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Role of Substituents in the Solid Acid-Catalyzed Cleavage of the β -O-4 Linkage in Lignin Models

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ABSTRACT: The role of substituents in the acidolysis of several lignin models bearing a β -O-4 linkage has been studied through experimental (by using Nafion SAC-13 as a heterogeneous catalyst) and theoretical data (including TS calculations). An equilibrium involving the protonation of either α -OH or β -OH groups as well as the dehydration of the α -OH protonated form to yield a benzylic carbocation is assumed. Phenylacetaldehyde and phenol derivatives are the major reaction products for a number of lignin models, though other products have also been identified (such as enol ethers and coumaran derivatives). The high reactivity observed for lignin models bearing an *ortho*-methoxy group on the O-bound phenyl ring has been attributed to the methoxy anchimeric assistance to the benzylic position. On the other hand, the low

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3 formaldehyde yields observed in the acidolysis of some lignin models have been attributed to the
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5 hydrogen bond formation between the hydroxymethyl group and the base abstracting the β
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7 hydrogen of the carbocationic intermediate.
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15 Lignin, a major component of woody biomass, is the second most abundant organic polymer on
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17 Earth. Not surprisingly, a great effort has been focused on the catalytic valorization of such a
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19 compound,^{1–5} having found a great potential for the production of bulk and fine aromatic
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21 chemicals. From a structural point of view, lignin can be regarded as a copolymer of *p*-coumaryl,
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23 coniferyl, and sinapyl alcohols, which are bound in different ways, the β -O-4 linkage constituting
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25 the most abundant link (45–50 % in softwood, 60–62 % in hardwood, 74–84 % in grasses).⁵
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30 Lignocellulose can be successfully fractionated into its main components (cellulose,
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32 hemicellulose, and lignin) by means of the organosolv technique (involving organic solvents and
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34 often acids).⁶ During such a wood treatment, lignin β -O-4 linkages are usually broken because of
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36 the lability of alkyl aryl ethers under acidic conditions.⁷
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40 Because of the structural complexity of lignin, a large number of studies aimed to the
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42 understanding of its reactivity are based on models including a characteristic lignin linkage as
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44 well as one (monomeric models) or two (dimeric models) aryl rings bearing –or not– some
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46 representative substituents.⁸ Lignin models are usually assumed to represent original lignin, but
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48 they may also mimic partially depolymerized lignin (such as organosolv lignin).
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52 Mechanistic studies on model compounds bearing β -O-4 linkages^{9–12} have allowed inferring
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54 two main pathways for the acid-catalyzed cleavage of the $C_{sp^3}-O_{ether}$ bond (Figure 1): route A,
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leading to the formation of Hibbert ketones (presenting a propylbenzene framework, C₆-C₃), and route B, involving formaldehyde loss and the concomitant formation of ethylbenzene derivatives (C₆-C₂) together with repolymerization and condensation reactions.

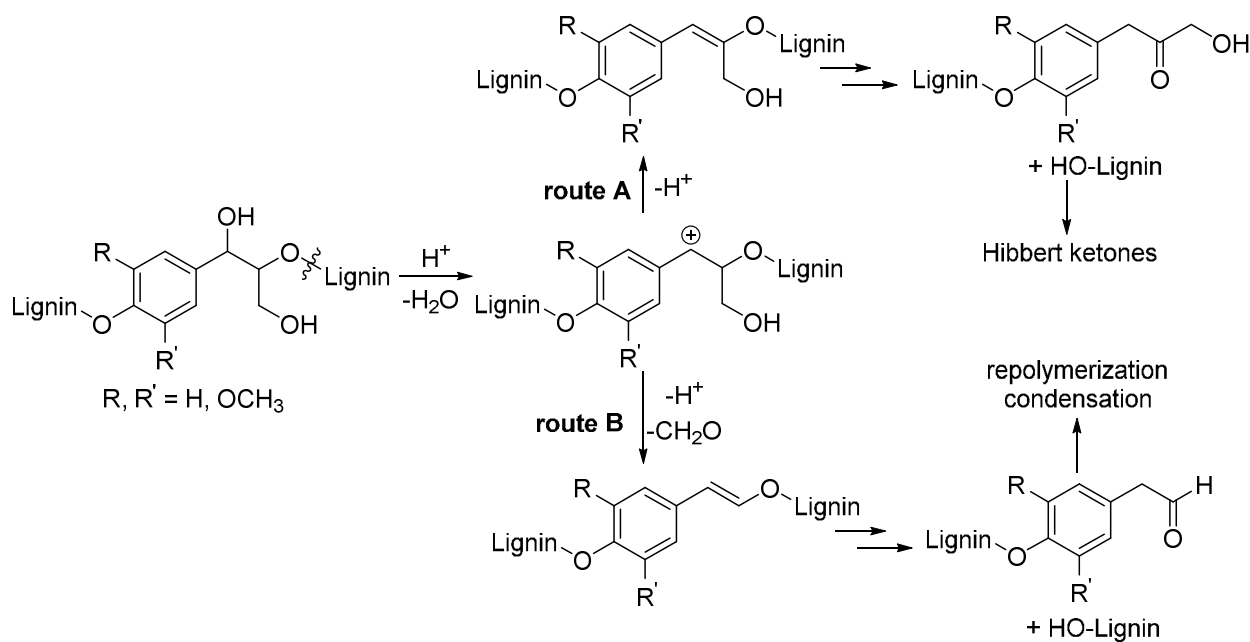


Figure 1. Major pathways for the acid-catalyzed lignin β -O-4 linkage cleavage.

Interestingly, the favored reaction mechanism is strongly dependent on the substrate but the nature of the acid used in the hydrolysis also plays a major role in the results of the reaction.¹² Thus, an experimental study on the acidolysis of lignin models in aqueous-dioxane solutions shows that HCl favors route A, while sulfuric acid induces path B.⁹ It has been inferred that the base acting in the elimination reaction would be a solvent molecule due to the larger basicity of water and dioxane relative to chloride, bromide, and hydrogen sulfate anions.¹³ However, anionic bases (such as chloride and bromide) react much faster than water in the deprotonation of carbocationic ion pairs.^{14,15} The direct participation of the conjugate base in the elimination reaction allows thus explaining the large kinetic dependence on the acid nature.¹⁶

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3 Simple treatment of lignin with mineral acids in aqueous/organic media usually leads to large
4 amounts of insoluble material, derived from recondensation reactions. A recent study on the path
5 of the hydrolysis of C₆-C₂ and C₆-C₃ model compounds by using catalytic amounts of triflic
6 acid¹⁷ has shown that in-situ transformation of aldehydes into acetals markedly suppresses the
7 formation of polymers.
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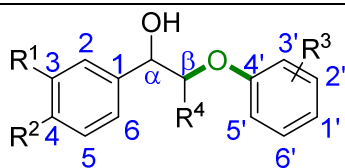
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12 Several computational studies have been carried out in order to understand the acidolysis
13 mechanism for β-O-4 linkages of lignin. Thus, a study including metal chlorides as Lewis acids
14 has focused on the C_{sp}³-O_{ether} bond cleavage of two simple substrates (2-phenoxyethanol and 1-
15 phenyl-2-phenoxyethanol), hence disregarding some major lignin features (such as substituents
16 on the aromatic ring or the occurrence of a CH₂OH group).¹⁸ A wider variety of substrates (2-
17 phenoxyethanol, 2-phenoxy-1-phenylpropane-1,3-diol and two derivatives of the latter bearing
18 substituents on the phenyl group) have been regarded in a work indicating the stabilization of
19 benzylic carbocations through a *p*-hydroxy group.¹⁰
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35 Despite the interest of using solid catalysts for the conversion of biomass and of
36 lignocellulosic materials in particular,^{1,5} very little attention has been devoted to the use of solid
37 acids for acidolysis of lignin, in spite of the easy separation and recovery of such catalysts.
38 Nafion© resins (highly fluorinated polymers bearing sulfonic acid groups) show very high
39 acidities, similar to that of concentrated sulfuric acid.¹⁹ The low specific activities of the original
40 Nafion resins have been overcome by Nafion-silica nanocomposites.^{20,21} In particular, SAC-13
41 has shown an analogous acidity to Nafion (H₀ -11 to -13), with much higher surface area and
42 hence improved accessibility to acid sites,²² as well as a high thermal stability.^{23,24} Not
43 surprisingly, that solid has been successfully used as a heterogeneous catalyst for a number of
44 organic reactions,²⁵ such as alcohol silylation,²⁶ carboxylic acid esterification,²⁷
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transesterification,²⁸ alkene isomerization²⁹ and dimerization,³⁰ or Strecker³¹ and Friedel–Crafts-type alkylation reactions.³²

