acid[17] present competitive properties compare to DGEBA ones and other bisphenol structures.

Our choice, like that of La Scala et al.,[14] focused on vanillin, which is extracted from biomass and produced on a large scale. Vanillin is the most commercially available mono-aromatic phenol isolated from lignin today. Around 20,000 tons of vanillin are produced per year, of which 15% comes from lignin (around 3,000 t/y).[18-19] For instance, Borregaard Company, the second largest vanillin producer in the world and the only one with a vanillin-from-lignin process, uses ultrafiltration technology, which helps reducing waste stream volumes. However, biobased vanillin is approximately twice as expensive as petroleum-based one, due to the many purification processes required by the food industry. The industrial

synthesis from petroleum, by the Solvay process **(Figure S1)**, currently represents 85% of vanillin (about 10 €/Kg) on the market.

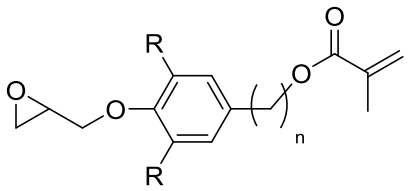
However, before being epoxidized, vanillin must be converted into vanillyl alcohol. The synthesis of vanillyl alcohol is carried out according to two main syntheses, the reduction of vanillin and the synthesis from guaiacol. [20-28]

Hence, these processes lead to mixtures of isomers of vanillyl alcohol (in ortho and para position) and sometimes to ethers of these derivatives on the methylol generated. The synthesis of epoxy materials from vanillyl alcohol requires the synthesis of epoxy resin (equivalent to DGEBA) by glycidylation reaction with epichlorohydrin. Concerning the vanillin derivatives, Stanzione et al.[14, 29-30] and our team [31-33] worked on the synthesis of epoxy resin according to this process of glycidylation of vanillin with epichlorohydrin. Stanzione et al. described the synthesis of vanillin diglycidyl ethers.[14] The reaction product contains around 70-85% of diepoxidized product and 15-30% of mono epoxidized product in which the hydroxyl group did not react. The authors also observed equivalent results on the gastrodigenin functionalization. The gastrodigenin alcohol corresponds to vanillyl alcohol without methoxy group. Stanzione et al.[30] reported that the purification by column chromatography (which is not an industrial process) necessary to remove the monoepoxidized is a drawback for the industrialization of DGEVA.

In the same way, Fache et al.[33] directly purified their product by column chromatography to obtain a pure diepoxidized product without indicating the presence of this monoepoxidized product. Thus, our previous results obtained as well as those of Stanzione et al. did not allow considering the industrialization of an epoxidized vanillyl alcohol to replace DGEBA, even if the synthesized materials had very interesting physico-chemical properties able to meet properties of DGEBA epoxy resin.

Recently, Boni et al. [16,34] synthesized diepoxidized isoeugenol as a similar replacement of DGEBA. Various products were obtained in addition to the desired monoglycidyl ether and the authors performed a column chromatography to isolate the monoglycidyl ether from isoeugenol. After the oxidation reaction on the unsaturation bond the authors obtained pure diepoxidized product. Hence, the authors studied in detail the presence of two types of oligomers during the glycidylation reaction of phenol.[35] After oxidation of the residual double bond, the authors obtained a mixture of diepoxidized monoeugeol and diepoxidized dieugenol. The materials obtained from this mixture exhibited high Tg. The authors concluded that ultimately, purification by column chromatography after their first step was

not necessary and the process can be industrialized.[35] More recently, Stanzione et al.[36-37] synthesized methacrylates from monoepoxidized vanillin **(Scheme 3).**

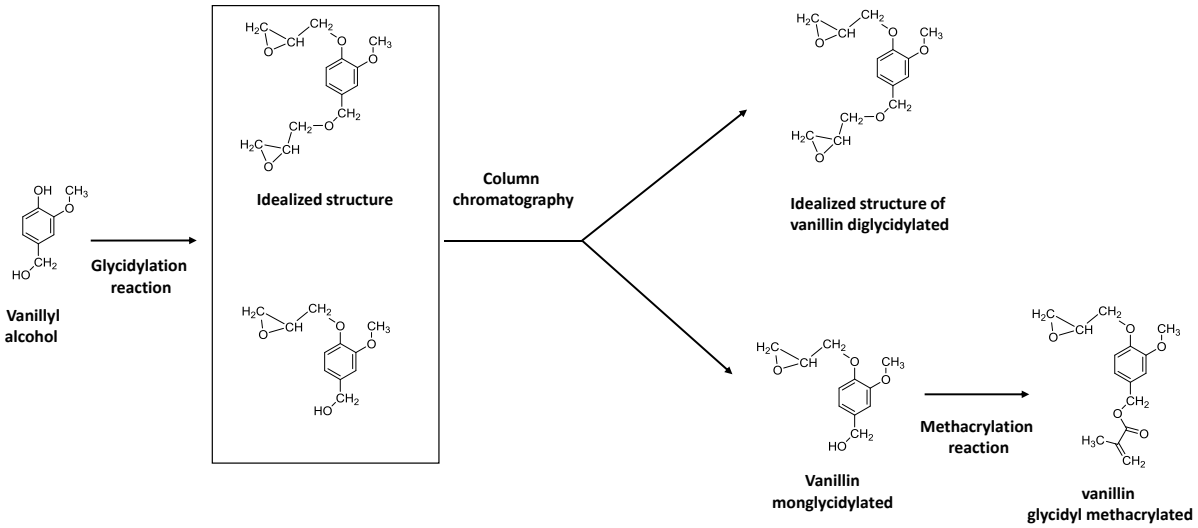


With R= -H or -OCH_3 and n=1 ou 2

Scheme 3 : Structures of dual functional monomers.

Their objective was the substitution of toxic glycidyl methacrylate. Their process simply reduced the amount of NaOH solution. Thus, the obtained product must be purified by column chromatography due to the presence of diepoxy compound. Indeed, the presence of diepoxy compound poses crosslinking problems during the polymerization of the obtained methacrylate. Hence, their final yield was only 55%.

Finally, the conclusion of all these works, as shown in Scheme 4, is that these monomers, monoepoxidized and diepoxidized vanillin, are very interesting monomers but their purification method (chromatography) and the obtained yields, do not allow their industrialization. Indeed, the presence of monoepoxy product is detrimental for replacing DGEBA in epoxy resins and paradoxically, the presence of diepoxy is detrimental for the manufacture of bifunctional monomers in acrylic resins. In addition, the large quantities of reagents (sodium hydroxide, epichlorohydrin) and the nature of the solvents are a limitation to industrialization.



Scheme 4 : Synthesis of monoepoxidized, diepoxidized, and glycidyl methacrylate monomers from vanillyl alcohol.

Thus, the objective of this work is to achieve a technological leap in the glycidylation reaction of vanillyl alcohol to obtain these both mono and diepoxy monomers by avoiding column chromatography to allow industrial scale-up. In addition, to anticipate an application as a substitute for BPA, the toxicological study of the synthesized monomers was carried out.

2. Experimental section

2.1. Materials

Vanillyl alcohol (VA) (98%), triethylbenzylammonium chloride (TEBAC) (99%), tetraethylamonium bromide (TEAB) (99%), 2,2′-Azobis(2-methylpropionitrile) (AIBN) (98%), Zirconium(IV) acetylacetonate (ZrAcAc) (97%), Hydroquinone (99%), Methyl methacrylate (MMA) (99%), anhydrous sodium sulfate (Na_2SO_4) (99%), Sodium Chloride (NaCl) (99%) and dichloromethane (DCM) all solvents used (>99.5%) were purchased from Sigma-Aldrich. Epichlorohydrin (EP) (>99%) were purchased from Fluka.

Sodium hydroxide, NaOH (99%), was purchased from Fisher. All reagents were used as received.

