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Nucleophilic cleavage of lignin model compounds under acidic conditions in an ionic liquid. A mechanistic study

William E. S. Hart,[a] Leigh Aldous[a],[b] and Jason B. Harper*,[a]

Abstract: A range of lignin model compounds have been examined for their reactivity with hydrogen bromide in the ionic liquid *N*-butylpyridinium triflate. It was found that the ionic liquid enabled rapid reaction at both the hydroxyl and methyl ether sites of the model compounds at room temperature. Reaction at the phenyl ether sites was more complex; rather than facilitating cleavage at these sites, alternate breakdown products that had not been seen in previous studies were observed; these products are consistent with functionalisation of the aromatic components of the model compounds.

Introduction

Lignin is one of the most abundant biopolymers on the planet,[1] second only to the holocelluloses (cellulose and hemicellulose). It contains a variety of aromatic components that can potentially be fractionated out of the biopolymer and subsequently used as feedstock chemicals for industry.[1] Lignin is formed through the polymerisation of paracoumaryl, coniferyl and synapyl alcohols;[1] (Figure 1) these compounds can connect in a variety of different ways and this variety results in lignin having a large variety of functional groups. The ratio of these functionalities will vary depending on the type of biomass. A common feature across the many different sources of lignin is that more than half of the linkages present[2] between these monomers are βO4 linkages (see Figure 1 for a general representation).

Ionic liquids have become of significant interest in recent years for their ability to dissolve biomass[3] as well as alter reaction outcomes compared to other solvents.[4] Current research focuses upon different techniques for the depolymerisation of lignin such as dealkylation under Brønsted acidic conditions,[5] hydrolysis in acidic ionic liquids,[6] oxidation,[7] and cleavage in ionic liquids catalysed by the presence of metals[8] amongst a range of other methods (for more details, see representative reviews[1, 3b, 9] covering the area). Generally, most studies consider the reactions of model compounds since the fractionation of native lignin is usually hindered by the complexity of lignin's structure; this complexity makes controlling the product(s) of any depolymerisation technique difficult. There have been a number of attempts[5a, 6c, 10] to examine the mechanism of the fractionation of lignin in order to gain some control over the breakdown of lignin and hence utilise lignin as a renewable source of chemical feedstocks

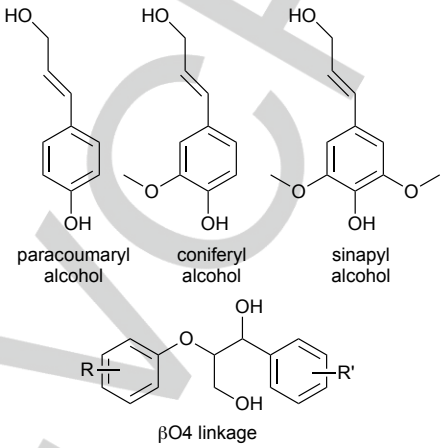

Figure 1: Representative monolignols that are polymerised to form lignin; the most common linkage between them is the βO4 linkage pictured. R substituents are a variety of hydroxyl groups, methoxyl groups and linkages to the rest of the lignin molecule.

One such study[11] monitored the reaction of a range of lignin model compounds with hydrogen bromide in the ionic liquid **1** (Figure 2). These compounds included models containing different ether linkages, to examine the selectivity of ether cleavage under these conditions. It was observed that there was marked selectivity for reaction at the less sterically hindered methyl ether site; this ether was effectively cleaved entirely prior to any reaction at the phenyl ether site. Reactivity at the phenyl ether site was also noted to be enhanced in more basic compounds because the initial step of the reaction involves protonation to give the oxonium ion; increased basicity results in a greater proportion of the starting material activated towards nucleophilic attack. Such increased protonation of the ether; either through electronic stabilisation (by substituents on the adjacent phenyl group) or through the presence of a bifurcated hydrogen bond (only possible when there is an *ortho* substituent on the adjacent phenyl group is capable of forming a hydrogen bond, *e.g.* methoxy); corresponded to a greater proportion of the starting material activated towards nucleophilic attack.

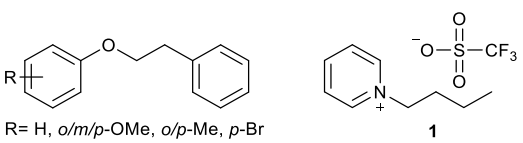

Figure 2: The model compounds studied in previous work (left) and the ionic liquid **1** (right) used as the solvent for the reaction of these compounds with hydrogen bromide.