In the present paper we describe an experimental study on the hydrolysis of several derivatives of 2-phenoxy-1-phenylethanol (**1**-type lignin models) and 2-phenoxy-1-phenylpropane-1,3-diol (**2**-type lignin models) bearing substituents on the aromatic rings. Lignin models are identified by a code (see Table 1) composed by a number corresponding to the parent framework (**1–4**, lignin models; **5–12**, reaction products) and two letters (one letter for split derivatives) indicating the substitution pattern on C- (first letter) and/or O-bound (second letter) phenyl groups: **n**, non-substituted; **d**, 3,4-dimethoxy; **e**, 3-ethoxy-4-methoxy; **h**, 4-hydroxy; **o** (from *ortho*), 3'-methoxy; **p** (from *para*), 1'-methoxy; **m** (from *meta*), 2'-methyl. Some transformations of the CH₂OH group have been also tested (derivatives **3eo** and **4eo**), in order to understand the influence of the γ substituent on the results of the reaction.

Table 1. Substrates (including atom numbering) regarded in the experimental work. The β -O-4 linkage is highlighted. Carbon atoms of the phenoxy group are labeled with prime numbering.³³



Lignin model	R ¹	R ²	R ³	R ⁴
1no	H	H	3'-OMe	H
1np	H	H	1'-OMe	H
1nm	H	H	2'-Me	H
1do	OMe	OMe	3'-OMe	H
1dm	OMe	OMe	2'-Me	H

2no	H	H	3'-OMe	CH ₂ OH
2eo	OMe	OEt	3'-OMe	CH ₂ OH
2em	OMe	OEt	2'-Me	CH ₂ OH
3eo	OMe	OEt	3'-OMe	CH ₂ OAc
4eo	OMe	OEt	3'-OMe	COOMe

Nafion® SAC-13 (nafion-silica composite,³⁴ 13 % wt nafion content, 0.17 mmol sulfonic groups per gram)³⁵ has been used in all cases throughout this work, as a heterogeneous analog of triflic acid, described in the literature for lignin depolymerization.¹⁷ Catalyst recovery has been also studied and SAC-13 has been compared with a sulfonic polystyrene resin (Dowex 50W×2, 2 % divinylbenzene, 50–100 mesh, 5.3 mmol sulfonic groups per gram,³⁵ H₀ -2.2)³⁶ to elucidate the influence of the solid acid nature on the reaction results.

In addition to this experimental work, a comprehensive theoretical study (including transition states) was carried out for the acid hydrolysis of several lignin models (see Table 1), considering different reaction pathways. In contrast with a previous theoretical study on β-O-4 lignin model acidolysis where no transition states (TS) were calculated,¹⁰ a special emphasis has been put here on the geometries and energies of such structures.

This work pretends to obtain some insight on the behavior of lignin polymers or oligomers with a heterogeneous catalyst through the use of experimental and theoretical β-O-4 linkage lignin models. Typical features of polymeric lignin reactivity (such as geometric constraints or diffusional limitations) have not been regarded here. Thus, some caution should be taken for the extrapolation of lignin model results to the behavior of actual polymeric lignin.

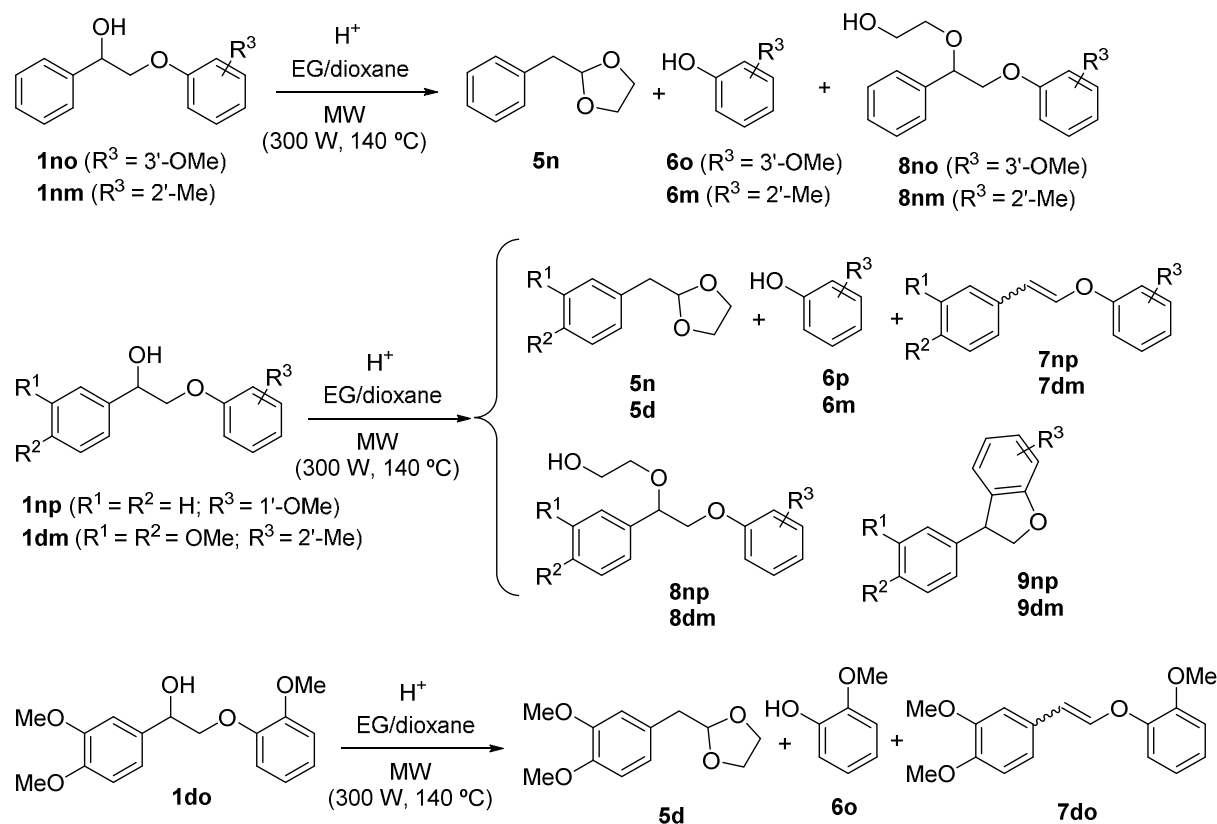
RESULTS

Acidolysis

All the reactions were carried out under microwave activation (300 W), keeping constant the temperature at 140 °C for 1 h. Dioxane was chosen as a solvent, and ethylene glycol was used to trap the aldehydes generated in the reaction, according to the literature.^{17,36} The conversion of **1**- and **2**-type lignin models and the yield of the corresponding phenol, as the easiest way to assess the acidolysis of the precursor, were determined by HPLC and/or GC after calibration with a suitable standard. The rest of the reaction products were detected and identified by GC-MS and/or ¹H-NMR, but only some of them were separated and purified. In contrast with the accurate phenol yields, the results for the remaining products were only estimated by direct integration of the chromatograms. Reproducibility of the experiments was tested in three random items showing small variations in conversions (3.2 % av.) and phenol yields (2.7 % av.).