2.2. Syntheses

2.2.1. Synthesis of oligomeric DGEVA

VA 130 g (0.84 moles), TEBAC 19.21 g (0.084 moles, 0.1 eq) and EP 234.06 g (2.53 moles, 3 or 10 eq) were added to a round-bottomed flask. The mixture was stirred for 16 hours at room temperature. The solution was then cooled at 10°C. An aqueous solution of NaOH at 33% (w/w) (5.06 moles, 6 eq) was added and the mixture was stirred for 20 hours at room temperature. The reaction mixture was dissolved in DCM and was shaken vigorously twice with an equal amount of saturated NaCl/water solution. Organic phase was dried on Na_2SO_4. DCM and EP excess were removed using a rotary evaporator under reduced pressure (10^{-2} mbars, 70°C).

2.2.2. Synthesis of vanillin monoglycidylated (mGEVA)

This synthesis occurs in two step. In first step, VA 100 g (0.65 moles), TEBAC 14.8 g (0.065 moles, 0.1 eq) and EP 300 g (3.24 moles, 5 eq) were added to a round-bottomed flask. The mixture was stirred for 16 hour at room temperature and at 70°C. The reaction mixture was dissolved in 200 g of DCM and was shaken vigorously twice with an equal amount of saturated NaCl/water solution. Organic phase was dried on Na_2SO_4. DCM and EP excess were removed using a rotary evaporator under reduced pressure (10^{-2} mbars, 70°C). In second step the product obtained in first step was dissolved in a round-bottomed flask with 200 g of

DCM and TEAB 19.21 g (0.084 moles, 0.1 eq), NaOH 25.95 g (0.65 moles) and demineralized water 104 g were added. The mixture was stirred vigorously for 3 hour at room temperature. The mixture was shaken vigorously twice with saturated NaCl/water solution. Organic phase was dried on Na_2SO_4. DCM was removed using a rotary evaporator under reduced pressure (10^{-2} mbars, 70°C) to obtain the product (130 g) as white crystalline solid (M = 210.2 g.mol^{-1}) in 95% yield.

2.2.3. Synthesis of vanillyl glycidyl – methacrylate (mGEVA-MMA)

mGEVA 130 g (0.62 moles), MMA 619 g (6.19 moles) and hydroquinone 0.7 g (0.0032 moles) were added to a 1L round-bottomed flask equipped with a Dean Stark. The mixture was stirred strongly at 100°C to realize an azeotropic distillation during 30 min order to eliminate water before added catalyst, the Zirconium(IV) acetylacetonate 8.8 g (0.018 moles, 3% mol). The mixture was stirred for 20 h at 100°C while removing the methanol fraction by distillation. MMA was removed using a rotary evaporator under reduced pressure (10^{-2} mbars, 70°C). The mixture was dissolved in DCM and was extracted three times with carbonate/water solution and a last one time with saturated NaCl/water solution. Organic phase was dried on Na_2SO_4 and DCM was removed using a rotary evaporator under reduced pressure (10^{-2} mbars, 70°C) to obtain the product (152 g) as beige crystalline solid (M = 278.3 g.mol^{-1}) in 88% yield.

2.2.4. Copolymerization of vanillyl glycidyl – methacrylate with MMA monomers

mGEVA-MMA 2 g (0.0072 moles, 10% mol), MMA 10 g (0.0647 moles, 90% mol) and toluene (17 g) were added to a 50 ml two neck round-bottomed flask. The mixture is brought at 70°C with magnetic stirring and a stream of argon. AIBN 0.19 g (0.0011 moles, 1.5% mol/monomers) was added and the mixture was left at 70°C for 16 h. The precipitation was realized in 300 ml of pentane and the white powder obtained was dried at room temperature. 8 g of white powder was obtained.

2.3. Characterization of monomers

2.3.1. Nuclear magnetic resonance (NMR)

The chemical structures of the oligomers were determined by 1H-NMR spectroscopy in a Bruker Avance 400MHz spectrometer at room temperature. Deuterated solvents used are given for each molecule Chemical shifts are given in ppm.

2.3.2. Gel permeation chromatography (GPC)

SEC was performed on a Varian ProStar Model 210 equipped with a refractive index detector. Two PLgel 5 mm MIXED-C 600 mm were used with DMF eluent, calibrated using PEG standards.

2.4. Toxicology tests

Toxicology tests were done on vanillic alcool and DGEVA to compare at BPA.

2.4.1. Cell lines

To characterize the bisphenol-induced ERα, AR, ERRγ, PXR and CAR activities, we used already established HELN ERα, UALH AR, HG5LN ERRγ, HG5LN PXR and HG5LN CAR reporter cell lines.[39-40] Briefly, HELN ERα cells were obtained by stably expression of ERα in HELN (HeLa ERE-luciferase) cells whereas HG5LN ERRγ, HG5LN PXR and HG5LN CAR cells were obtained by stably expression of individual ligand binding domains fused to GAL4 DNA binding domain in HG5LN (HeLa GAL4REx5-luciferase) cells. UALH AR cells were obtained by stably expression of AR in UALH (U2OS ARE-luciferase) cells

HG5LN and HELN cells were cultured in Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12 (DMEM/F-12) containing phenol red and 1 g/l glucose and supplemented with 5% fetal bovine serum, 100 units/ml of penicillin, 100 µg/ml of streptomycin and 1 mg/ml geneticin in a 5% CO_2 humidified atmosphere at 37°C. UALH cells were cultured in Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12 (DMEM/F-12) containing phenol red and 1 g/l glucose and supplemented with 5% fetal bovine serum, 100 units/ml of penicillin, 100 µg/ml of streptomycin and 0,25 mg/ml hygromycin in a 5% CO_2 humidified atmosphere at 37°C.

HG5LN ERRγ, HG5LN PXR and HG5LN CAR cells were cultured in the same medium than HG5Ln cells supplemented with 0.5 µg/ml puromycin. HELN ERα cells were cultured in Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12 (DMEM/F-12) without phenol red and 1 g/l glucose and supplemented with 5% stripped fetal bovine serum, 100 units/ml of penicillin, 100 µg/ml of streptomycin, 0.5 µg/ml puromycin and 1 mg/ml geneticin in a 5% CO2 humidified atmosphere at 37°C. UALH AR cells were cultured in the same medium than UALH cells supplemented with 0.5 µg/ml puromycin.

2.4.2. Methods

Transactivation experiments

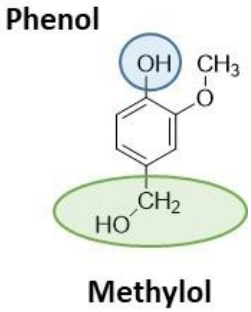
Reporter cell lines were seeded at a density of 25,000 cells per well in 96-well white opaque tissue culture plates (Greiner CellStar) in Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12 (DMEM/F-12) without phenol red and 1 g/l glucose and supplemented with 5%

stripped fetal bovine serum, 100 units/ml of penicillin, 100 µg/ml of streptomycin (test medium). Compounds to be tested were added 24 h later, and cells were incubated at 37°C for 16 h. At the end of the incubation period, culture medium was replaced with test medium containing 0.3 mM luciferin. Luciferase activity was measured for 2 s in intact living cells using a MicroBeta Wallac luminometer (PerkinElmer). Tests were performed in quadriplicate in at least 3 independent experiments. Data were expressed as % of the maximal activity obtained with E2 10 nM (for ERα), R1181 10 nM (for AR) SR12813 3 µM (for PXR) and CITCO 1µM (for CAR). For ERRγ reporter cells, data were expressed as % of the basal activity.

Agonistic activities of the different NRs were tested in presence of bisphenol A (BPA) and vanillyl alcohol at 10 µM. Antagonistic assays were also performed using a concentration approximately 80% of maximal luciferase activity. The antagonistic activity of BPA and vanillyl alcohol were determined by co-incubation with E2 0.1 (for ERα), R1181 1 nM (for AR) SR12813 1 µM (for PXR), CITCO 0.3 µM (for CAR). Due to the strong basal activity of ERRγ, the antagonistic activity of BPA on this receptor were measured in absence of agonist ligand.

3. Results and discussion

Unlike a diphenol, vanillyl alcohol has two different alcohol groups, phenol and aromatic methylol **(Scheme 5)**.