The compounds initially studied[11] were phenyl phenethyl ethers functionalised on the phenyl substituent. They were not

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functionalised on the aliphatic linkages between the aromatic rings. Such functionalisation, particularly with an oxygen substituent such as a hydroxyl group, is prevalent in native lignin and therefore of significant interest.[1] Given that this functionalisation occurs adjacent to the phenyl ether, it was expected that the group at this position would have a significant effect on the reactivity of these model compounds, particularly the rate of phenyl ether cleavage since substitution on the alkyl chain has previously been shown to have significant effect on the reactivity of αO4 model compounds.[5c] We have therefore considered models more representative of the native lignin structure, in order to elucidate what additional effect, if any, that functionalised aliphatic linkages have upon ether cleavage reactions in ionic liquids.

Results and Discussion

The work herein describes a kinetic analysis of the reactivity of compounds **2-5** (Figure 3) with hydrogen bromide in the ionic liquid **1** in order to ascertain how a hydroxyl group at the α position on a βO4 linkage can affect the rates and selectivities of ether cleavage in these systems. Particularly, the various substitutions allow demonstration of the importance of the electronic nature of the aromatic ring and comparison to previous data allows the importance of the hydroxyl functionality to be assessed. These compounds are clearly models for the extended structure of lignin, noting that steric requirements of the tertiary structure may also affect reactivity.

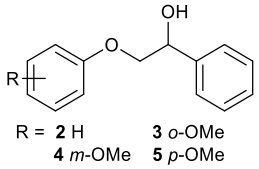
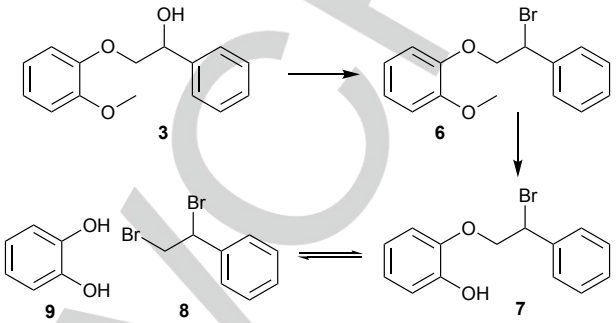


Figure 3: The βO4 model compounds used in this work.

Under conditions equivalent to those reported previously (*ca.* 0.5 M HBr,[12] >10 equivalents, either 298 or 343 K[13]), all reactions were followed using ^{1}H NMR spectroscopy to obtain the rate constants presented in this work. The reaction mixtures were generated through combining the ionic liquid *N*-butylpyridinium triflate ([Bpyr][OTf], **1**), *N*-butylpyridinium bromide ([Bpyr][Br]) and triflic acid to generate a solution of hydrogen bromide in the ionic liquid **1**. This ionic liquid has been shown previously to be an appropriate solvent for dissolving lignin.[14] It was noted that the initial site of reaction for each of the compounds **2-5** was at the α position, with >95% reaction at this site occurring before significant (<5%) reaction at either of the ether sites in the molecule. Changes in the ^{1}H NMR spectra in each case, specifically an upfield shift (*ca.* 0.08 ppm) of the signal due to the proton at the α position, are consistent with the hydroxyl group being substituted by something less electron withdrawing. It is reasonable to suggest that this is the result of bromination, likely through a nucleophilic substitution pathway, to yield a brominated compound such as species **6** in reaction of the model **3** (Scheme 1). This outcome is in contrast to previous studies where the first reaction was elimination of water to give an alkene functionality.[6a, 6c] Those studies, however, focussed on hydrolysis pathways (in both cases, reagents were dissolved in various acidic ionic liquids without a strong nucleophile) rather than the nucleophilic substitution conditions used here.



Scheme 1: The major pathway for the reaction of compound **3** with hydrogen bromide in ionic liquid **1**. Limited formation of products **8** and **9** was observed and is discussed later in this manuscript.

The reaction at the α position was followed by cleavage of the methyl ether in compounds **3-5**, which was evidenced by the reduction in integration of the ^{1}H NMR signal due to the methyl protons during the second reaction, consistent with formation of the corresponding phenol, such as species **7** in the case of reaction of model compound **3** (Scheme 1). Finally, cleavage at the phenyl ether was observed; the complete reaction pathway is shown in Scheme 1 for the model **3**. The rate constants for each step are presented in Tables 1-2 below. This is an interesting result as previous studies[5a, 5b, 5d, 6, 8] of acid catalysed hydrolysis in a range of different solvents with varied temperature, acids (Lewis and Brønsted acids) and reaction times, noted cleavage of the βO4 ether but not cleavage of the methyl ether.