Scheme 1 summarizes the reaction products obtained in the acidolysis of every **1**-type lignin model, including those coming from the cleavage of the β -O-4 linkage, namely the 2-arylacetaldehyde in the form of ethylene glycol acetal **5** and the corresponding phenol **6**. The other products come from the three possible evolution pathways of the benzylic carbocation, the two isomeric alkenes (**7**) from the dehydration pathway, the ether **8** from the addition of ethylene glycol, and the coumaran (dihydrobenzofuran) derivative **9** from an intramolecular Friedel–Crafts-type alkylation reaction.³⁷

Scheme 1. Acidolysis of **1**-type lignin models in dioxane with ethylene glycol under microwave activation.



The values obtained for conversions and phenol yields of all lignin models with two different amounts of catalyst (1 and 10 mol %) are represented in Figure 2. As can be seen, when the C-bound aryl group has no substituents (compounds **1no**, **1np**, **1nm**, and **2no**), the reactivity is controlled by substitution on the aryloxy group. Interestingly, both conversion (62 and 99 % with 1 mol % and 10 mol %, respectively) and phenol yield (31 and 84 %) are higher for **1no** (bearing an *ortho* (3')-OMe group). The acetal **5n** is also obtained, as expected, and the only side product (hereafter, a reaction product keeping the β -O-4 linkage) observed is the ether **8no**. The presence of the methoxy group in *para* (1') position in **1np** does not produce the same activation (conversions of 19 and 79 %, and yields of 11 and 46 %), indicating that the *ortho* (3')-methoxy activation is not due to a resonance effect. Interestingly, the low phenol yields found for the reactions of **1np** (in comparison with **1no**) are accompanied by the significant formation of **8np**,

both stereoisomeric enol ethers **7np** (analogously to those found in triflic acid-catalyzed hydrolysis of β -O-4 lignin models),¹⁷ and the coumaran **9np**.

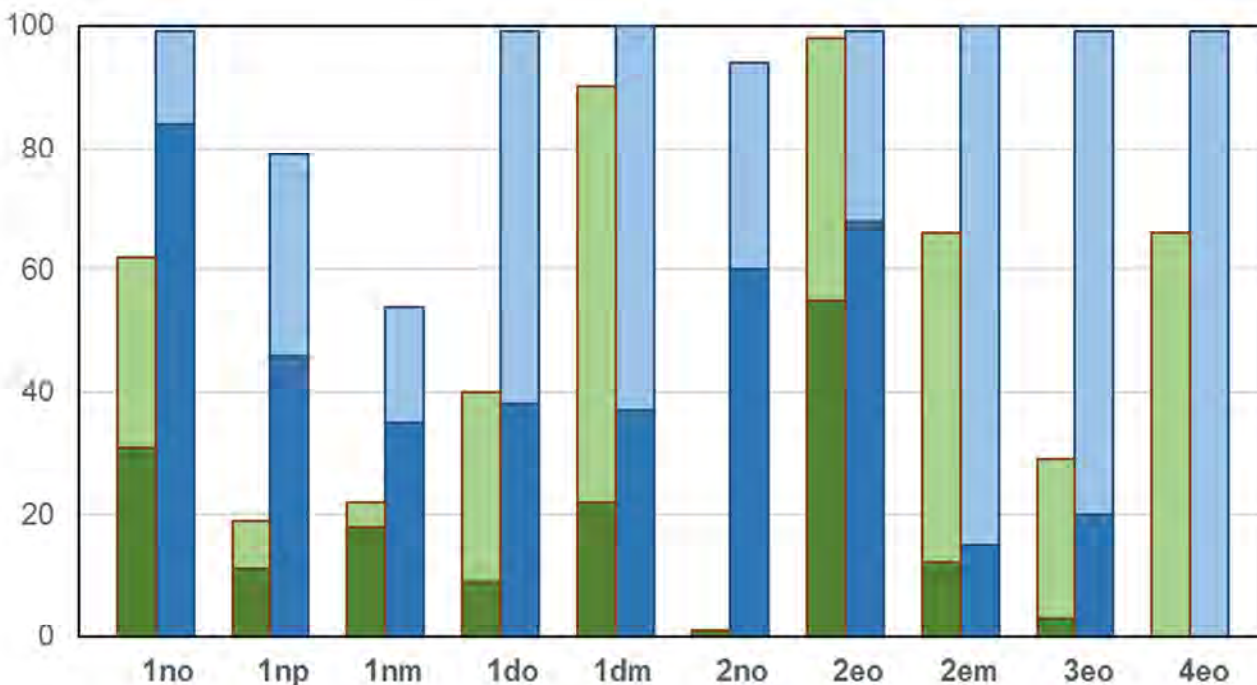


Figure 2. Conversion (full bars) and phenol yield (darker bars) in the acidolysis of 1- and 2-type lignin models at 140 °C (MW 300 W) for 1 h in dioxane catalyzed by 1 mol % (green) and 10 mol % (blue) of SAC-13.

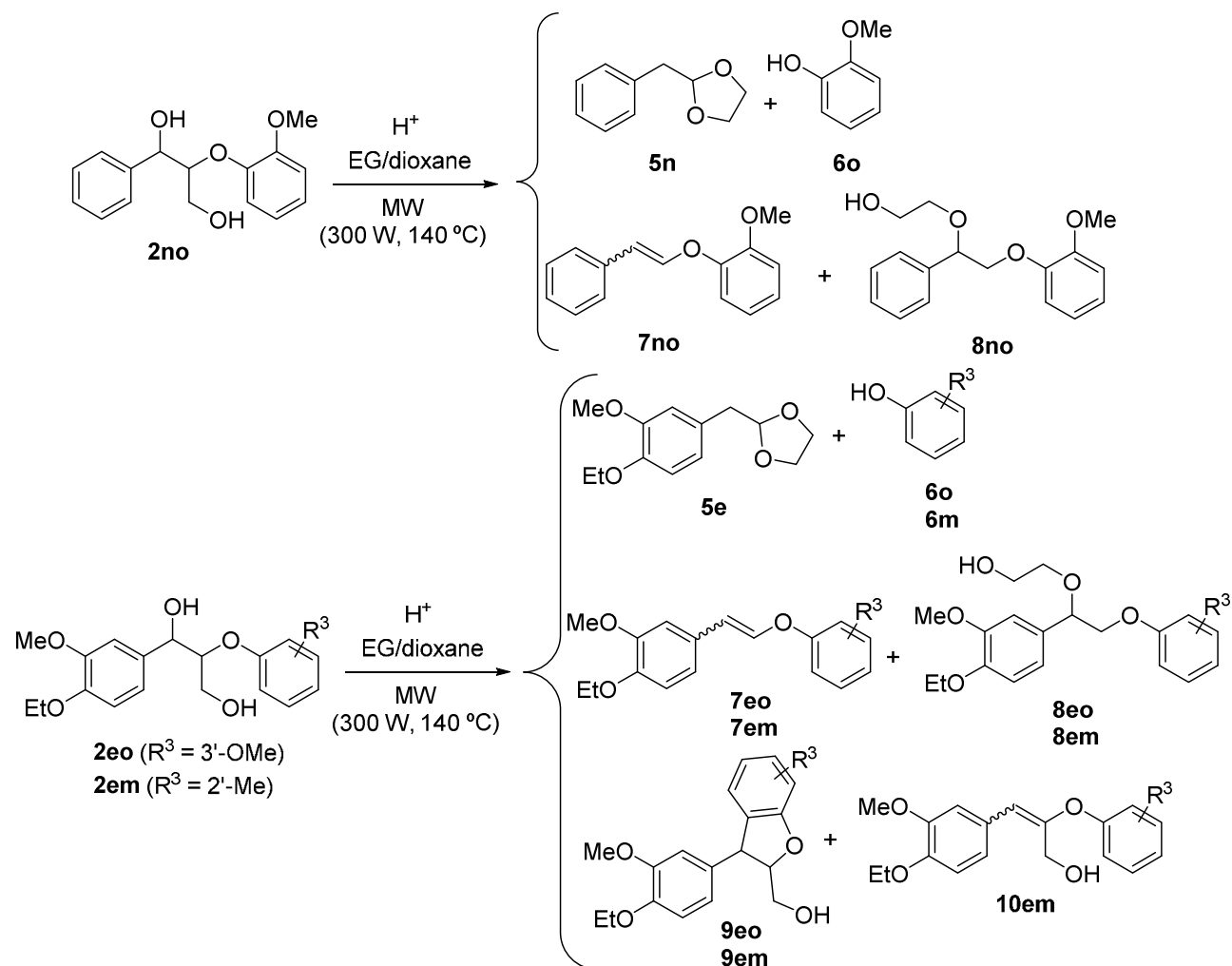
Although large reactivity differences between **1np** and **1nm** may be expected on the basis of the high electron-donor ability of the *p*-methoxy group, only minor variations on conversions and phenol yields have been found, especially for low catalyst amounts. As a confirmation of the lack of an important electronic effect, the reactivity of **1np** is quite similar to that of **1nm**, but only **8nm** was identified as a side product in this reaction.