Scheme 5: Vanillyl alcohol

Thus, these alcohols exhibit a different reactivity and in particular in basic medium. Indeed, the phenol hydrogen is more acid than methylol hydrogen. Thus, the presence of methylol leads to the use of a strong base to obtain DGEVA. Like the glycidylation of BPA, the oligomerization reaction depends on reaction conditions as the alcohol/epichlorohydrin ratio, and the base concentration. As for diphenol, it is necessary to use an excess of epichlorohydrin to limit the oligomerization reaction.

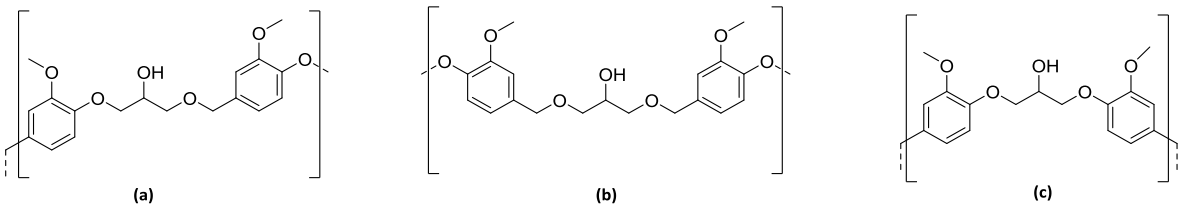
Regarding the traditional glycidylation process, Stanzione et al. and Fache et al. carried it out with the solubilization of vanillyl alcohol (1 eq) and epichlorohydrin (10 eq) in presence of phase transfer catalyst (0.1 eq). This solubilization took 4 h at room temperature for Fache et al. and 3 h at 40-50°C for Stanzione et al. to obtain a limpid solution. After solubilization, a sodium hydroxide solution was added (Stanzione et al. 6,4 eq, Fache et al. 15 eq) at 0°C to carry out intramolecular nucleophilic substitution (SNi) to form epoxy groups and to allow the reaction of methylol with epichlorohydrin by the regular mechanism of phase transfer catalysis. The authors showed by ^{1}H NMR that before the addition of NaOH solution all phenolates had reacted to yield chlorohydrin (70%) and glycidyl function (30%) as reported in literature.[38]

After the addition of sodium hydroxide solution, the production of DGEVA generally yields 70−85% of diepoxidized product and 15−30% of monoepoxidized product in which the methylol hydroxyl did not react. The formation of a mono-epoxidized product during this process necessarily requires a purification step by column chromatography to obtain a pure difunctional product, which represents a problem for the industrial development.

Synthesis of oligomeric diglycidylated vanillyl alcohol (DGEVA)

To avoid the presence of mono functional co-product and thus obtain a pure diepoxy compound, it is necessary to adapt the reaction conditions. The reaction mixture (vanillyl alcohol, epichlorohydrin and TBAB) was stirred at room temperature for 16 h. Then the reaction mixture is maintained at 10-15°C with the addition of 33% (w/w) sodium hydroxide solution (5.06 moles, 6 eq) and left at this temperature for 20 hours to carry out the addition onto all alcohol groups. This step allowed to carry out the SNi to close the epoxy rings and to react the methylol with the excess of epichlorohydrin. Thus, these new reaction conditions led to a higher content of oligomers and avoided the presence of mono-epoxidized product.

The different oligomers, as shown in **Scheme 6**, can be obtained during this reaction.



Scheme 6 : Structure of the oligomeric sequences obtained.

The oligomeric sequences (a) must be formed preferentially compare to (b) and (c). Indeed, for the formation of (b), the methylolate adduct should have reacted first with epichlorohydrin and then with glycidyl adduct. For c) a remaining (unlikely) phenate adduct should react on a

glycidyl adduct already formed. Thus the highest probability is that the methylolate reacts either with free epichlorohydrin or onto the glycidyl already formed (a).

Thus, the higher is the excess of epichlorohydrin, the more pure solid diglycidyl is obtained in the presence of monofunctional. By working in slight excess, a difunctional and slightly oligomerized product is obtained, which is an asset for obtaining a low viscosity product. .

The NMR spectrum **(Figure 1)** shows the presence of diglycidyl of vanillyl alcohol (DGEVA) as well as the oligomers.

According to the ^{1}H NMR analysis and taking into account e and e' protons we can determine that there is about 35% of Glycidyl-O-CH_2-Ph and 65% of Glycidyl-O-Ph. NMR also allowed us to determine the polymerization degree (DP) by calculating the ratio of the aromatic (a) to the glycidyl (e and e') protons which is 1.51. The oligomerization is also confirmed by GPC analysis **(Figure S2)**.

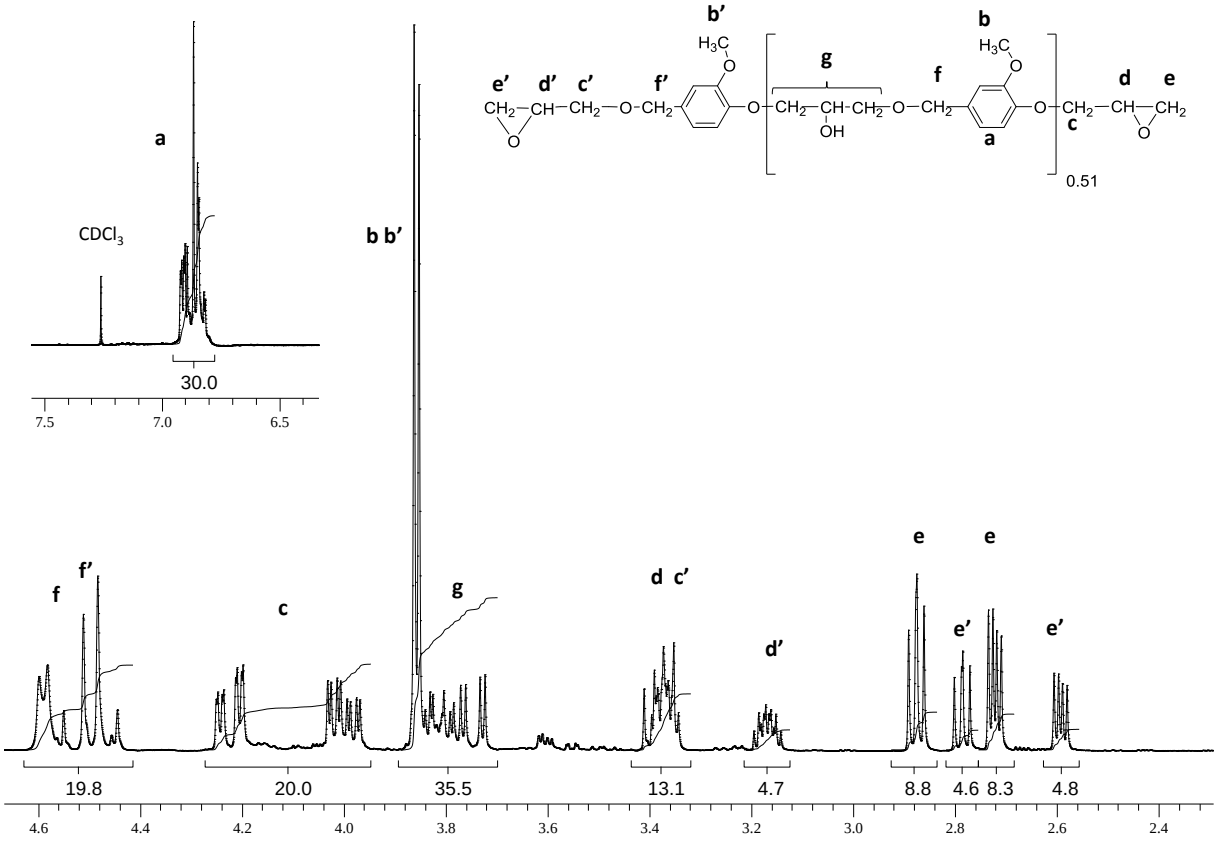


Figure 1: ^{1}H NMR Spectra of oligomeric diglycidylated of vanillyl alcohol (DGEVA).