Table 1: The rate constants for reaction of compounds **2-5** with hydrogen bromide at the α carbon in the ionic liquid **1** at 298 K.

Compound	k_2 / 10^{-5} M^{-1} s^{-1} [a]
2	61.5 ± 1.6
3	168 ± 7
4	22.2 ± 1.8
5	81.2 ± 2.0

[a] Uncertainties quoted are half the range of triplicate measurements.

Consider initially the reaction at the alpha position. Importantly, reaction at this site is effectively complete before significant cleavage of either of the ether sites; such a comparison is useful for potential fractionation of real lignin samples, noting again the effects the extended structure of lignin might have. Some analysis into the cause of this reactivity difference is worthwhile and, in order to do this, comparison of the rates of reaction across the series is necessary. There is a significant difference

in the rate constants for reaction at the α position across the range of model compounds **2-5** (Table 1) considered, with the fastest reaction (compound **3**) being approximately 8 times faster than slowest case (compound **4**). It seems unlikely that this is simply an electronic effect, particularly given the distance between the reactive site and the position of the various substituents. This assertion is supported by the proton at the α position of each of the compounds **2-5** having very similar ^{1}H NMR chemical shift.

Given that it is unlikely that electronic effects are purely the cause for the order of reactivity at the alpha position of compounds **2-5**, steric factors should be considered. As the βO4 linkage between the two phenyl rings is made entirely of sigma bonds, it can be considered to have reasonably free rotation around each of these bonds. As such, the compounds can readily adopt conformations that are susceptible to nucleophilic attack and as such it is also unlikely that the differences in rate constants are due to steric considerations.

As was demonstrated in previous work,[11] the primary cause of difference in the reactivities of the different model compounds was due to the position of equilibrium of the initial protonation of the ether oxygen. It was seen that the *ortho* substituted compound, analogous to compound **3** studied in this work but without the hydroxyl group, exhibited the fastest rate of ether cleavage. This effect was argued to be due to the formation of a bifurcated hydrogen bond between the two oxygen centres, which in turn, further stabilised the protonated form of the starting material, favouring formation of the protonated intermediate and hence increasing the rate of reaction.

In the case of compound **3**, the three oxygen centres can bind a proton in an analogous fashion to that discussed in the previous work but involving three oxygen centres (Figure 4); this would be expected to stabilise the protonated form of the ether. This increased extent of protonation might explain the increased rate of reaction of the *ortho* substituted compound **3** relative to the other species **2, 4** and **5** where such stabilisation is not possible.[15]

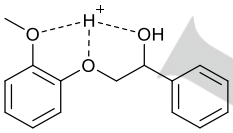


Figure 4: Proposed structure for the initial protonation of compound **3** showing the stabilised proton.

Compounds **4** and **5** also contain the same methoxy functionality as compound **3** but the position of substitution on the ring means that the formation of the equivalent species to that shown in Figure 4 is much less likely.[16] The rate constants for reaction at the hydroxyl position in compounds **2, 4** and **5** are in the order **5** > **2** > **4**. This order is consistent with either electronic stabilisation (in the case of the *para* substituent) or destabilisation (in the case of the *meta* substituent) of the protonated form of the compounds (likely involving a bifurcated hydrogen bond between the α hydroxyl and βO4 oxygen centres). This electronic effect is consistent with that seen previously for the corresponding systems without the hydroxyl group.[11]

The formation of bridged protonated species involving the hydroxyl group can be used to explain why substitution at the α hydroxyl group occurs faster than at methyl and phenyl ethers in other systems,[11] and in compounds **2**, **4** and **5**. The selectivity in the *ortho* case **3** suggests that in the bridged species, the extent of localisation of the proton on the hydroxyl group is greater than on the ethers (given that steric arguments would likely favour reaction at the methyl ether otherwise). This might be due to the hydroxyl group being at a benzylic position, with protonation being favoured by stabilisation of incipient positive charge at that site by the neighbouring aromatic ring.[17]