Interestingly, the presence of electron-donating groups on the C-bound aryl moiety changes this behavior. The propensity of **1do** to the β -O-4 linkage cleavage is significantly lower than

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3 that of **1no** (38 vs. 84 % phenol yields with 10 mol % catalyst). In contrast with **1no**, the only
4 detected side product of the acidolysis of **1do** is the mixture of alkenes **7do**, without traces of
5 ether **8do**. When lignin models bearing non-activated aryloxy moieties are compared (**1nm** vs.
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8 **1dm**), the presence of the electron-donating groups on the C-bound phenyl group (**1dm**) leads to
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10 the formation of a similar phenol yield (18 vs. 22 % with 1 mol % catalyst), but a significant
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12 increase of side products (22 vs. 90 % conversions with 1 mol % catalyst). In contrast with the
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14 less reactive **1nm**, the acidolysis of **1dm** produces all the possible reaction products, **7dm**, **8dm**
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16 and **9dm**.
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23 Scheme 2 summarizes the products obtained in the acidolysis of each **2**-type lignin model, as
24 a mixture of *erythro* (S^* or u , according to the IUPAC recommendations for diastereoisomers
25 with two chirality elements having opposite absolute configurations)³⁸ and *threo* (R^* or l , as
26 recommended for diastereomers having two chirality elements with identical absolute
27 configurations) distereomers. *Erythro* and *threo* isomers of some β -O-4 lignin models have
28 shown different reaction rates for basic hydrolysis, which has been attributed to conformational
29 population differences.³⁹ However, no significant reactivity differences between *erythro* and
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31 *threo* isomers should be expected in our reaction conditions because of the fast epimerization
32 between β -O-4 lignin models in acidic media.⁴⁰ All experimental reactions of **2**-type lignin
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34 models were carried out by using stereoisomer mixtures.
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47 **Scheme 2.** Acidolysis of **2**-type lignin models in dioxane with ethylene glycol under microwave
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Besides the 2-arylacetaldehyde acetal **5** and the corresponding phenol **6**, coming from the cleavage of the β -O-4 linkage with loss of one carbon atom, the two isomeric alkenes (**7**) and the ether **8** were also detected. Since no Hibbert ketones were detected in such reactions, one can infer that the carbon loss is produced before the cleavage. The coumarans **9**, derived from an intramolecular Friedel-Crafts-type alkylation reaction without carbon loss, were also detected, whereas the alkenes (**10**) were only detected in the case of the less activated aryloxy moiety (**2em**).

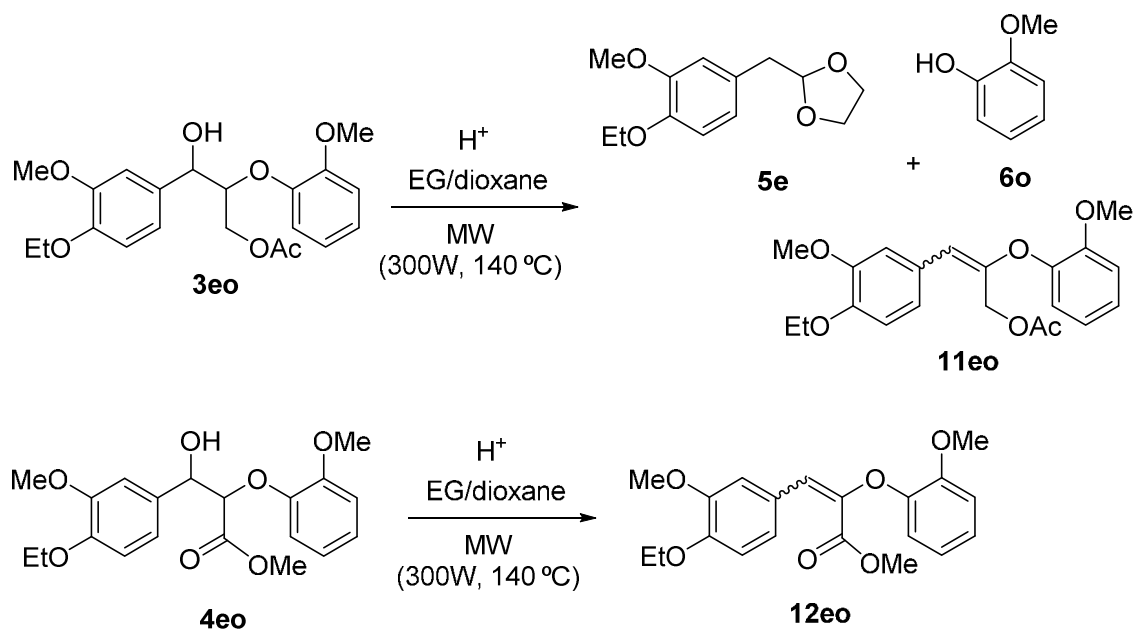
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3 At a high catalyst loading, **2no** and **1no** exhibit about the same reactivity, but **2no** leads to
4 much lower phenol yields (60 vs. 84 %). At a low catalyst loading, **2no** is hardly reactive
5 whereas **1no** exhibits a significant reactivity. The **2eo** model, bearing two electron-donating
6 groups in the aryl moiety, would be comparable to **1do**, and in this case, the model **2** is more
7 reactive, with nearly total conversion and 55 % phenol yield with only 1 mol % catalyst.
8 However, the opposite is true when the aryloxy moiety is not activated, as the **2em** model is less
9 reactive (66 % conversion) than the analogous **1dm** (90 %). In order to determine the nature of
10 the leaving species of one single carbon atom, the acidolysis of **2eo** was carried out using
11 glycerol instead of ethylene glycol. In that case, the formaldehyde acetal (glycerol formal) was
12 detected, indicating the formaldehyde loss in the process. Formaldehyde formation is consistent
13 with previous results on acidolysis of some lignin models⁴¹ as well as lignin from spruce⁴² and
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31 The products obtained from the **2**-type lignin model reactions are dependent on the
32 substitution pattern. The only ethylene glycol ethers obtained in the reactions of **2**-type lignin
33 models (**8no**, **8eo**, **8em**) present a C₆-C₂ (not C₆-C₃) backbone, showing the fast irreversible
34 formaldehyde loss. Interestingly, the variety of reaction products is dependent on the type of
35 substituents on the C-bound aryl group. Thus, the **2no** reaction leads only to products lacking the
36 hydroxymethyl substituent. Instead, **2eo** and **2em** yield some reaction products (**9eo**, **9em**, **10em**)
37 bearing such a group, thus indicating the concurrence of reactions keeping the β-O-4 linkage
38 taking place at similar rates than formaldehyde loss (presumably related with the stabilization of
39 benzyl carbocations through alkoxy substitution).