Purification is an important process parameter to obtain a pure diepoxidized product without epichlorohydrin in high yield. At the end of the reaction, Fache et al.[31-32] carried out a treatment by liquid extraction with ethyl acetate/water followed by flash chromatography. A

pure product (n=0) with a yield of 89% is obtained. Regarding the study of Stanzione et al.[14,29-30], the product is characterized at the end of the reaction by proton NMR. It thus demonstrates the presence of mono-epoxidized vanillin (15-30%) as by product. To eliminate the mono-epoxidized vanillin (which is detrimental to the properties of the materials due to the loss of functionality), they carry out a liquid extraction with CH_2Cl_2/water followed by a flash chromatography. The product obtained after treatment is characterized by NMR, by GPC and by calorimetric assay of the epoxy functions. The diepoxidized product of pure vanillin is obtained and used in epoxy materials.

Despite the good thermo-mechanical properties of materials based on diepoxidized vanillin, flash chromatography purification methods to purify diepoxidized vanillin are prohibitive for industrialization.

Thus, we were interested in the choice of solvent to perform the liquid extraction to improve both processability and yield. The use of ethyl acetate during the liquid extraction is not possible given the exothermic energy generated during this extraction due to the amount of sodium hydroxide to be removed. Toluene was tested as an extraction solvent. The yield of the product obtained after drying and evaporation of the organic phase depends on the amount of epichlorohydrin used. Hence, 70% and 95% yield were obtained when 3 eq and 10 eq were used during the reaction, respectively. Toluene extraction fractionates the product. Chloroform or dichloromethane extraction allowed to recover almost all of the product with a yield of 95%. So, the solvent extraction is an important parameter which led various yield and various physical state (crystalline or fluid product).

These results on the synthesis of DGEVA made it possible to optimize the operating conditions, ratio of reagents, purification to obtain a pure difunctional product with the lowest viscosity. Thus this synthesis could be considered on a larger scale. It should be noted that pure glycidyl (n=0) can only be obtained by purification by column chromatography, as we were able to show in a previous publication. The pure difunctional product is obtained in solid form contrarily to DGEVA, like DGEBA which is a viscous liquid. So the viscosity is linked to the degree of polymerization and therefore to the operating conditions.

Then, in order to replace BPA which is a recognized endocrine disruptor, we have also performed toxicological tests of vanillyl alcohol.

Toxicology tests

A major concern when developing a new chemical to replace bisphenol A (BPA) is its propensity to interact with nuclear receptors (NR)s and how that interaction compares to current BPA. The ERa, AR, ERRg, PXR and CAR agonistic and antagonistic activities of

vanillyl alcohol and DGEVA were compared to BPA. As previously shown BPA is an ERa, ERRg, PXR and CAR agonist whereas it antagonizes AR.[39-40] On the contrary, vanillyl alcohol and DGEVA were unable to modulate ERa, AR, ERRg, PXR and CAR activity **(Figure 2)**. The lack of nuclear receptor-c activity for the vanillyl alcohol and DGEVA relative to BPA is consistent with the structures of these compounds. Thus, the fact of using a monoaromatic phenol, unlike all the bisphenols used, explains the reduction in the endocrine disrupting effect. This endocrine disrupting effect of BPA is due to the distance of approximately 10Å between the phenol groups. Thus the modification of this distance between the phenol groups prevents the complexation of the molecule on the endocrine receptors. Thus monophenolic compounds such as vanillin, eugenol and their derivatives can be used, unlike toxic monophenolic derivatives such as hydroquinone and resorcinol.

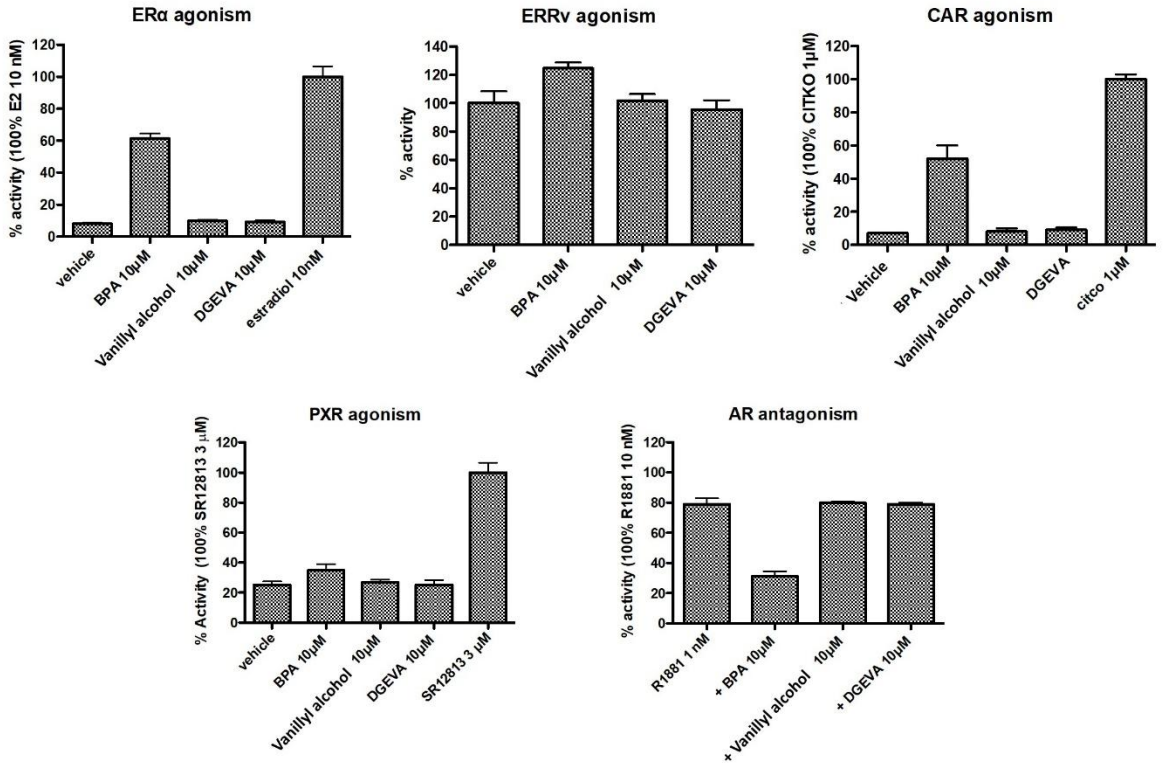


Figure 2: Results of ERa, AR, ERRg, PXR and CAR agonistic and antagonistic activities of vanillyl alcohol, DGEVA and BPA.

Synthesis of mono glycidyl vanillyl alcohol

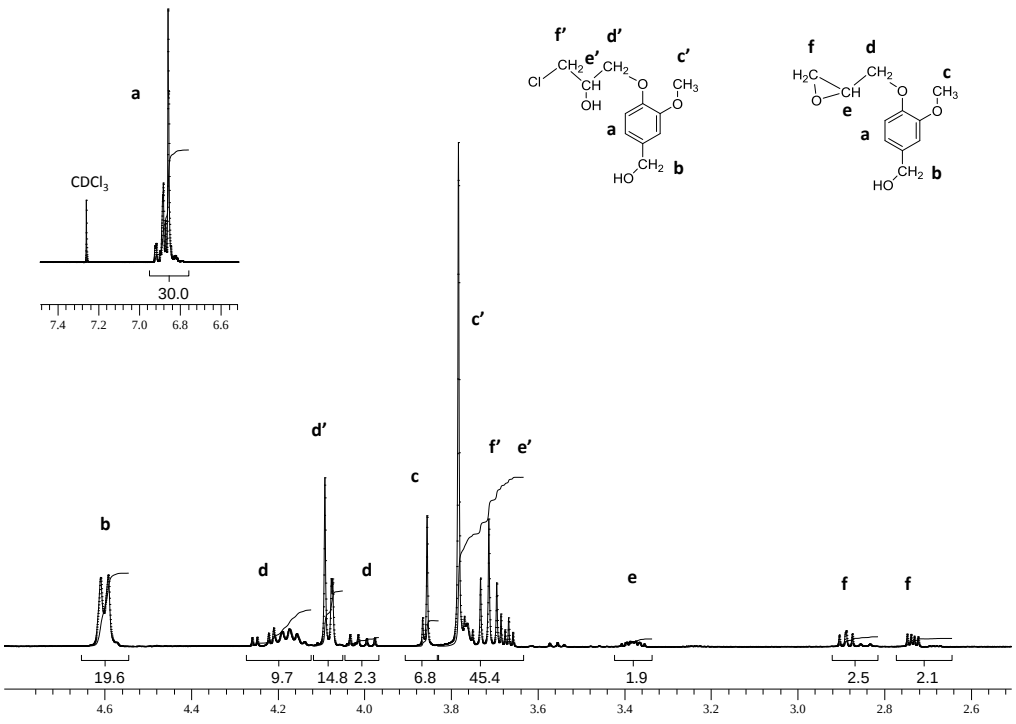
Vanillyl alcohol can be used to synthesize a monomer such as 3-Methoxy-4-(Oxiran-2-ylmethoxy) benzyl methacrylate (VAEM) **(Scheme 3)** having dual reactivity. The pure monoglycidyl vanillin alcohol must be synthesized first.

