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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

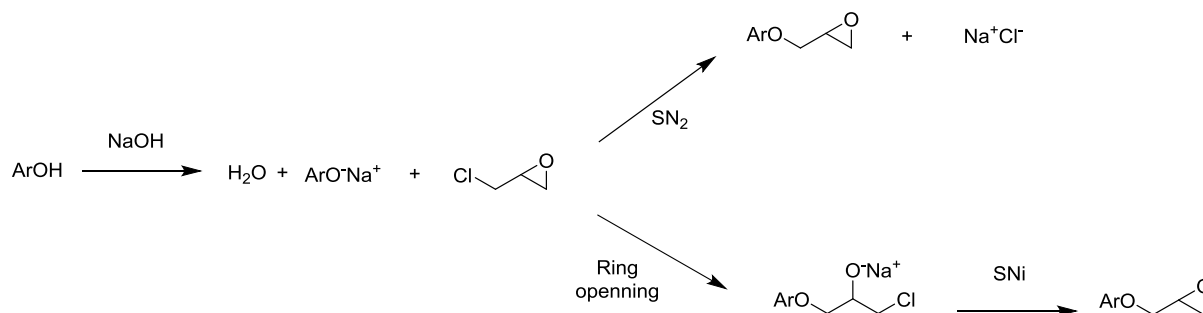
The mono epoxy methacrylate and the diepoxy of vanillyl alcohol (DGEVA) are products already known and reported in literature. However, their respective synthesis processes lead to mixtures of products and side-products. Hence, the final reaction yields are low, mainly due to the purification steps. 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 vanillin, 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.

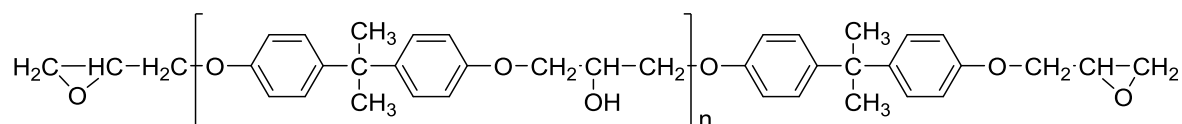
Generally, DGEBA is synthesized by the reaction between bis (4-hydroxyphenylene)-2,2-propane (called bisphenol A) and epichlorohydrin in the presence of NaOH. The mechanism of the reaction between phenols and epichlorohydrin has been reported in literature.^[1-3] In the procedure, epichlorohydrin is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

34 aqueous sodium hydroxide solution. It is clearly reported that the reaction between the
 35 phenate ion (ArO^-) and epichlorohydrin follows two competitive mechanisms. A one-step
 36 mechanism corresponding to nucleophilic substitution ($\text{S}_{\text{N}}2$ mechanism) with cleavage of the
 37 C–Cl bond; and a two-step mechanism based on ring opening of epichlorohydrin with ArO^-
 38 followed by intramolecular cyclization ($\text{S}_{\text{N}}\text{i}$) of the corresponding alcoholate (**Scheme 1**).



41 **Scheme 1: mechanism of glycidylation reaction between phenols and epichlorohydrin**

42 Concerning the synthesis of DGEBA, the main product strongly depends on the stoichiometry
 43 of the reactants. Generally, DGEBA (**Scheme 2**) is commercialized with n between 0.03 and
 44 10 to cover all applications, from coating to composites. At room temperature these pre-
 45 polymers are crystalline solids for n values close to 0, viscous liquids for $n \sim 0.5$, and vitreous
 46 ($T_g \sim 40\text{--}80^\circ\text{C}$) for higher values.



48 **Scheme 2: Commercial DGEBA**

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

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

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

67 Among biobased products^[8], which are non-hazardous and available in large quantities to
68 replace BPA, there are plant oils, furan derivatives, tannins and lignin. To achieve the
69 physico-chemical properties of DGEBA, oils and to a lesser extent furans, cannot be
70 considered. Concerning oils, the literature is abundant with many derivatives reported.
71 However, the Tg of materials thereof are still below ambient temperature, which is not
72 acceptable for composite applications. Regarding furan, the materials obtained from the
73 diepoxy derivative, eg 2,5-bis [(2-oxiranylmethoxy) methyl] furan (BOF), have Tgs around
74 100°C, much lower than those of DGEBA based materials with equivalent hardeners.^[9-10]

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

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

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

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

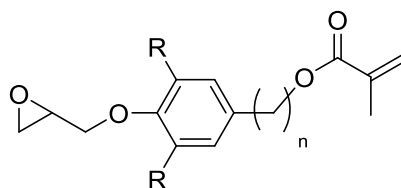
97 However, before being epoxidized, vanillin must be converted into vanillyl alcohol. The
98 synthesis of vanillyl alcohol is carried out according to two main syntheses, the reduction of
99 vanillin and the synthesis from guaiacol.^[20-28]

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

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

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

128 not necessary and the process can be industrialized.^[35] More recently, Stanzone et al.^[36-37]
 129 synthesized methacrylates from monoepoxidized vanillin (**Scheme 3**).
 130