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53 The role of the hydroxymethyl group in the reactivity of **2**-type lignin models was tested by
54 using two modified substrates (Scheme 3), whose results are also collected in Figure 2. On the
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3 one hand, the hydroxy group was protected in the form of acetate (**3eo**). As expected, this model
4 was less reactive than the analogous **2eo** (29 vs. 99 % conversion with 1 mol % catalyst), but
5 rather surprisingly, the cleavage of the β -O-4 linkage was also accompanied by the loss of the
6 one carbon fragment (presumably involving the previous ester hydrolysis). Although the
7 formation of **5e** may be attributed in some extension to the formation of **2eo** by
8 transesterification of **3eo** with ethylene glycol, the formation of isomeric allylic esters **11eo** (but
9 neither related allylic alcohols nor derivatives from formaldehyde loss, as it happens in reaction
10 of **2eo**) suggests a negligible role for such a side reaction. Despite compounds closely-related to
11 **11eo** are typically acid sensitive (due to the enol ether group),⁴³ they have been detected in the
12 acidolysis of β -O-4 lignin models at incomplete conversion.¹⁷

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27 **Scheme 3.** Acidolysis of lignin models **3eo** and **4eo** in dioxane with ethylene glycol under
28 microwave activation.



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3 The role of the hydroxymethyl group was also studied through replacement by a
4 methoxycarbonyl substituent (**4eo**). In that case, the only product of the reaction was the alkene
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7 **12eo** (Scheme 3), with no cleavage of the β -O-4 linkage. Hence, no evidence of
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9 transesterification with ethylene glycol was found.
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13 Regarding selectivity, considered as phenol yield/conversion, the values range between 18
14 and 82 % with 1 mol % catalyst and between 15 and 85 % with 10 mol %. In four cases (**1no**,
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16 **1do**, **2eo**, **1dm**) the increase in amount of catalyst produces an increase in selectivity, whereas in
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18 two cases (**1np**, **2em**) the selectivity does not significantly change and in one (**1nm**) the
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20 selectivity is lower with more catalyst. The lowest selectivities (15–38%) correspond to models
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22 bearing two electron donating groups in the aryl moiety (**2em** < **1do** \approx **1dm**). The only exception
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24 is **2eo** that reaches 69 % selectivity. On the other hand, models without substitution in the aryl
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26 moiety (**1np** < **2no** < **1nm** < **1no**) lead to moderate to high selectivity (58–85 %). These results
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28 indicate that the models evolve through different mechanisms after protonation, and the
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30 prevalence of one or another mechanism depends on the substituent pattern of each type of lignin
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32 model.
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40 The performance of SAC-13 as catalyst for the acidolysis of **2eo** was compared with that of
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42 two other catalysts, triflic acid as an analogous homogeneous catalyst, and Dowex 50WX2 as a
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44 less acidic aryl sulfonic heterogeneous catalyst (Figure 3). As can be seen, all the catalysts, used
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46 in a 10 mol %, lead to full conversion of **2eo**, but SAC-13 is the most efficient one for cleavage,
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48 as indicated by the guaiacol (*o*-methoxyphenol) yield. Surprisingly, even Dowex is more
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50 efficient than triflic acid, in spite of its weaker acidity. Nevertheless, higher phenol yields may be
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52 envisaged for all tested acids through the choice of convenient reaction conditions allowing the
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54 further transformation of some side products (**7eo**, **8eo**) into the phenol (here, guaiacol).
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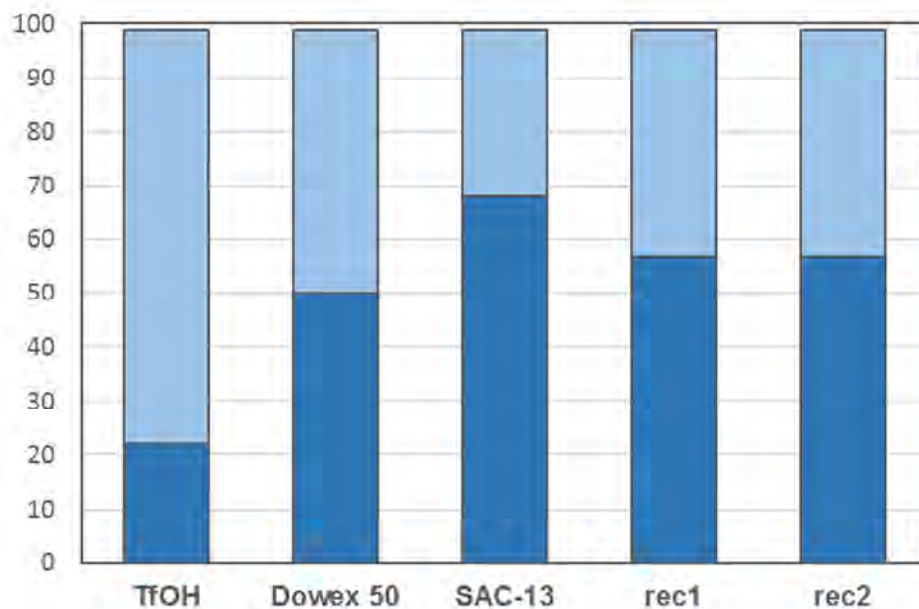


Figure 3. Conversion (full bars) and phenol yield (darker bars) in the acidolysis of **2eo** at 140 °C (MW 300 W) for 1 h in dioxane with 10 mol % catalyst.

The uncatalyzed reaction was ineffective, with total recovery of the unchanged lignin model, under the same conditions, even in the presence of molecular sieves, indicating the lack of microwave activation in the absence of an acid catalyst. Finally, SAC-13 was recovered by simple filtration and reused in two consecutive runs, with total conversion and a slight drop in acidolysis activity in the second run, that was kept constant in the third one.

Theoretical results

A theoretical study was designed in order to rationalize the experimental results. An overview of all reaction mechanisms regarded in this work has been gathered on Scheme 4 (substituents shown in Table 2), other alternative mechanisms (such as those involving bond homolysis⁴⁴ or retro-ene reactions)⁴⁵ being disregarded because of the involved prohibitive activation barriers.

Scheme 4. First steps of the calculated pathways for the acid-catalyzed hydrolysis of a general lignin model. All routes lead to Hibbert ketones, excepting those labeled in red (involving formaldehyde loss) and blue (yielding coumaran derivatives).