Monoglycidylated vanillin was synthesized by La Scala et al. with a yield of 55% by a one-step procedure which yielded monoglycidylated vanillin as well as difunctional monomers and oligomers. Thus, flash chromatography (hexane/ethyl acetate) was necessary to obtain pure monoglycidylated vanillin. Following the results obtained above and in order to avoid the formation of difunctional monomers and oligomers by this process, a two-step procedure was proposed to synthesize pure monoglycidylated vanillin.

In our process, the epichlorohydrin excess was removed to avoid the reaction of methylol on epichlorohydrin during the SNi reaction catalyzed by NaOH. First, the vanillyl alcohol was solubilized in epichlorohydrin (1/10 excess) with TEAB (tetraethylamonium bromide) as phase transfer catalyst. This solubilization was carried out at room temperature during 16-24 h, and the product was analyzed by ^{1}H NMR **(Figure 3)**.

The SN1/ring opening ratio can be calculated thanks to OMe protons (c and c') compared to aromatic protons a. In Indeed, the protons of the -OMe group (c and c') have different resonances in the molecule comprising a chlorohydrin and in that comprising an epoxy group, unlike the aromatic protons. Thus, at room temperature the obtained product showed a SN1/ring opening ratio of 1/5 (thanks to the -OMe protons compared to the aromatic protons).

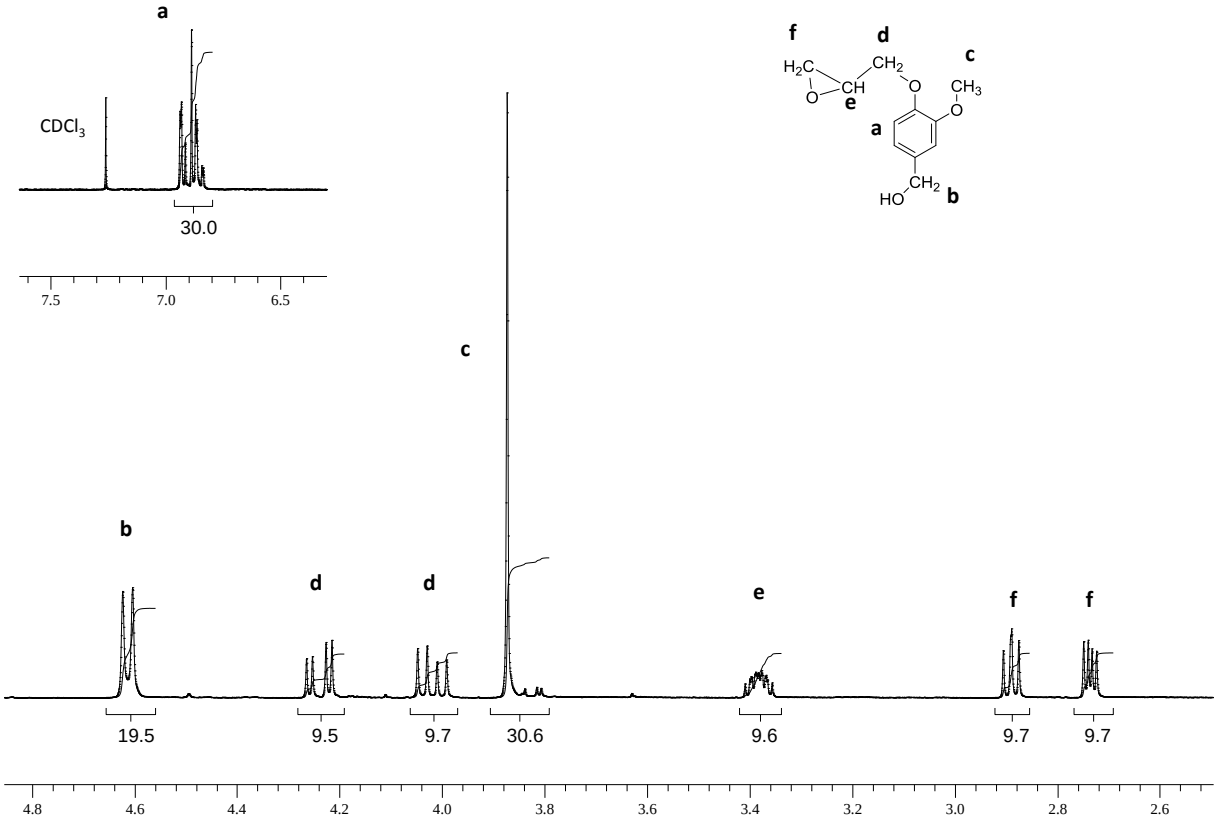
Before the closing step of chlorohydrines catalyzed by NaOH solution, it is necessary to remove epichlorohydrin to avoid the reaction of epichlorohydrin with methylol activated by sodium hydroxide. A liquid extraction allowed to obtain a pure mono glycidyl product **(Figure 4)** with 95% yield. The ^{1}H NMR showed the complete disappearance of chlorohydrines characteristic protons.



399

400 **Figure 3: ^{1}H NMR spectrum of the vanillyl alcohol reaction with epichlorohydrin at**

401 **room temperature**



402

403 **Figure 4: ^{1}H NMR spectrum of hydrochloride closure at room temperature.**

404

The integration of aromatic protons at 6.8ppm (a; 30; 3H) compared to methylol ones at 4.6ppm (b; 19,5; 2H;) and the absence of the quadruplet at 4.25 ppm corresponding to functionalized methylol protons prove that methylol did not react with epichlorohydrin. Moreover, the integration of aromatic protons at 6.8ppm (a; 30; 3H) and the integration of glycidyl protons (d, e and f) show that the hydroxyl of phenol has totally reacted. Thus, a 100% monofunctional product was obtained in the presence of an excess of epichlorohydrin and with the first step at room temperature.

The synthesis of mono glycidyl vanillyl alcohol with the first step carried out at 70°C for 16 hour showed that methylol reacted at higher temperature. The ^{1}H NMR results **(Figure S3)** showed the presence of quadruplet characteristic of functionalized methylol. Compared to the total quantity of methylol protons, 17.5% have reacted. Moreover, there is no presence of OMe protons at 3.78 ppm characteristic of chlorohydrin. At 70°C, the SN1 reaction is predominant.

The synthesis of this pure monofunctional monomer from vanillyl alcohol without chromatography purification has enabled us to synthesize a dual functional monomer: a vanillin glycidyl-methacrylate.

Synthesis of methacrylated glycidyl vanillin

Several synthesis methods can be used for the synthesis of methacrylated glycidyl vanillin monomer. Hence, Stanzione et al.[36-37] performed this synthesis with methacryloyl chloride in the presence of triethylamine as catalyst and obtained a pure white solid product, after flash chromatography with a 62% yield. We carried out this reaction by transesterification of methyl methacrylate with glycidylated vanillic alcohol in the presence of ZrAcac as a catalyst to form methacrylated glycidyl vanillin. After purification by liquid extraction, a pure product is obtained with 88% yield. The product is analyzed by ^{1}H NMR **(Figure 5)**. We observe an evolution of the methylol proton resonance before (4.6ppm) and after (5.15ppm) the reaction. Thus the absence of methylol proton signals at 4.6 ppm proves that the reaction was quantitative.