The second site to react in each of the compounds **3-5** is the methyl ether on the aromatic ring (Table 2). This site is the second to react in the model compounds studied here since it is sterically more available than the βO4 ether, which is consistent with previous studies;[11] the order of reactivity is not changed as a result of the additional substitution though the effect on the absolute rate constants is discussed below. Note that bridged protonated species involving the substituent at the alpha position suggested above are unlikely to significantly contribute in this case given that the bromine atom is less likely to be involved than a hydroxyl group. The rate constants for these reactions for this series of compounds are in the order of **3** > **5** > **4**. This order of reactivity is consistent with the results of the previous report.[11] In that case it was suggested that a methoxy substitution in the *ortho* position allows formation of a bifurcated bond and stabilisation of the protonated starting material which in turn enhances the overall rate of reaction; once again, this argument can again be used to rationalise the order of reactivity. The *para* substituted compound **5** reacts faster than compound **4** since a *para* substituted ether is electronically more capable of stabilising the positive charge built up during protonation.[18]

Table 2: The rate constant for reaction of the compounds **3-5** reacting with hydrogen bromide at the methyl ether site in the ionic liquid **1** at 298 K.

Compound	k_2 / 10^{-6} M^{-1} s^{-1} [a]
2	n/a
3	27.0 ± 1.3
4	7.37 ± 0.25
5	19.9 ± 1.8

[a] Uncertainties quoted are half the range of triplicate measurements.

Directly comparing these rate constants with those reported previously is not possible as the rate constants presented here were obtained at a different temperature to the previous report (298 K instead of 343 K); this was necessary to allow monitoring of the reaction at the hydroxyl site and hence comparison with those rate data. When reaction of these species was carried out at the higher temperature, the rate constant data (see ESI) was comparable but *ca.* 30-40% slower for compounds **4** and **5** than their non-hydroxylated counterparts. This decrease might be due to the α bromide present as a result of initial substitution (as

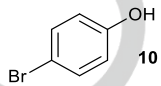
exemplified in compound **6**). Given the distance of the bromine atom from the reactive centre, this is unlikely to be simply a steric effect, suggesting the electronic nature is significant. Any electronic effect is unlikely to be simply an inductive, through *σ* bonds, effect (again, given the distance between the site of protonation and the bromine atom) suggesting a through space effect. In this case, protonation at the phenyl ether might be slightly favoured relative to the methyl ether through formation of an analogous (though less effective, *vida supra*) bifurcated hydrogen bond involving the bromine centre.

In a manner analogous to what was seen with the relative reactivities of the hydroxyl group and the methyl ether site, reaction at the methyl ether was complete (>95%) prior to any visible change in the ^{1}H NMR spectra indicating cleavage of the phenyl ether (conservatively estimated at <5% reaction after the same length of time). Cleavage of the phenyl ether, was noted after extended periods of time but the reaction was found to not progress further after *ca.* 400 h; the extent of conversion at this time varied between *ca*. 8% for compound **5** and 20% for compound **2** (see ESI for plots showing the proportion of residual starting material with time). No further change in the ^{1}H NMR spectrum was observed up to 1000 h. Importantly, this outcome is very different to that in the previous work,[11] indicating the importance of substitution at the benzylic position to the reactivity of the phenyl phenethyl ethers.

It is not immediately obvious why the cleavage of the phenyl ether would not proceed to completion in compounds **2-5**. Likely causes for the cleavage of the phenyl ether to halt at 298 K include (i) the reaction being an equilibrium (*i.e*. in the case of the starting material **3**, compounds **7** and **8** are in equilibrium, Scheme 3) and (ii) the other reagent (hydrogen bromide) has been either exhausted or removed from the system such that it can no longer react with either compounds **2-5** or any breakdown products. These options were assessed through the addition of more of the respective model compound.

It was noted that on addition of more of each of the model compounds **2-5** to the appropriate reaction mixture, reaction of the hydroxyl groups and cleavage of the methyl ethers was observed. This outcome immediately indicates that the reaction mixtures still contain reagent and indicates option (ii) introduced above cannot account for the observations; option (i) remains possible given these results. Whilst little cleavage of the phenyl ether was noted, reaction at the other sites suggests that the phenyl ether cleavage reached equilibrium under these conditions. It should be noted that the phenyl ether moiety was completely cleaved in the previous work;[11] this suggests that either the presence of a substituent at the alpha position or the change in temperature accounts for this different extent of phenyl ether cleavage.