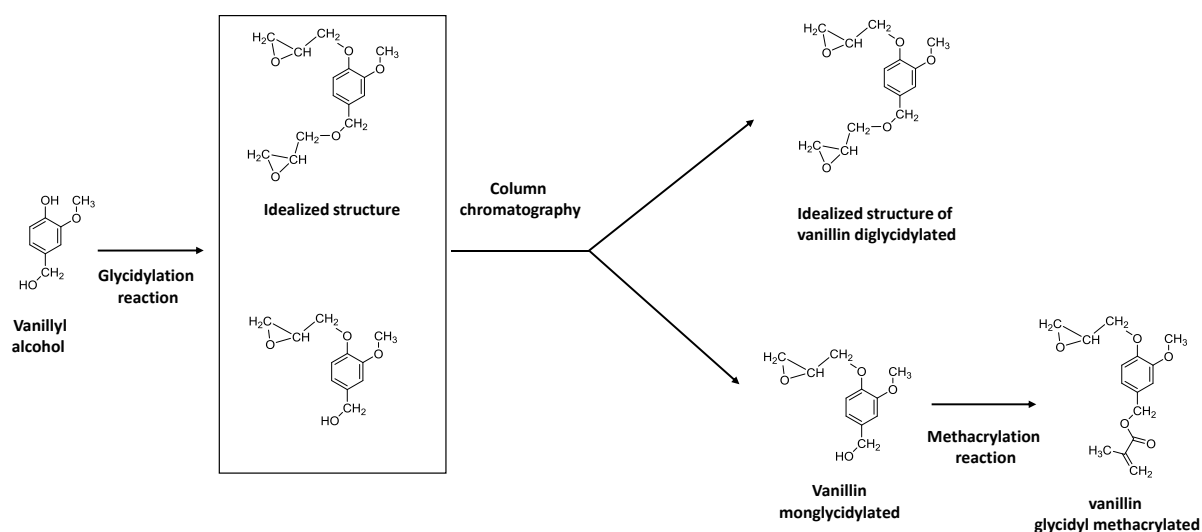


With R= -H or -OCH₃ and n=1 ou 2

131
 132 **Scheme 3 : Structures of dual functional monomers.**

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

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



146
 147 **Scheme 4 : Synthesis of monoepoxidized, diepoxidized, and glycidyl methacrylate**
 148 **monomers from vanillyl alcohol.**

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

153

154 **2. Experimental section**

155 **2.1. Materials**

156 Vanillyl alcohol (VA) (98%), triethylbenzylammonium chloride (TEBAC) (99%),
157 tetraethylammonium bromide (TEAB) (99%), 2,2'-Azobis(2-methylpropionitrile) (AIBN)
158 (98%), Zirconium(IV) acetylacetonate (ZrAcAc) (97%), Hydroquinone (99%), Methyl
159 methacrylate (MMA) (99%), anhydrous sodium sulfate (Na₂SO₄) (99%), Sodium Chloride
160 (NaCl) (99%) and dichloromethane (DCM) all solvents used (>99.5%) were purchased from
161 Sigma-Aldrich. Epichlorohydrin (EP) (>99%) were purchased from Fluka.

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

164 **2.2. Syntheses**

165 *2.2.1. Synthesis of oligomeric DGEVA*

166 VA 130 g (0.84 moles), TEBAC 19.21 g (0.084 moles, 0.1 eq) and EP 234.06 g (2.53 moles,
167 3 or 10 eq) were added to a round-bottomed flask. The mixture was stirred for 16 hours at
168 room temperature. The solution was then cooled at 10°C. An aqueous solution of NaOH at
169 33% (w/w) (5.06 moles, 6 eq) was added and the mixture was stirred for 20 hours at room
170 temperature. The reaction mixture was dissolved in DCM and was shaken vigorously twice
171 with an equal amount of saturated NaCl/water solution. Organic phase was dried on Na₂SO₄.
172 DCM and EP excess were removed using a rotary evaporator under reduced pressure (10⁻²
173 mbars, 70°C).

174 *2.2.2. Synthesis of vanillin monoglycidylated (mGEVA)*

175 This synthesis occurs in two step. In first step, VA 100 g (0.65 moles), TEBAC 14.8 g (0.065
176 moles, 0.1 eq) and EP 300 g (3.24 moles, 5 eq) were added to a round-bottomed flask. The
177 mixture was stirred for 16 hour at room temperature and at 70°C. The reaction mixture was
178 dissolved in 200 g of DCM and was shaken vigorously twice with an equal amount of
179 saturated NaCl/water solution. Organic phase was dried on Na₂SO₄. DCM and EP excess
180 were removed using a rotary evaporator under reduced pressure (10⁻² mbars, 70°C). In second
181 step the product obtained in first step was dissolved in a round-bottomed flask with 200 g of

182 DCM and TEAB 19.21 g (0.084 moles, 0.1 eq), NaOH 25.95 g (0.65 moles) and
183 demineralized water 104 g were added. The mixture was stirred vigorously for 3 hour at room
184 temperature. The mixture was shaken vigorously twice with saturated NaCl/water solution.
185 Organic phase was dried on Na₂SO₄. DCM was removed using a rotary evaporator under
186 reduced pressure (10⁻² mbars, 70°C) to obtain the product (130 g) as white crystalline solid (M
187 = 210.2 g.mol⁻¹) in 95% yield.

188 2.2.3. Synthesis of vanillyl glycidyl – methacrylate (mGEVA-MMA)

189 mGEVA 130 g (0.62 moles), MMA 619 g (6.19 moles) and hydroquinone 0.7 g (0.0032
190 moles) were added to a 1L round-bottomed flask equipped with a Dean Stark. The mixture
191 was stirred strongly at 100°C to realize an azeotropic distillation during 30 min order to
192 eliminate water before added catalyst, the Zirconium(IV) acetylacetonate 8.8 g (0.018 moles,
193 3% mol). The mixture was stirred for 20 h at 100°C while removing the methanol fraction by
194 distillation. MMA was removed using a rotary evaporator under reduced pressure (10⁻² mbars,
195 70°C). The mixture was dissolved in DCM and was extracted three times with
196 carbonate/water solution and a last one time with saturated NaCl/water solution. Organic
197 phase was dried on Na₂SO₄ and DCM was removed using a rotary evaporator under reduced
198 pressure (10⁻² mbars, 70°C) to obtain the product (152 g) as beige crystalline solid (M = 278.3
199 g.mol⁻¹) in 88% yield.