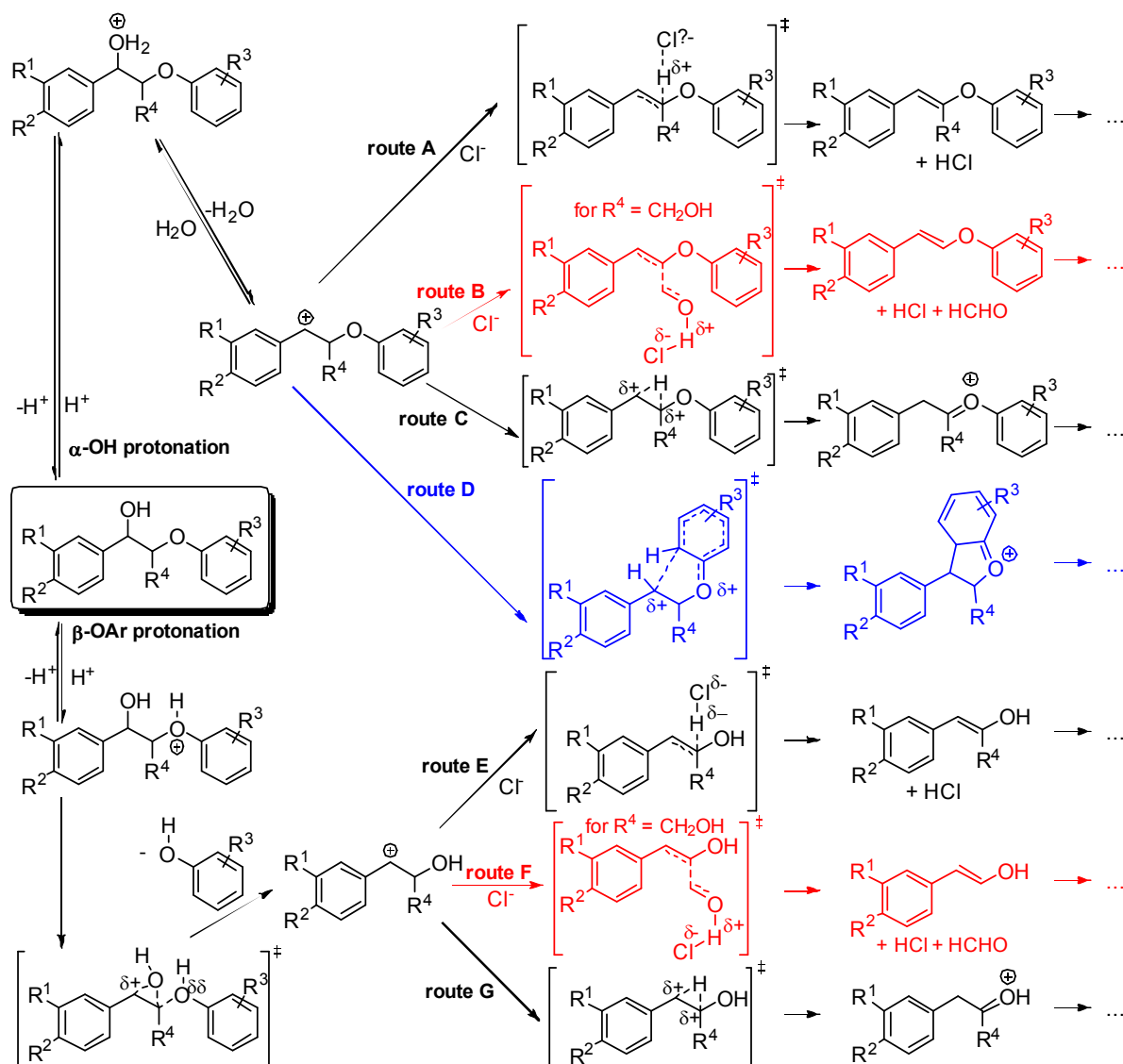


Table 2. Substrates studied in the theoretical work (see Scheme 4).

Lignin model	R ¹	R ²	R ³	R ⁴
1nn	H	H	H	H

1no	H	H	3'-OMe	H
1hn	H	OH	H	H
1ho	H	OH	3'-OMe	H
2nn	H	H	H	CH ₂ OH
2no	H	H	3'-OMe	CH ₂ OH
2hn	H	OH	H	CH ₂ OH
2ho	H	OH	3'-OMe	CH ₂ OH

Hydroxy groups were considered as electron-donor substituents on the C-bound phenyl ring (phenolic groups) for the sake of simplicity of lignin models, analogously to other theoretical studies.^{10,46} Nevertheless, OH groups were replaced by methoxy or ethoxy substituents in three selected cases, though no significant changes on the relative energies of several structures were observed. Hence, the results obtained in this study can be indistinctly applied to hydroxy or alkoxy derivatives.

Only the first step of each route is shown in Scheme 4, though structures involved in subsequent steps (leading to the final products) are included in the Supporting Information. Since rotations around single bonds show low activation barriers, only the most stable conformation of every structure was considered, consistently with the Curtin–Hammett principle. No significant changes should be expected for a full conformer Boltzmann distribution because of the simplicity of our lignin models.

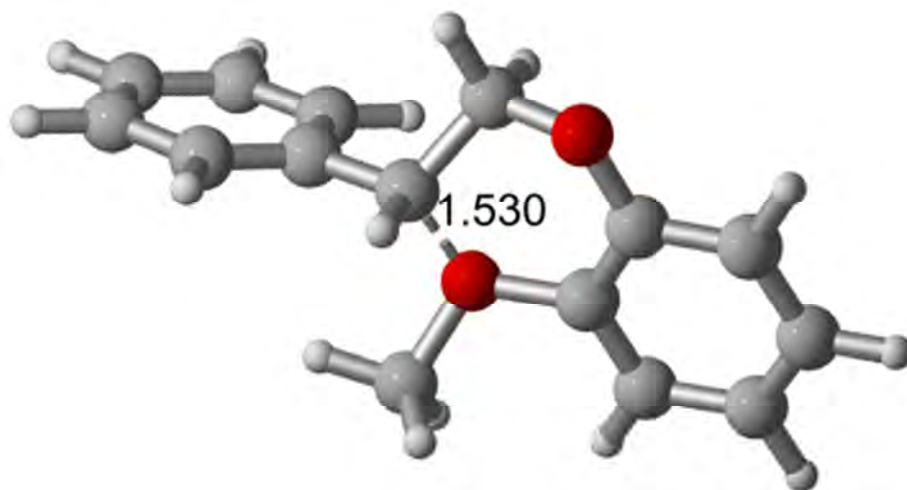
An overall insight for the mechanistic pathway can be obtained for all considered theoretical lignin models. Thus, an intramolecular O–H···OAr hydrogen bond is found in all lignin models lacking a 3'-methoxy group, in agreement with previous M06-2X/6-311++G(d,p)//M06-2X/6-31G(d) calculations for **1nn**.¹⁰ Instead, all substrates bearing a 3'-methoxy group show an