In order to examine the importance of temperature, examples of each of the cases containing compounds **2-5** where reaction progress had halted at 298 K were then heated at 343 K. After heating for *ca*. 1000 h, key changes in the ^{1}H NMR spectra were noted. Firstly, no signals due to the aliphatic hydrogens were detectable. Secondly, there were significant changes in the aromatic region (see Figures S1-S4); whilst some small changes (potentially due to the limited cleavage of the phenyl ether) were noted after 1000 h at 298 K, the changes after 1000 h at 343 K were much more marked. In the cases starting with models **3**, **4** and **5**, many signals were seen, with no clear major product formed (Figures S1-S4). In the case of the unsubstituted starting material **2**, a pair of coupled doublets *ca.* 0.4 ppm apart dominate the spectrum. Such signals are indicative of a *para* disubstituted benzene with substituents of notably different electronic natures. The compound was identified as *para*-bromophenol **10** through the addition of an authentic sample to the reaction mixture (see ESI).



10

Whilst no intermediates were isolated, the formation of compound **10** can be rationalised through a nucleophilic attack at the 4-position of the benzene ring in the hydroxyl breakdown product from compound **2** (analogous to compound **6** above). Such attack is likely made possible by protonation of the oxygen atom (hence activating the ring towards nucleophilic attack). [For full discussion of this mechanism, see ESI.][19]

It should be noted that consecutive substitution processes involving two bromide nucleophiles might occur for compounds **3-5**. This, and addition at other positions would lead to multiple substituted variants of species **10**, resulting in the complex spectra seen (Figures S1-S4). This would also account for the other minor signals seen in the aromatic region of the ^{1}H NMR spectrum of the mixture derived from compound **2**. In the case of the other compounds **3**, **4** and **5**, the more complex mixture suggests that these additional reaction pathways are more significant. Irrespective, over long times at elevated temperatures, nucleophilic aromatic substitution occurs in all of these systems.

It is possible that nucleophilic attack on the phenyl ring occurred in the previous study,[11] however brominated products were not observed, likely due to the reaction being stopped after the phenyl ether cleavage, before significant amounts of brominated products might have formed. Importantly, the very slow rates of reaction as a result of the additional substitution in these model compounds allows observation of this additional pathway that might have particular relevance in the fractionation of lignin.

The effect of water on the cleavage of the methyl and phenyl ethers in compounds **4** and **5** were also examined at 343 K in order to assess the effect of water on the reaction. [The reaction at the α hydroxy site was not examined as, under these conditions, it proceeded too quickly to practically monitor]. It was noted that as the water content of the reaction mixture increased the rate constant for the reaction at the methyl ether site decreased, similar to what was seen in the previous study;[11] rate constants were also comparable for analogous compounds at the same water concentrations (see Table S2 for data).

Differences were noted, however, in the cleavage of the phenyl ether in compound **5** at 343 K when the ionic liquid solvent contained an additional 30 mol % water relative to the ionic liquid. Over the course of the methyl ether cleavage, the ^{1}H

NMR signals due to the aliphatic βO4 protons completely disappeared, to give a spectrum similar to those seen after extended periods of time (during which aromatic substitution had occurred) in the previous samples. These changes indicate that the presence of water in the mixture is causing the aromatic substitution to be the favoured pathway for cleavage of the phenyl ether in compound **5**; the enhancement is sufficient that this process occurs during the reaction of the methyl ether (which would normally be at least an order of magnitude faster[11]). No further examination was made into why the presence of water causes the reaction of compound **5** to proceed *via* a different pathway. This result does demonstrate, however, that the addition of another solute (such as water) can modify the reaction pathways in this system.

Conclusions

The work described immediately demonstrates the importance of considering substation on the α position on a βO4 linkage. The presence of a substituent at this site has a notable effect on the selectivity of reactions of the molecule, their rates relative to cases in its absence and the importance of other breakdown pathways.

It can be seen from the kinetic data presented that there is selectivity between the three different reactive sites on the model compounds examined in this work (at 298 K). As has been noted previously,[11] protonation of oxygen centres is required for reaction and the selectivity observed is a combination of steric effects and relative stabilities of each site of protonation. In relation to the reactivity of lignin, this work indicates that lignin would likely react at sites where the positive charge developed during protonation is the most stable, noting that this selectivity might be altered by the steric availability of reactive sites in lignin; all other factors being equal such protonation effects would dominate. The kinetic selectivity observed could potentially be exploited in the fractionation of lignin through either adding a sub-stoichiometric amount of hydrogen bromide or quenching the reaction after a comparatively short period of time.