200 2.2.4. Copolymerization of vanillyl glycidyl – methacrylate with MMA monomers

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

207 2.3. Characterization of monomers

208 2.3.1. Nuclear magnetic resonance (NMR)

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

212 2.3.2. Gel permeation chromatography (GPC)

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

216 **2.4. Toxicology tests**

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

218 *2.4.1. Cell lines*

219 To characterize the bisphenol-induced ER α , AR, ERR γ , PXR and CAR activities, we used
220 already established HELN ER α , UALH AR, HG5LN ERR γ , HG5LN PXR and HG5LN CAR
221 reporter cell lines.^[39-40] Briefly, HELN ER α cells were obtained by stably expression of ER α
222 in HELN (HeLa ERE-luciferase) cells whereas HG5LN ERR γ , HG5LN PXR and HG5LN
223 CAR cells were obtained by stably expression of individual ligand binding domains fused to
224 GAL4 DNA binding domain in HG5LN (HeLa GAL4REx5-luciferase) cells. UALH AR cells
225 were obtained by stably expression of AR in UALH (U2OS ARE-luciferase) cells
226 HG5LN and HELN cells were cultured in Dulbecco's Modified Eagle Medium: Nutrient
227 Mixture F-12 (DMEM/F-12) containing phenol red and 1 g/l glucose and supplemented with
228 5% fetal bovine serum, 100 units/ml of penicillin, 100 μ g/ml of streptomycin and 1 mg/ml
229 geneticin in a 5% CO₂ humidified atmosphere at 37°C. UALH cells were cultured in
230 Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12 (DMEM/F-12) containing phenol
231 red and 1 g/l glucose and supplemented with 5% fetal bovine serum, 100 units/ml of
232 penicillin, 100 μ g/ml of streptomycin and 0,25 mg/ml hygromycin in a 5% CO₂ humidified
233 atmosphere at 37°C.

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

241 *2.4.2. Methods*

242 *Transactivation experiments*

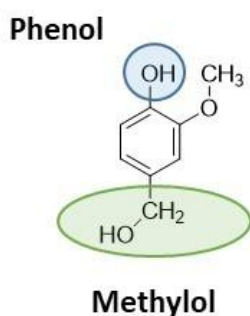
243 Reporter cell lines were seeded at a density of 25,000 cells per well in 96-well white opaque
244 tissue culture plates (Greiner CellStar) in Dulbecco's Modified Eagle Medium: Nutrient
245 Mixture F-12 (DMEM/F-12) without phenol red and 1 g/l glucose and supplemented with 5%

246 stripped fetal bovine serum, 100 units/ml of penicillin, 100 $\mu\text{g/ml}$ of streptomycin (test
247 medium). Compounds to be tested were added 24 h later, and cells were incubated at 37°C for
248 16 h. At the end of the incubation period, culture medium was replaced with test medium
249 containing 0.3 mM luciferin. Luciferase activity was measured for 2 s in intact living cells
250 using a MicroBeta Wallac luminometer (PerkinElmer). Tests were performed in quadruplicate
251 in at least 3 independent experiments. Data were expressed as % of the maximal activity
252 obtained with E2 10 nM (for $\text{ER}\alpha$), R1181 10 nM (for AR) SR12813 3 μM (for PXR) and
253 CITCO 1 μM (for CAR). For $\text{ERR}\gamma$ reporter cells, data were expressed as % of the basal
254 activity.

255 Agonistic activities of the different NRs were tested in presence of bisphenol A (BPA) and
256 vanillyl alcohol at 10 μM . Antagonistic assays were also performed using a concentration
257 approximately 80% of maximal luciferase activity. The antagonistic activity of BPA and
258 vanillyl alcohol were determined by co-incubation with E2 0.1 (for $\text{ER}\alpha$), R1181 1 nM (for
259 AR) SR12813 1 μM (for PXR), CITCO 0.3 μM (for CAR). Due to the strong basal activity of
260 $\text{ERR}\gamma$, the antagonistic activity of BPA on this receptor were measured in absence of agonist
261 ligand.

262 3. Results and discussion

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



266 **Scheme 5: Vanillyl alcohol**

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

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

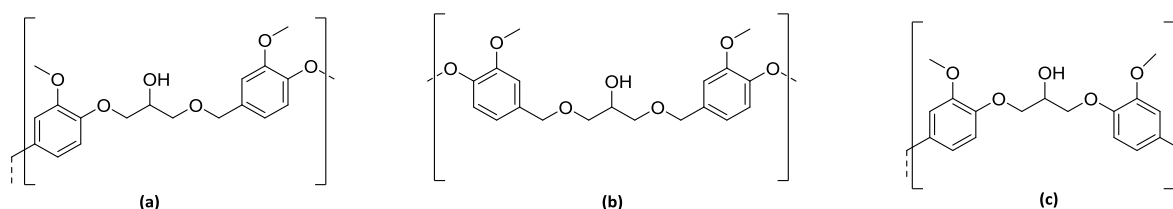
283 After the addition of sodium hydroxide solution, the production of DGEVA generally yields
284 70–85% of diepoxidized product and 15–30% of monoepoxidized product in which the
285 methylol hydroxyl did not react. The formation of a mono-epoxidized product during this
286 process necessarily requires a purification step by column chromatography to obtain a pure
287 difunctional product, which represents a problem for the industrial development.