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3 intramolecular bifurcated hydrogen bond⁴⁷ (involving a three-centered interaction between the
4 alcohol hydrogen and both ether oxygens), consistently with X-ray diffraction data on other
5 lignin models bearing 3'-methoxy groups.⁴⁸⁻⁵² but contrasting with a previous M06-2X/6-
6 311++G(d,p)//M06-2X/6-31G(d) study where no hydrogen bond was found for **1no**.⁵³ Such a
7 calculated bifurcated hydrogen allows supporting the reliability of our gas-phase calculations,
8 though slight energetic variations should be expected for comparison of our theoretical results
9 with experimental data in solution. Two diastereomers are possible for **2**-type lignin models
10 bearing such a feature depending on the relative configurations of C_α and C_β: *erythro* and *threo*.
11 Both diastereomers have been studied here, as previously done in a related study on lignin
12 models.³³ Our computed relative energies show a slight *threo* preference (by 5.4 kJ mol⁻¹),
13 whereas a very slight *erythro* predilection (by 0.6 kJ mol⁻¹) is experimentally found for some
14 lignin models in a refluxing 0.2 M HCl dioxane-water (9:1) solution.⁵⁴ The resulting discrepancy
15 (6.0 kJ mol⁻¹) is acceptable and can be partially attributed to the differences between the
16 description of a gas phase system with the complexity of the actual system in solution.
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36 The lignin model can be protonated on either α-OH or β-OPh groups to yield the
37 corresponding protonated forms. The protonation of the α-OH group is favored over that of the
38 β-OPh group in most cases, excepting for **1nn** and **1hn**. Such a preference for α-OH protonation
39 is consistent with pK_a values for protonated forms of related compounds (benzyl alcohol, -2.81,⁵⁵
40 anisole, -6.54).⁵⁶
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49 The α-OH protonated form can dehydrate to yield the corresponding benzylic carbocation
50 through an endergonic reaction (by 3.7–80.5 kJ mol⁻¹). Benzylic carbocations are known to play
51 a major role in the acidolysis of α-O-4⁵⁷ and β-O-4⁵⁸ linkages of lignin models.
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3 Interestingly, the carbocation derived from lignin model **1no** shows the methoxy group
4 coordination to the benzylic carbon atom (Figure 4). Such an anchimeric assistance of an *ortho*-
5 methoxyphenyl group is analogous to that found for the intramolecular S_N2 reaction of 2-(2-
6 methoxyphenyl)ethyl chloride, according to experimental⁵⁹ and theoretical⁶⁰ studies. Such an
7 anchimeric assistance can be observed in all benzylic carbocations from lignin models bearing
8 *ortho* (3') methoxy groups. However, lignin models bearing a 4-hydroxy group show a lower
9 stabilization through anchimeric assistance than those lacking of such a feature, according to
10 C···O distances (**1ho**: 1.545 Å; **2ho**: 1.550 Å; **1no**: 1.530 Å; **2no**: 1.535 Å), thus supporting that
11 the anchimeric assistance magnitude depends on the carbocation electron deficiency.⁶¹
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43 **Figure 4.** Structure of the benzylic carbocation derived from **1no** showing anchimeric assistance
44 (C···O distance in Å).
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48 The occurrence of *o*-methoxy anchimeric assistance is consistent with the significant
49 stereospecificity (73:27) observed in the acid-catalyzed hydrolysis of some α -ether derived lignin
50 models, where configuration retention should be considered as the major stereochemical feature
51 (contrarily to the assumption in the original paper).⁴⁰ As a consequence of the *o*-methoxy
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3 anchimeric assistance, lignin models lacking such a feature⁶² cannot satisfactorily represent the
4 behavior of guaiacyl and syringyl moieties.
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9 Three steps (α -OH and β -OAr protonation, as well as dehydration of the α -OH protonated
10 form) are assumed to take place in a reversible way, as demonstrated in an experimental study on
11 the acidolysis of a β -O-4 C₆-C₃ lignin model.⁶³ In that study, it has shown that the C _{β} -H bond is
12 broken in the rate-determining step. Hence, a faster hydrolysis of the resulting enol ether can be
13 inferred. Such results can be attributed to the fast formation of a benzylic carbocation, two
14 alternative mechanisms being possible: β -proton abstracting by a base to yield an enol ether as
15 well as a carbocation rearrangement to yield a carboxonium ion (route C).
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26 Accordingly, that equilibrium might be shifted towards the benzylic carbocation formation by
27 the occurrence of an electron-donating substituent. Such a hypothesis is consistent with
28 experimental data showing that the rate of acid-catalyzed β -O-4 cleavage in dimers exhibiting a
29 phenolic hydroxyl group is 2 orders of magnitude faster than non-phenolic dimers.¹⁰
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36 Several irreversible mechanistic pathways can be considered now. Route A involves the
37 abstraction of the β hydrogen of the benzylic carbocation by a base (here modeled by chloride
38 anion) to yield an enol ether, consistently with a kinetic study showing the irreversible feature of
39 such a step in the acidolysis of lignin models.¹³ In route B (only available for **2**-type lignin
40 models), the abstraction of the γ -CH₂OH alcoholic proton induces the formaldehyde loss thus
41 yielding an enol ether lacking the γ carbon atom through a retro-Prins reaction. Alternatively, a
42 1,2-hydride shift yields an carboxonium cation (route C). As the last option, the benzylic
43 carbocation can undergo an intramolecular Friedel–Crafts-type alkylation reaction to generate a
44 coumaran derivative via route D. On the other hand, the β -OAr protonated form can lose a
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phenol molecule, though the hypothetically resulting non-rearranged carbocation could not be located as an energy minimum in any case. Indeed, the $\alpha \rightarrow \beta$ migration of the OH group takes place simultaneously to the phenol loss leading to a new benzylic carbocation. Such a cation – bearing only one aromatic ring – shows a similar reactivity to the related carbocation bearing two aromatic rings. Thus, such a species can undergo one of the following reactions: β -proton elimination (route E), retro-Prins reaction (route F), or carbocation rearrangement (route G), whereas an intramolecular Friedel–Crafts-type alkylation reaction is not possible here.

According to the Curtin–Hammett principle, the product ratio depends on the Gibbs free energy differences of the transition states between the first irreversible step for each alternative pathway. Accordingly, relative Gibbs free energies for each irreversible step (routes A–D and phenol loss) are shown in Table 3.

Table 3. Relative Gibbs free energies for every TS corresponding to the first irreversible step for different mechanistic pathways (kJ mol^{-1}).

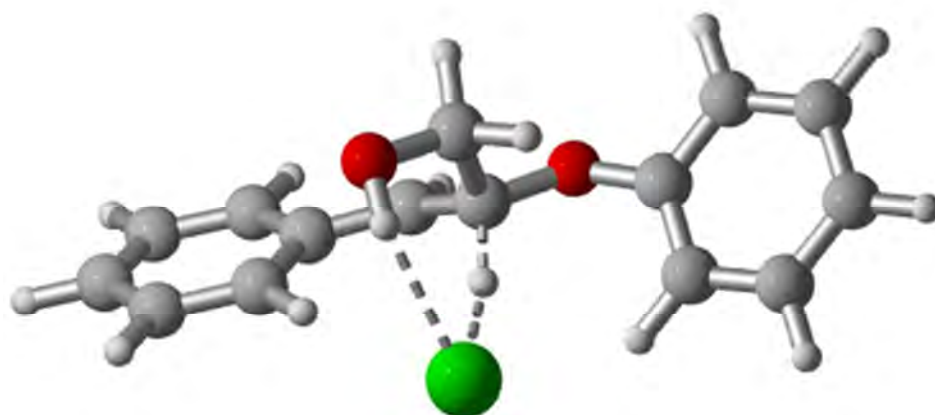
Lignin model	Route A	Route B	Route C	Route D	ArOH loss
1nn	0.0	-	423.5	406.1	468.9
1no	0.0	-	398.3	406.0	446.4
1hn	0.0	-	434.0	410.1	491.5
1ho	0.0	-	408.7	406.0	466.9
2nn	0.1	0.0	456.2	417.1	463.1
2no	0.0	12.1	439.3	426.1	446.3
2hn	6.6	0.0	449.9	429.5	469.4
2ho	15.5	0.0	446.2	407.6	470.0