It was also seen that variation of the reaction conditions (temperature and water content, particularly) can result in different functionalization and fractionation of lignin; cleavage of the βO4 ether was seen at higher (343 K) temperatures but was stalled midway at lower (298 K) temperatures, whilst nucleophilic aromatic substitution at the aromatic ring was observed after prolonged reaction time and in the presence of water. These results indicate that in a single process, the reaction of hydrogen bromide with lignin in the ionic liquid **1**, could both fractionate and functionalise lignin through multiple different pathways.

Overall, this work represents an advancement in the understanding of how various functionalities which are found in lignin can be selectively cleaved through the use of an ionic liquid in an attempt to develop methodologies to obtain useful feedstock chemicals from lignin.

Experimental Section

Triflic acid was purchased from Sigma-Aldrich and was used without further purification. Lignin (alkaline) was purchased from TCI chemicals and was used as received. The ionic liquid **1** was prepared from its bromide precursor, which itself was prepared through alkylation of the parent heterocycle.[20] The substrates **2-5** were prepared based on literature methods.[21] For details of all synthetic preparations, see ESI.

For each of the kinetic analyses, samples were prepared that contained the reagent compound (one of species **2-5**, *ca.* 15 mM) and [Bpyr][Br] (>10 equivalents) in [Bpyr][OTf] **1**. Triflic acid was then added (one equivalent relative to [Bpyr][Br]) to initiate the reaction.

Pseudo first order rate constants were obtained through monitoring the aliphatic signals of the reagents and products using ^{1}H NMR spectroscopy (see ESI for the signals that were used in each case). These rate constants were then converted to the corresponding bimolecular rate constants using the concentration of the bromide for subsequent analysis.

For kinetic measurements with half-lives shorter than 3 h, the reaction was maintained at a constant temperature (either 298 K or 343 K) inside the NMR spectrometer used; temperature calibration was verified using a temperature probe suspended in ethylene glycol prior to beginning the reactions. For kinetic measurements with half-lives longer than 3 h, reactions were kept at the desired temperature (either 298 K or 343 K) in a water bath and their ^{1}H NMR spectra were obtained periodically, enabling at least 10 measurements over at least three half-lives of the reaction in question. For all compounds **2-5**, a mixture of both techniques was used; the rate of reaction was measured for the substitution at the α position in the spectrometer prior to the rate of reaction for the methyl and phenyl ether cleavage being measured using the water bath technique described above.

Acknowledgements

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Keywords: ionic liquids • solvent effects • lignin model compounds

Supporting Information available:

Synthesis of ionic liquid **1** and compounds **2-5**, ^{1}H NMR spectra of reactions of compounds **2-5** with hydrogen bromide after extended periods, mechanism for the nucleophilic attack of bromide in the aromatic ring of a compound **2**, rate constants for all kinetic analysis in this work, graphs of relative integration over time demonstrating the halting of phenyl ether cleavage in compound **2-5**, ^{1}H NMR spectra confirming the identity of the aromatic substitution product in the reaction of compound **2**.

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[12] The concentration of the acid was kept constant throughout. Changing this concentration will change the extent of protonation of the the starting materials, as discussed below and previously (reference 11). Importantly, the concentration is significantly larger than the concentration of the model compound present.
[13] In the previous work, all reactions were carried out at 343 K. As will be noted here, the greater difference in the relative rate of reactions at the different sites mean that that multiple temperatures were necessary.
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[15] During the review process, it was noted that there is the potential for bridged interactions with other electron deficient species (such as a pyridinium cation). Whilst this can not explicitly be ruled out by the experimental data, it is considered that the comparatively large steric requirements make protonation the most likely explaination here.
[16] The formation of a hydrogen bonded bridged species is well-described in literature, with distances between electronegative atoms up to *ca.* 3 Å.[22] The geometrical constraints in compound **4** (the distance between the relevant oxygen atoms in compound **4** is *ca.* 4.8 Å) and the steric requirements of the benzene ring mean a hydrogen bond as in Figure 4 is extremely unlikely.
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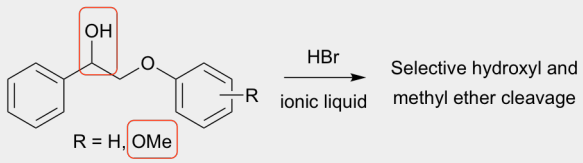

Selective cleavage of lignin model compounds is observed in an ionic liquid. Reaction at the phenyl ether site was notably slower and different to what has been observed previously. These processes have application in the functionalisation and fractionation of lignin.

*William E. S. Hart, Leigh Aldous and Jason B. Harper**

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Nucleophilic cleavage of lignin model compounds under acidic conditions in an ionic liquid. A mechanistic study