288 **Synthesis of oligomeric diglycidylated vanillyl alcohol (DGEVA)**

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

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

298



299

300 **Scheme 6 : Structure of the oligomeric sequences obtained.**

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

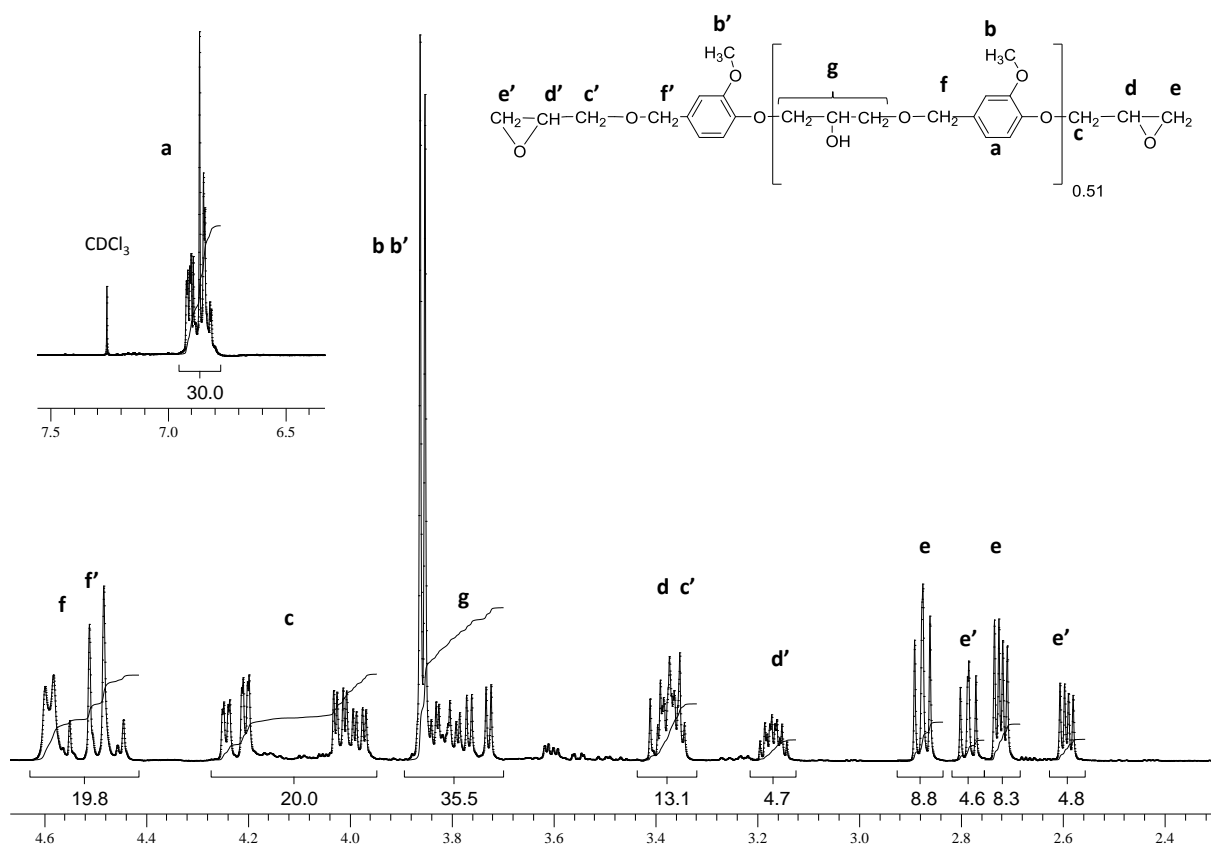
304 glycidyl adduct already formed. Thus the highest probability is that the methylolate reacts
305 either with free epichlorohydrin or onto the glycidyl already formed (a).

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

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

311 According to the ^1H NMR analysis and taking into account e and e' protons we can determine
312 that there is about 35% of Glycidyl-O-CH₂-Ph and 65% of Glycidyl-O-Ph. NMR also allowed
313 us to determine the polymerization degree (DP) by calculating the ratio of the aromatic (a) to
314 the glycidyl (e and e') protons which is 1.51. The oligomerization is also confirmed by GPC
315 analysis (**Figure S2**).

316



317
318 **Figure 1: ^1H NMR Spectra of oligomeric diglycidylated of vanillyl alcohol (DGEVA).**

319
320 Purification is an important process parameter to obtain a pure diepoxidized product without
321 epichlorohydrin in high yield. At the end of the reaction, Fache et al.^[31-32] carried out a
322 treatment by liquid extraction with ethyl acetate/water followed by flash chromatography. A

323 pure product (n=0) with a yield of 89% is obtained. Regarding the study of Stanzone et
324 al.^[14,29-30], the product is characterized at the end of the reaction by proton NMR. It thus
325 demonstrates the presence of mono-epoxidized vanillin (15-30%) as by product. To eliminate
326 the mono-epoxidized vanillin (which is detrimental to the properties of the materials due to
327 the loss of functionality), they carry out a liquid extraction with CH₂Cl₂/water followed by a
328 flash chromatography. The product obtained after treatment is characterized by NMR, by
329 GPC and by calorimetric assay of the epoxy functions. The diepoxidized product of pure
330 vanillin is obtained and used in epoxy materials.

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

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

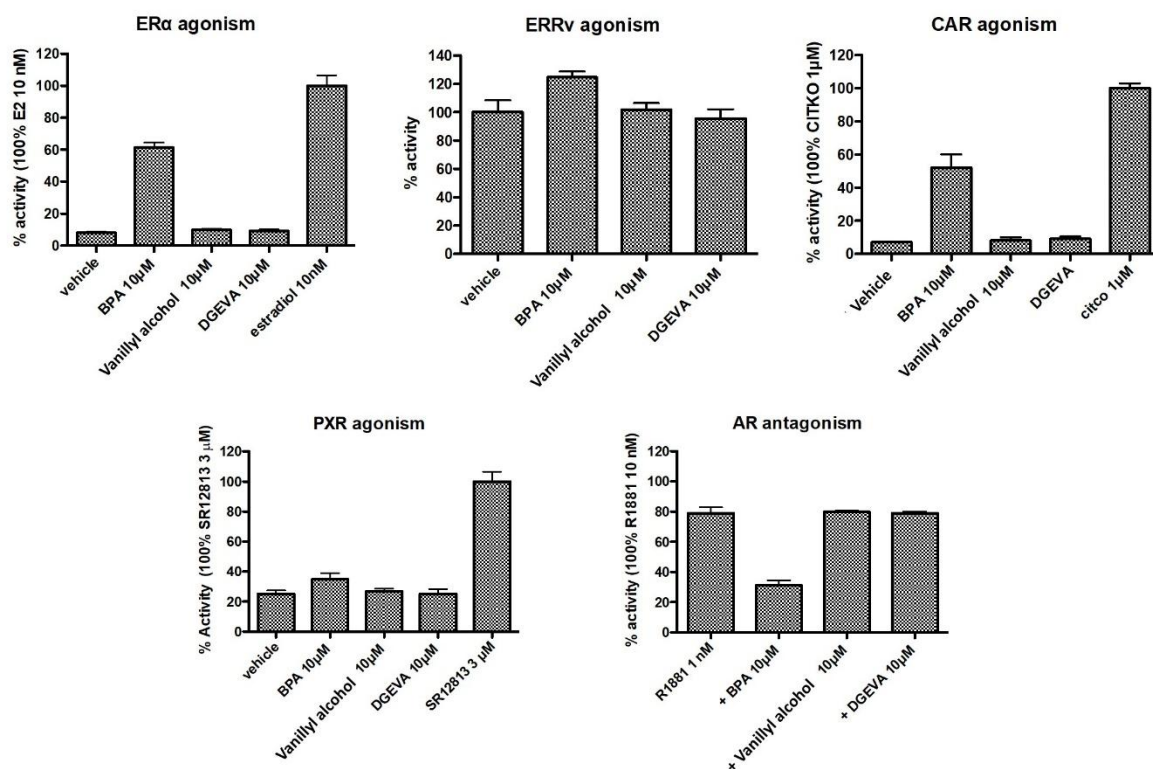
344 These results on the synthesis of DGEVA made it possible to optimize the operating
345 conditions, ratio of reagents, purification to obtain a pure difunctional product with the lowest
346 viscosity. Thus this synthesis could be considered on a larger scale. It should be noted that
347 pure glycidyl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