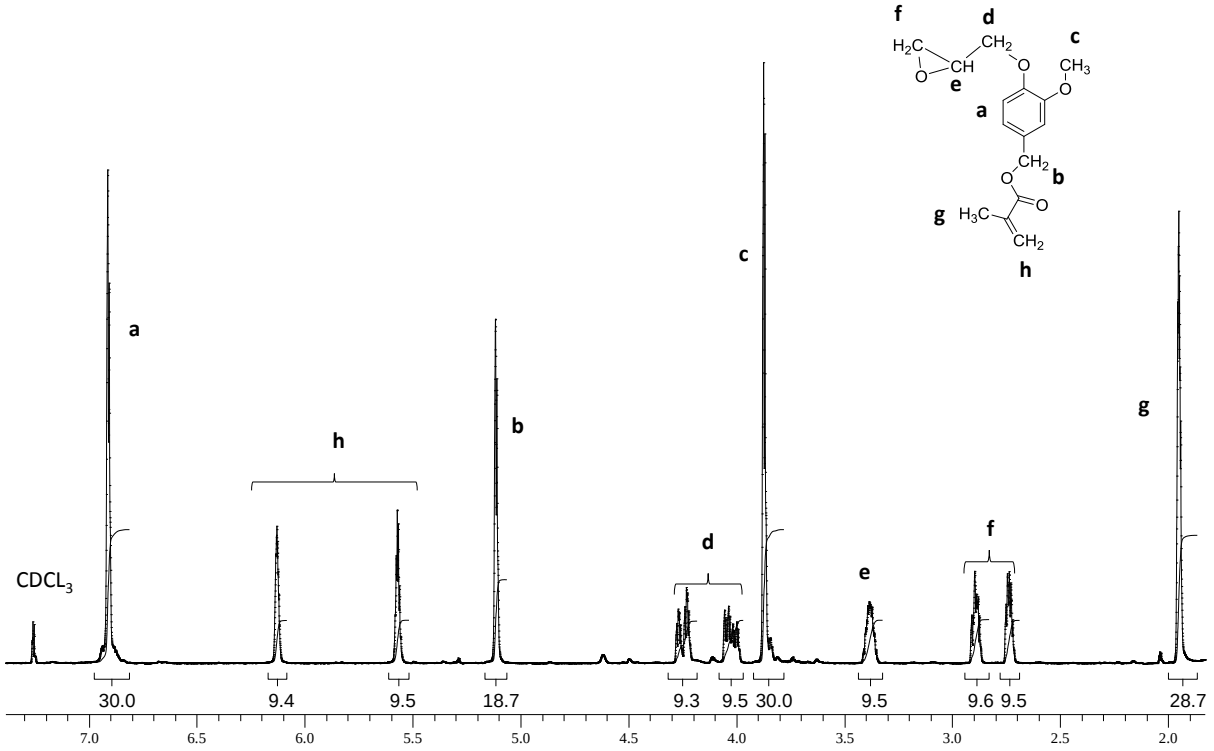
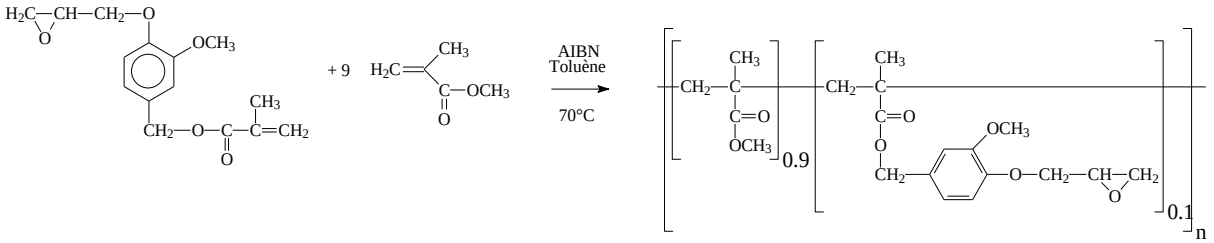


Figure 5 : ^{1}H NMR spectrum of methacrylated glycidyl vanillin .

Copolymerization of methacrylated glycidyl vanillin

The copolymer synthesis **(Scheme 7)** was carried out using conventional radical polymerization in the presence of 10 mol% of methacrylated glycidyl vanillin, 90% of mol MMA and AIBN as initiator, at 70°C in toluene.



Scheme 7 : Copolymer synthesis of methacrylated glycidyl vanillin and MMA monomers.

^{1}H NMR **(Figure S4)** allowed us to calculate the ratio between MMA and MMA of glycidyl vanillin which is 9/1 corresponding to molar ratio of the monomers introduced into the reactor. After purification, this copolymer remained soluble, which clearly demonstrated that no crosslinking occurred and therefore that there is no presence of dimethacrylate.

Conclusion:

In this paper, glycidylation reaction of vanillyl alcohol was studied taking into account the difference in reactivity between phenol and the aromatic methylol of vanillyl alcohol. The

analysis of reaction of epichlorohydrin on phenol and methylol alcohols allowed to demonstrate that the phase transfer catalysts (TBAC) activate phenol and not the methylol at room temperature, whereas Soda activates both phenol and methylol alcohols. Additionally, the elimination of the epichlorohydrin excess must be carried out before closing the chlorohydrin in the presence of NaOH to obtain pure mono glycidyl derivatives. Finally, the amount of reagents (epichlorohydrin and NaOH) has a minor role on the selectivity but not on the oligomerization. Thus, we obtained pure mono- and diglycidyl monomers without purification by column chromatography. Hence, the present study demonstrated that mono-glycidyl, diglycidyl and dual monomers from vanillyl alcohol can be produced at industrial-scale following this routes, which is an important result allowing industrialization. This work on the optimization of the synthesis thus completes the work of Stanzione and ours, which had already demonstrated thermo-mechanical properties equivalent to those of the DGEBA. Thus by providing for the first time the demonstration of the absence of endocrine effect, we offer real substitutes for DGEBA and MAGLY.

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Conflict of Interest

All authors must declare no financial/commercial conflicts of interest.

References

[1] W. Bradley, J. Forrest, O. Stephenson, *J. Chem. Soc.* **1951**, 1589.

[2] Y. M. Beasley, V. Petrow, O. J. Stephenson *J. Pharm. Pharmacol.* **1958**, *10*, 47.

[3] R. Auvergne, S. Caillol, G. David, B. Boutevin, J.P. Pascault *Chemical reviews* **2013**, *114*, 1082-1115.

[4] J. Pal, M. S. Parameswar, S. Swaminathan, G. Mediratta, US Patent WO 2018/129012 (A1) **2018**

[5] H. Okada, T. Tokunaga, X. Liu, S. Takayanagi, A. Matsushima, Y. Shimohigashi *Environmental Health Perspectives*, **2007**, *116(1)*, 32–38. doi:10.1289/ehp.10587

[6] A. M. Nelson, T. E. Long *Polymer International*, **2012**, *61(10)*, 1485–1491. doi:10.1002/pi.4323

[7] M. V. Maffini, B. S. Rubin, C. Sonnenschein, A. M. Soto *Molecular and Cellular Endocrinology*, **2006**, 254-255:179–186. doi:10.1016/j.mce.2006.04.033

[8] D. Zhang, M. J. Dumont *J. Polym. Sci. Part Polym. Chem.* **2017**, *55 (9)*, 1478–1492. https://doi.org/10.1002/pola.28527.