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3 Relative energies for TS's corresponding to routes A and B are significantly lower than the
4 other ones (by *ca.* 400–500 kJ mol⁻¹) due to the occurrence of chloride anion (playing here as a
5 base model) inducing a large Coulombic stabilization with the rest of the structure, positively
6 charged. Interestingly, lignin model acidolysis studies using HCl or HBr have shown that the
7 experimentally preferred reaction mechanism for the β-O-4 linkage cleavage corresponds to
8 route A.¹²
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18 The fate of **1**-type lignin models is firstly studied. Whereas route D (involving a Friedel–
19 Crafts-type alkylation reaction) is almost insensitive to the substitution pattern, both carbocation
20 rearrangement (route C) and phenol loss paths are clearly affected by two substituent effects. On
21 the one hand, the 3'-methoxy group favors both the carbocation rearrangement (route C),
22 presumably due to an electrostatic interaction of the methoxy group with the migrating proton,
23 and the phenol loss path through OH···OMe hydrogen bonding. In addition, the stabilization of
24 the benzylic positive charge through the 4-hydroxy group leads to a larger preference for route A
25 in comparison with other paths. These results allow explaining the high reactivity experimentally
26 found for **1no** acidolysis reactions. The high energy for the phenol loss TS allows inferring that
27 phenol is formed by hydrolysis through routes A–C. The occurrence of side products derived
28 from olefinic intermediates is consistent with that statement.
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44 Results from **2**-type lignin models allow understanding the paths leading to alkene formation:
45 either keeping the C₆-C₃ framework (route A) or through formaldehyde loss (route B). Almost
46 identical energies are found for TS's leading to both routes for **2nn**, whereas small changes are
47 found depending on the substitution pattern: route A is favored for **2no**, whereas route B is
48 favored for **2ho**. Route C is again favored for the **no** substitution pattern, consistently with
49 experimental results.
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3 The role of the CH₂OH group in 2-type lignin models was also investigated. Thus, the relative
4 destabilization of route C for 2- (vs. 1-) type lignin models can instead be attributed to a larger
5 preference for route A. Such a result can be attributed to the formation of a hydrogen bond
6 between the CH₂OH group and the chloride anion in the TS for the first step of route A, as
7 shown for the reaction of **2nn** (Figure 5).
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31 **Figure 5.** TS for the β hydrogen abstraction (route A) for lignin model **2nn**.
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34 The participation of the acid-derived conjugate base in the rate-limiting step is consistent with
35 experimental results indicating the participation of bromide anion in HBr-catalyzed reactions of
36 lignin acidolysis.⁶³ The CH₂OH...base interaction allows thus explaining the dependence of the
37 reaction route on the used acid for which no convincing justification was previously available.¹²
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44 The fate of the benzylic carbocation formed through phenol loss has also been studied (Table
45 4). Such a benzylic carbocation shows a similar reactivity than that obtained from the α -OH
46 protonated form. Thus, base-induced deprotonation leads here to an enol (route E). Instead, 1,2-
47 hydride shift leads to protonated phenylacetaldehyde (route G). Evidently, the substitution
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3 pattern on the aryloxy group is irrelevant after phenol loss. Interestingly, route F (leading to
4 formaldehyde loss) is slightly disfavored through γ -CH₂OH and 4-hydroxy substitution.
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9 **Table 4.** Relative Gibbs free energies for every TS corresponding to the step subsequent to the
10 phenol loss (kJ mol⁻¹).
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Lignin model	Route E	Route F	Route G
1n-	0.0	-	428.5
1h-	0.0	-	432.1
2n-	0.0	6.7	458.1
2h-	0.0	14.4	462.7

24 25 26 27 CONCLUSIONS

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31 The reactivity of lignin models bearing a β -O-4 linkage as a function of the substitution pattern
32 can be rationalized on the basis of experimental and theoretical results. Thus, an equilibrium
33 involving the protonation of either α -OH or β -OAr groups as well as dehydration of the α -OH
34 protonated form yielding a benzylic carbocation can be assumed. Since the subsequent
35 irreversible steps are typically exergonic, results can be easily understood in terms of the relative
36 stability of the benzylic carbocation and the β -OAr protonated form through the Hammond
37 postulate.
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49 Despite the large variety of reaction products found in all cases, the phenol (here, guaiacol) is
50 the major product from the 3'-methoxy derivatives of lignin models with or without CH₂OH
51 group. Such a result can be attributed to the stabilization of the benzylic carbocation through
52 *ortho*-methoxy anchimeric assistance. Nevertheless, the occurrence of 3'-methoxy group in
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3 combination with a C-bound phenyl group bearing an electron-donating group leads to a lower
4 phenol (here, guaiacol) formation, consistently with the lower stabilization of the benzylic
5 carbocation through anchimeric assistance.
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11 The role of the hydroxymethyl group was also studied. Interestingly, the CH₂OH group leads
12 to the formation of a lower amount of phenol. Such a result can be attributed to the CH₂OH
13 hydrogen bonding to the base abstracting the β hydrogen in route A. This result is consistent
14 with the strong dependence of the reaction rates of lignin models acidolysis on the nature of the
15 acid.^{9,16} Replacement of the CH₂OH group by other non-HBD substituents (–CH₂OAc, –
16 COOMe) led to lower reaction rates.
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26 This combination of theoretical and experimental results allows thus obtaining a better insight
27 of the role played by substituents and from the nature of the acid in lignin acidolysis through the
28 study of the convenient models. We hope that this work helps to a better design of the lignin
29 acidolysis conditions.
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36 METHODS

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39 **General acidolysis procedure.** The lignin model **1–4** (0.2 mmol) was dissolved in anhydrous
40 dioxane (2 mL) in a microwave vial. To this solution were added powdered 4 Å molecular
41 sieves, ethylene glycol (0.2 mmol) and the acid catalyst (1 or 10 mol %). The vial was heated
42 under 300 W microwave irradiation up to a maximum temperature of 140 °C (10 min ramp) and
43 the heating was maintained for 60 min. Lignin model conversions were determined by HPLC
44 (**1nm**, **1no**, **1np**, **1dm**, **1do**, **2no**, **2eo**, **2em**, **3eo**). CG-FID (**1nm**, **1no**, **1np**, **1dm**, **1do**) or ¹H-
45 NMR (**4eo**). Phenol yields were determined by HPLC and CG-FID. Lignin models **1-4** and
46 commercial samples of phenols **6** were calibrated using 1-methylnaphthalene as standard in both
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3 HPLC and CG-FID. The other reaction products were identified by GC-MS and, in some cases,
4 by purification and NMR spectroscopy. They were not calibrated and quantified, and only a
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6 semiquantitative determination was carried out using the integrals in GC-FID.
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11 **Computational methodology.** Calculations were carried out at M06-2X/6-311++G(d,p) level
12 by using the Gaussian 09 software package.⁶⁴ Energy minima and transition states were fully
13 optimized in gas phase and characterized by the right number of imaginary frequencies (0 and 1,
14 respectively). Relative Gibbs free energies are used by default for the energy discussion
15 throughout the paper. Further computational details are provided in the Supporting Information.
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23 ASSOCIATED CONTENT

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27 **Supporting Information.** The Supporting Information is available free of charge on the ACS
28 Publication website at DOI:

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32 Energies and geometries of all calculated structures. Synthetic procedures and spectra of all the
33 lignin models.
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29 Notes

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31 The authors declare no competing financial interest.
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50 ABBREVIATIONS

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52 DFT, Density Functional Theory
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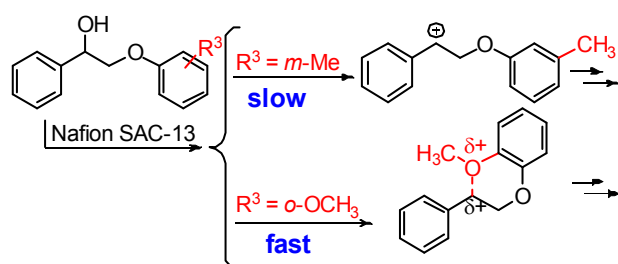
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23 SYNOPSIS. Substituent effects on lignin model acidolysis have been rationalized through a
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