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

353 **Toxicology tests**

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

357 vanillyl alcohol and DGEVA were compared to BPA. As previously shown BPA is an ERa,
 358 ERRg, PXR and CAR agonist whereas it antagonizes AR.^[39-40] On the contrary, vanillyl
 359 alcohol and DGEVA were unable to modulate ERa, AR, ERRg, PXR and CAR activity
 360 (**Figure 2**). The lack of nuclear receptor-c activity for the vanillyl alcohol and DGEVA
 361 relative to BPA is consistent with the structures of these compounds. Thus, the fact of using a
 362 monoaromatic phenol, unlike all the bisphenols used, explains the reduction in the endocrine
 363 disrupting effect. This endocrine disrupting effect of BPA is due to the distance of
 364 approximately 10Å between the phenol groups. Thus the modification of this distance
 365 between the phenol groups prevents the complexation of the molecule on the endocrine
 366 receptors. Thus monophenolic compounds such as vanillin, eugenol and their derivatives can
 367 be used, unlike toxic monophenolic derivatives such as hydroquinone and resorcinol.
 368



369
 370 **Figure 2: Results of ERa, AR, ERRg, PXR and CAR agonistic and antagonistic activities**
 371 **of vanillyl alcohol, DGEVA and BPA.**

373 Synthesis of mono glycidyl vanillyl alcohol

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

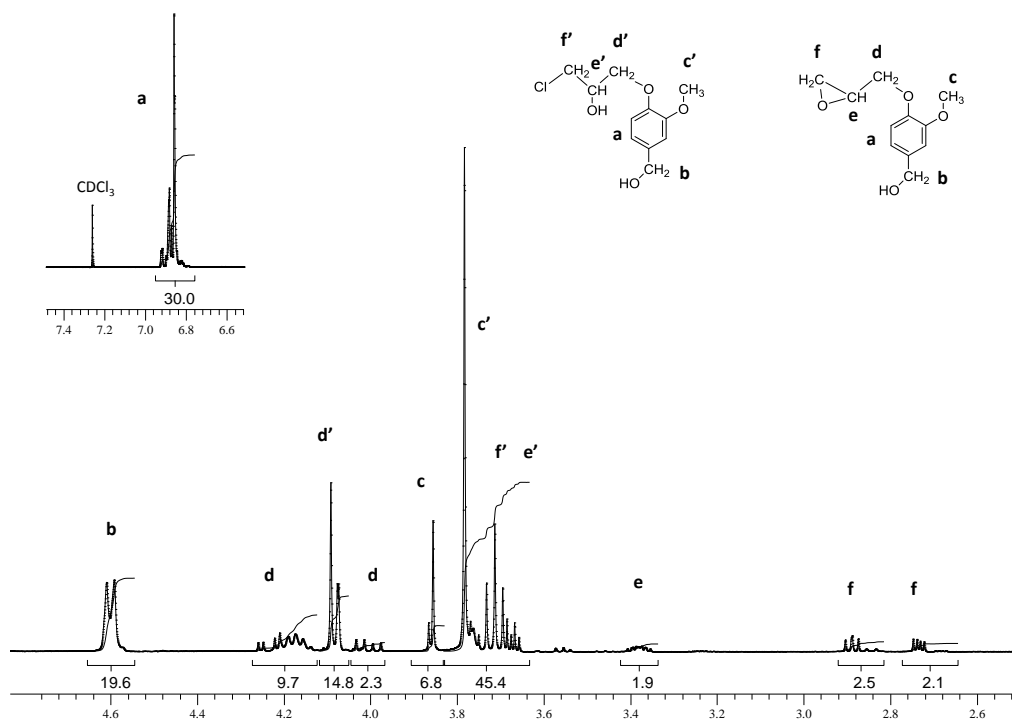
377 Monoglycidylated vanillin was synthesized by La Scala et al. with a yield of 55% by a one-
378 step procedure which yielded monoglycidylated vanillin as well as difunctional monomers
379 and oligomers. Thus, flash chromatography (hexane/ethyl acetate) was necessary to obtain
380 pure monoglycidylated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

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

388 The S_N1/ring opening ratio can be calculated thanks to OMe protons (c and c') compared to
389 aromatic protons a. In Indeed, the protons of the -OMe group (c and c') have different
390 resonances in the molecule comprising a chlorohydrin and in that comprising an epoxy group,
391 unlike the aromatic protons. Thus, at room temperature the obtained product showed a
392 S_N1/ring opening ratio of 1/5 (thanks to the -OMe protons compared to the aromatic protons).