[9] N. Eid, B. Ameduri, B. Boutevin *ACS Sustainable Chemistry & Engineering*, **2021**, *9(24)*, 8018-8031

[10] P. Czub, A. Sienkiewicz *Bio-Based Epoxy Polymers, Blends and Composites: Synthesis, Properties, Characterization and Applications*, Ed Wiley-VCH GmbH, Weinheim Germany, **2021,** p 1-72. doi:10.1002/9783527823604.ch1

[11] B. Lochab, S. Shukla, I. K. Varma *RSC Adv.*, **2014**, 4(42), 21712–21752. doi:10.1039/c4ra00181h

[12] Sun, Z., Fridrich, B., de Santi, A., Elangovan, S., & Barta, K. (2018). Bright Side of Lignin Depolymerization: Toward New Platform Chemicals. Chemical Reviews, 118(2), 614–678. doi:10.1021/acs.chemrev.7b00588

[13] M. Fache, A. Viola, R. Auvergne, B. Boutevin, S. Caillol *European Polymer Journal*, **2015**, *68*, 526–535. doi:10.1016/j.eurpolymj.2015.03.048

[14] E. D. Hernandez, A. W. Bassett, J. M. Sadler, J. J. La Scala, J. F. Stanzione *ACS Sustainable Chemistry & Engineering*, **2016**, *4(8)*, 4328–4339. doi:10.1021/acssuschemeng.6b00835

[15] S. Caillol, B. Boutevin, R. Auvergne *Polymer*, **2021**, *223*, 123663.

[16] C. François, S. Pourchet, G. Boni, S. Rautiainen, J. Samec, L. Fournier, C. Robert, C. M. Thomas, S. Fontaine, Y. Gaillard, V. Placet, L. Plasseraud *C. R. Chim.* **2017**, *20*, 1006–1016. doi: 10.1016/j.crci.2017.10.005

[17] A. Maiorana, A. F. Reano, R. Centore, M. Grimaldi, P. Balaguer, F. Allais, R. A. Gross **2016**, *18(18),* 4961–4973. doi:10.1039/c6gc01308b

[18] E. A. Borges da Silva, M. Zabkova, J. D. Araújo, C. A. Cateto, M. F. Barreiro, M. N. Belgacem, A. E. Rodrigues *Chemical Engineering Research and Design*, **2009**, *87(9)*, 1276–1292. doi:10.1016/j.cherd.2009.05.008

[19] Hans Evju (Borregaard Industries) United States Patent US4151207A **1979**

[20] Z. Zhu, H. Tan, J. Wang, S. Yu, K. Zhou *Green Chem.*, **2014**, *16(5)*, 2636–2643. doi:10.1039/c3gc42647e

[21] Y. Duan, R. Bai, J. Tian, L. Chen, X. Yan *Synthetic Communications*, **2014**, *44(17)*, 2555–2564. doi:10.1080/00397911.2014.909489

[22] D Setamdideh, M Rafigh *E-Journal of Chemistry*, **2012**, *9(4)*, 2338-2345. DOI:10.1155/2012/391643

[23] Z. Lu, C. Hu, J. Guo, J. Li, Y. Cui, Y. Jia *Organic Letters*, **2010**, *12(3)*, 480–483. doi:10.1021/ol902672a

[24] L. Shi, C. A. Fan, Y. Q. Tu, M. Wang, F. M. Zhang *Tetrahedron*, **2004**, *60(12)*, 2851–2855. doi:10.1016/j.tet.2004.01.073

[25] Y. Ni, P. L. Hagedoorn, J. H. Xu, I. W. C. E. Arends,.F. Hollmann *Chemical Communications*, **2012**, *48(99)*, 12056. doi:10.1039/c2cc36479d

[26] I. Iovel, Y. Goldberg, M. Shymanska *Journal of Molecular Catalysis*, **1989**, *57(1)*, 91–103. doi:10.1016/0304-5102(89)80129-4

[27] C. Moreau, F. Fajula, A. Finiels, S. Razigade, L. Gilbert, R. Jacquot, M. Spagnol *Catalysis of Organic Reactions, F.A.* Herkes (ed.), Marcel Dekker, New York, **1998**, p.51

[28] M. Bolognini, F. Cavani, L. Dal Pozzo, L. Maselli, F. Zaccarelli, B. Bonelli, E. Garrone *Applied Catalysis A: General*, **2004**, *272(1-2)*, 115–124. doi:10.1016/j.apcata.2004.05.021

[29] J. F. Stanzione, J. M. Sadler, J. J. La Scala, K. H. Reno, R. P. Wool, *Green Chemistry*, **2012**, *14(8),* 2346. doi:10.1039/c2gc35672d

[30] E. Hernandez *Theses and Dissertations, Rowan University*, **2015**, 458. https://rdw.rowan.edu/etd/458

[31] M. Fache, R. Auvergne, B. Boutevin, S. Caillol *European Polymer Journal*, **2015**, *67*, 527–538. doi:10.1016/j.eurpolymj.2014.10.011

[32] M. Fache, B. Boutevin, S. Caillol *European Polymer Journal*, **2015**, *68*, 488–502. doi:10.1016/j.eurpolymj.2015.03.050

[33] M. Fache, E. Darroman, V. Besse, R. Auvergne, S. Caillol, B. Boutevin Green Chem., **2014,** *16(4)*, 1987–1998. doi:10.1039/c3gc42613k

[34] C. François, S. Pourchet, G. Boni, S. Fontaine, Y. Gaillard, V. Placet, L. Plasseraud *RSC Advances*, **2016**, *6(73)*, 68732–68738. doi:10.1039/c6ra15200g

[35] Q. Ruiz, S. Pourchet, V. Placet, L. Plasseraud, G. Boni *Polymers*, **2020**, *12(1)*, 229. doi:10.3390/polym12010229

[36] A. W. Bassett, K. R. Sweet, R. M. O'Dea, A. E. Honnig, C. M. Breyta, J. H. Reilly, J. J. La Scala, T. H. Epps, J. F. Stanzione *J. Pol. Sci.* **2020,** *58(5)*, 673-682 doi:10.1002/pol.20190110

[37] A. W. Bassett, J. F. Stanzione, J. J. La Scala US Patent 2020048301 (A1), **2020**

[38] B. K. Pchelka, A. Loupy, A. Petit *Tetrahedron* **2006,** *62*, 10968–10979

[39] V. Delfosse, M. Grimaldi, J. L. Pons, A. Boulahtouf, A. le Maire, V. Cavailles, G. Labesse, W. Bourguet, P. Balaguer *Proc. Natl. Acad. Sci. U S A.* **2012**, *109*, 14930-5.

[40] M. Grimaldi, A. Boulahtouf, L. Toporova, P. Balaguer *Toxicology* **2019**; *4*, *20*, 39-45.

[41] C. Ménez, L. Mselli-Lakhal, M. Foucaud-Vignault, P. Balaguer, M. Alvinerie, A. Lespine, *Biochem Pharmacol.* **2012,** *83*, 269-78.

Supporting information

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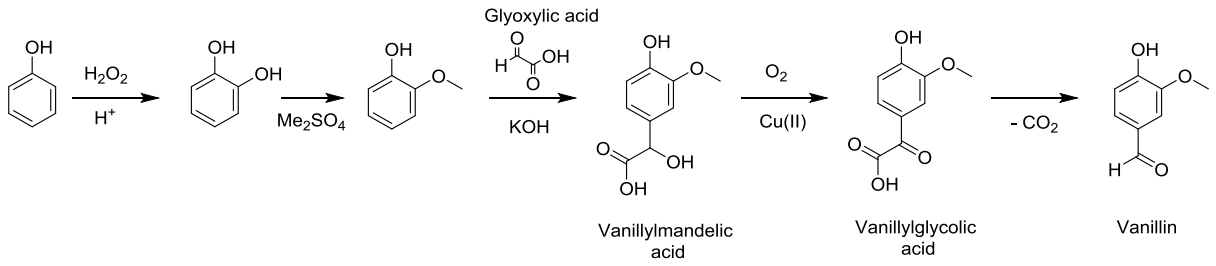