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

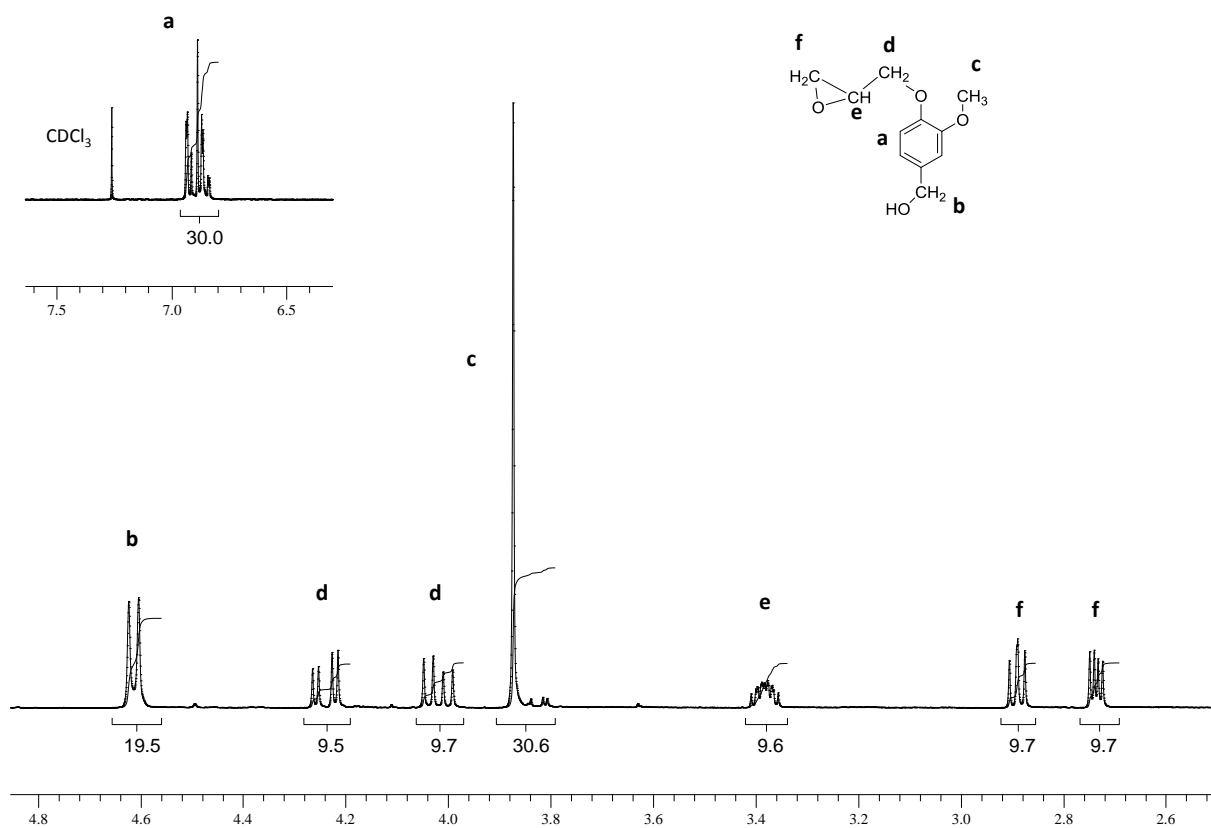
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399

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

401 **room temperature**



402

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

404

405 The integration of aromatic protons at 6.8ppm (a; 30; 3H) compared to methylol ones at
406 4.6ppm (b; 19,5; 2H;) and the absence of the quadruplet at 4.25 ppm corresponding to
407 functionalized methylol protons prove that methylol did not react with epichlorohydrin.
408 Moreover, the integration of aromatic protons at 6.8ppm (a; 30; 3H) and the integration of
409 glycidyl protons (d, e and f) show that the hydroxyl of phenol has totally reacted. Thus, a
410 100% monofunctional product was obtained in the presence of an excess of epichlorohydrin
411 and with the first step at room temperature.

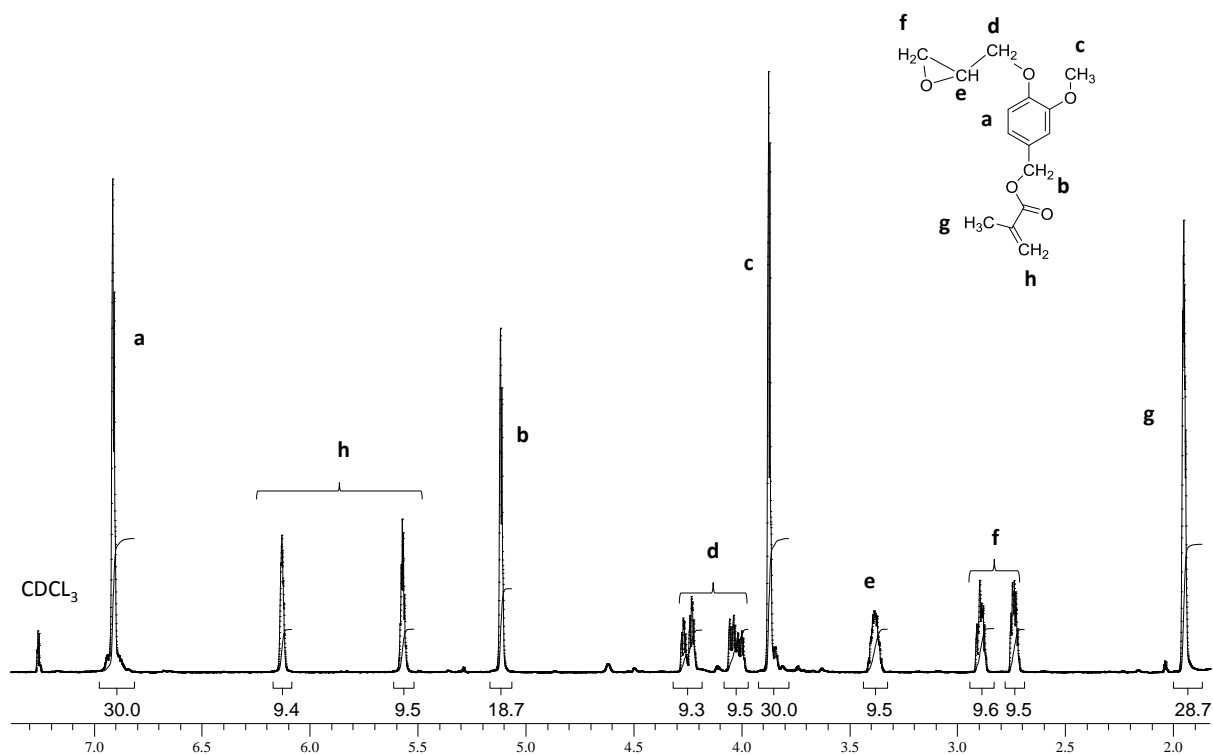
412 The synthesis of mono glycidyl vanillyl alcohol with the first step carried out at 70°C for 16
413 hour showed that methylol reacted at higher temperature. The ¹H NMR results (**Figure S3**)
414 showed the presence of quadruplet characteristic of functionalized methylol. Compared to the
415 total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

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

421 **Synthesis of methacrylated glycidyl vanillin**

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

432

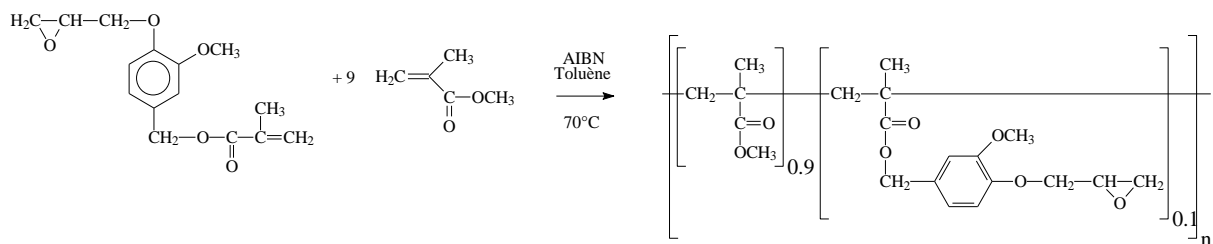


433

434 **Figure 5 : ¹H NMR spectrum of methacrylated glycidyl vanillin .**

435 **Copolymerization of methacrylated glycidyl vanillin**

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



439

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

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

446 **Conclusion:**

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

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

463 **Acknowledgment:**

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465 DIAM, Resipoly, Sogatra, COP and Colas Companies.

466 **Conflict of Interest**

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

468

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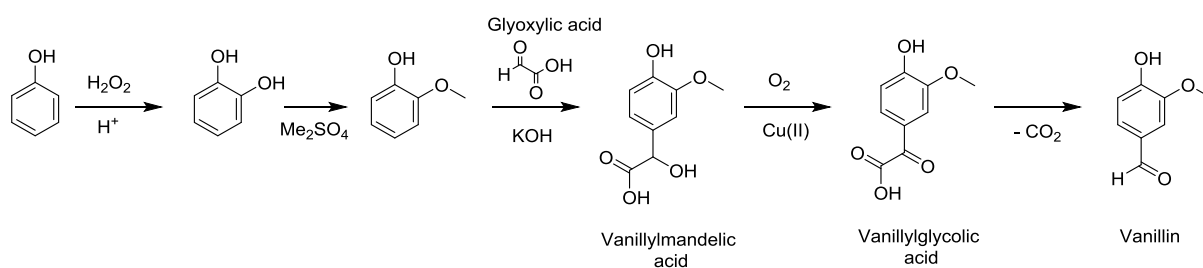
Supporting information

555 Authors : Sylvain Caillol, Rémi Auvergne, Abdelatif Manseri, Gilles Boutevin, Bernard

556 Boutevin, Marina Grimaldi, Patrick Balaguer

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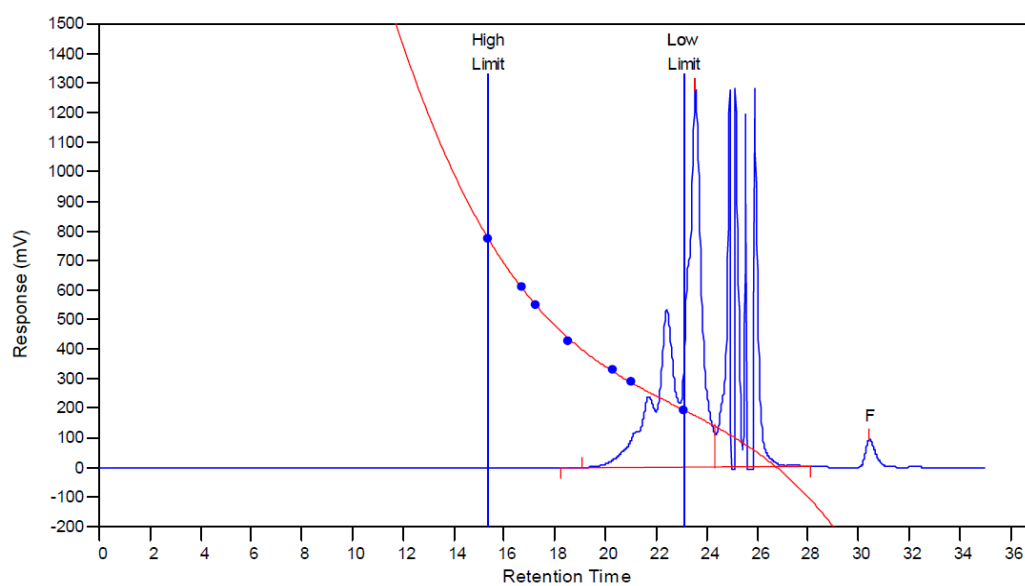
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560 **Figure S1: Solvay process of vanillin production from phenol**