Figure S1: Solvay process of vanillin production from phenol

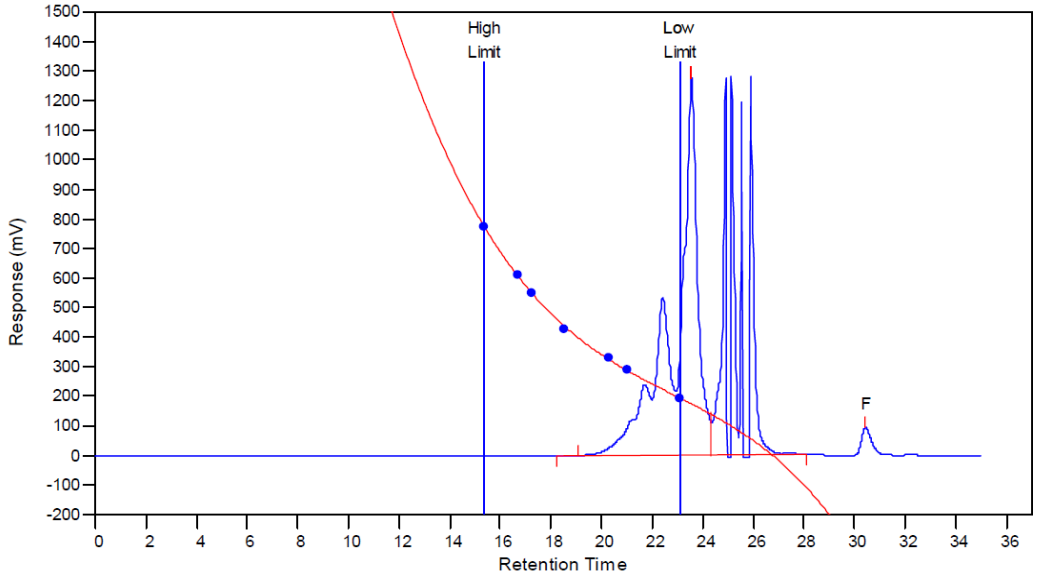


Figure S2: GPC Chromatogram of diepoxidized vanillin.

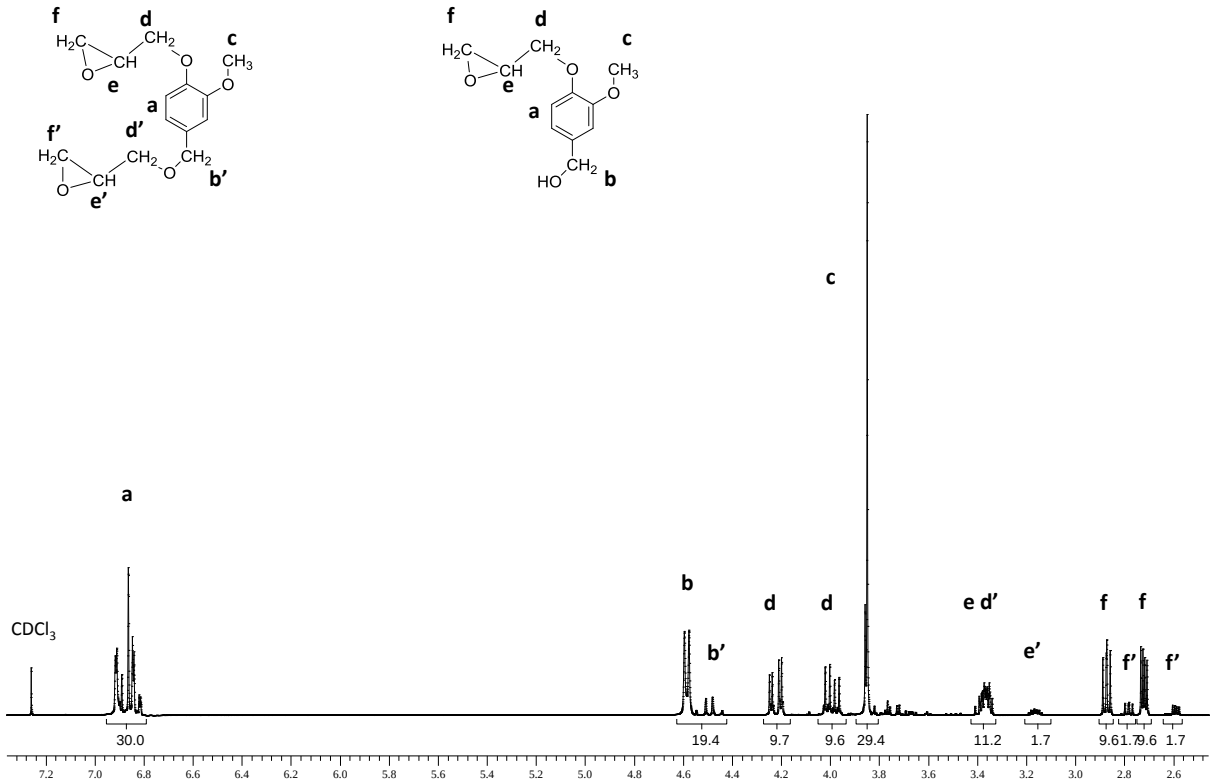


Figure S3: ^{1}H NMR spectrum of the vanillyl alcohol reaction with epichlorohydrin at 70°C.

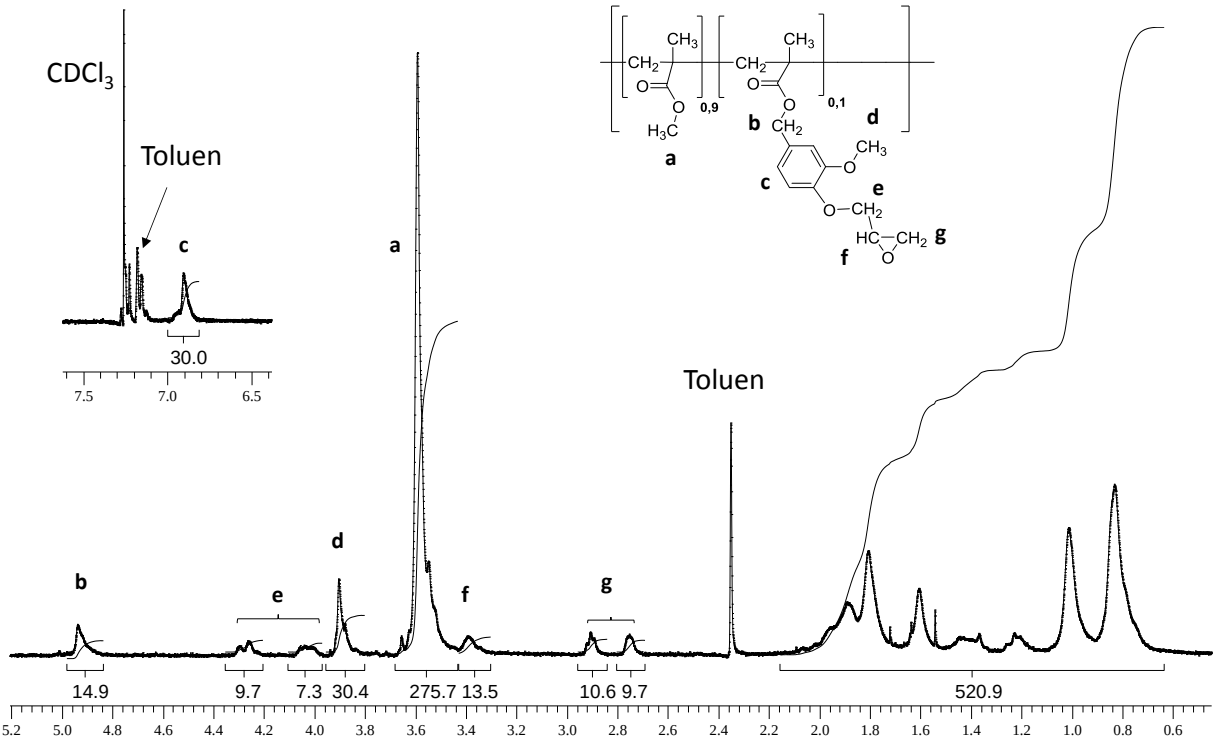


Figure S4: ^{1}H NMR spectrum of vanillin glycidyl methacrylated-MMA copolymers.

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