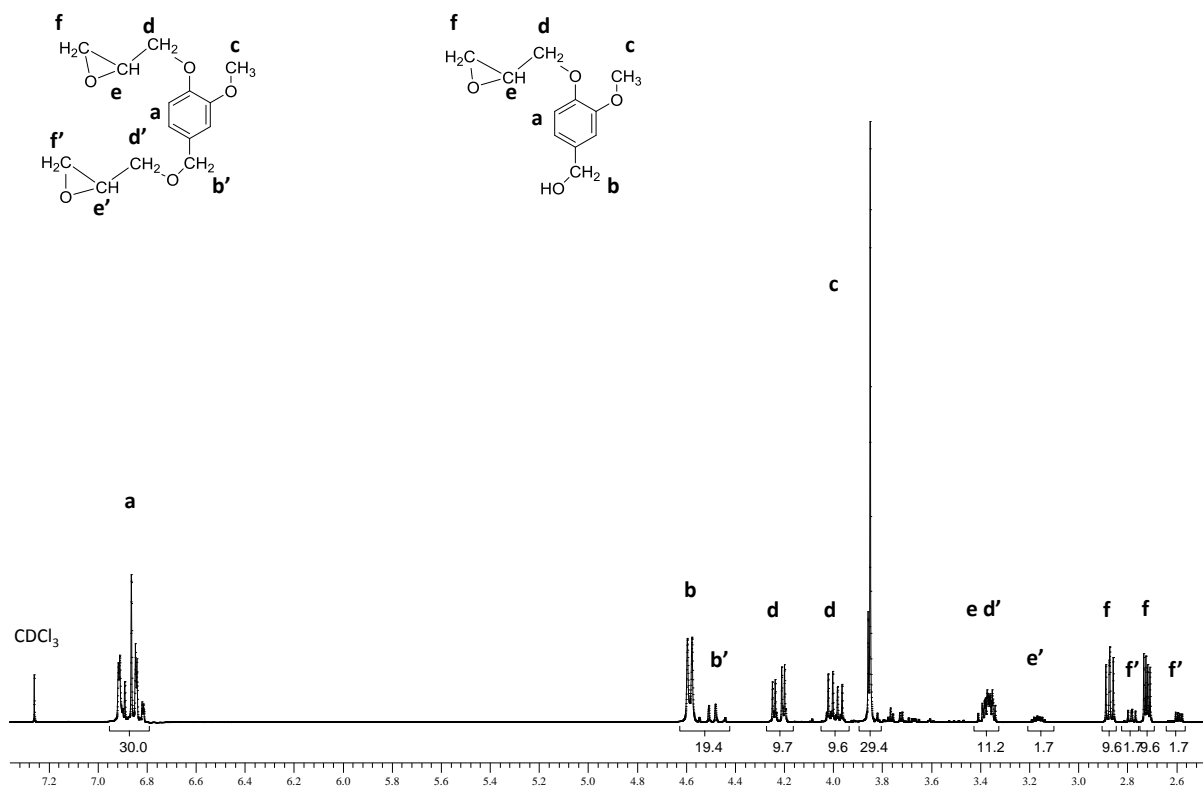
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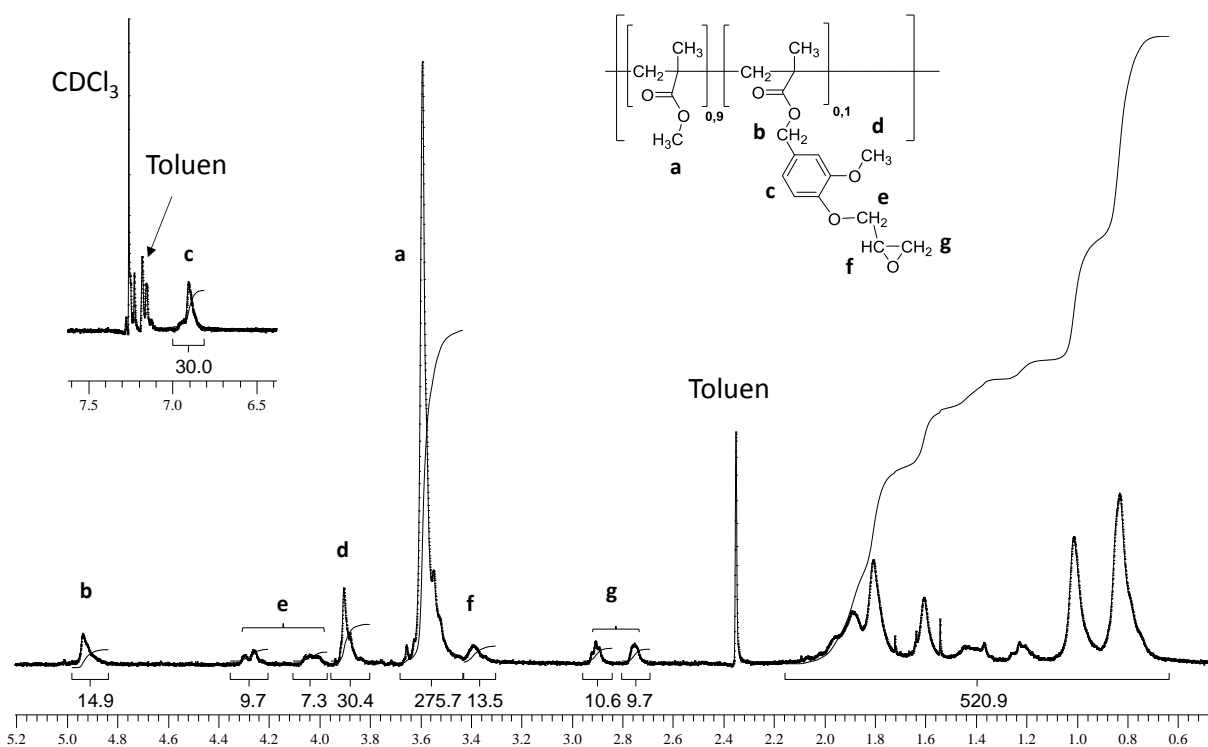
563 **Figure S2: GPC Chromatogram of diepoxidized vanillin.**

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



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

