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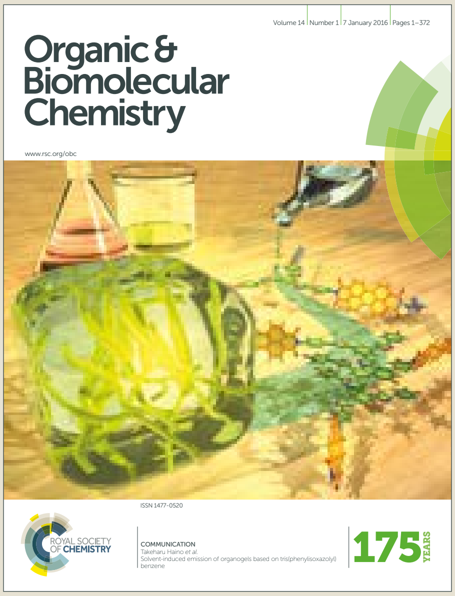

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ARTICLE

Cleavage of ethers in an ionic liquid. Enhancement, selectivity and potential application†

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The cleavage of a series of ethers was examined in an ionic liquid containing hydrogen bromide. Reactions that did not proceed in either water or DMSO were found to proceed readily in this system, with notable selectivity between the cleavage of the different ether types examined herein. Increasing the proportion of water in the reaction mixture dramatically decreased the rate constant of ether cleavage; this could, in part, be attributed to a decrease in the solvent stabilisation of the transition state. Through analysis of the electronic requirements of the reaction (using substrates containing substituents with different Hammett parameters) and observation of rate enhancements for an *ortho* substituted system, the importance of the extent of protonation of the ether prior to nucleophilic attack was demonstrated.

Introduction

The cleavage of ethers usually requires relatively harsh conditions due to the inherent stability of this bond.[1] As a result of this stability, they find use as protecting groups in organic synthesis.[2] Ethers are also a very common functional group found in nature, with more than 50% of the linkages between the phenolic monomers comprising lignin being ethers.[3] Given how common ether linkages are, significant efforts have been made to make the cleavage of ethers more efficient and selective.[2, 4, 5] One such avenue of exploration is in the use of ionic liquids to both enhance the reactivity as well as improve the selectivity of reactions involving ethers.[5-8]

Ionic liquids are arbitrarily defined as salts with a melting point below 100 °C.[9] Given that they consist of essentially unsolvated anions and cations,[10] they affect reactions differently than molecular solvents.[11-14] These solvents are also capable of dissolving a wide range of molecules that are otherwise insoluble or sparingly soluble in conventional solvents.[15]

Ionic liquids have been examined for their ability to facilitate the cleavage of a range of ethers; predominately those that can be related to the ether linkages in lignin. Conditions examined for this cleavage include dealkylation under Brønsted acidic conditions,[16-18] hydrolysis in acidic ionic liquids,[19-21] oxidation,[22] and cleavage in ionic liquids catalysed by the presence of metals.[23] Although mechanisms have been proposed, the microscopic origin of why ionic liquids enable these reactions has not yet been determined; if these origins were known, it might be possible to develop new ionic liquids in order to control the rate of reaction and/or the selectivity of a process in a rational fashion. Achieving reaction selectivity is particularly desired as ether cleavage reactions in ionic liquids are known to rapidly undergo a range of side reactions.[17] As such, the work described herein aims to develop an understanding of how ionic liquids affect the cleavage of ethers towards developing a selective method for the breakdown of compounds containing a large range of structurally similar ethers, such as lignin in biomass.

Results and discussion

The initial reaction considered, the cleavage of anisole **1**, is shown in Scheme 1. The reaction mixture was generated through combining the ionic liquid *N*-butylpyridinium triflate ([Bpyr][OTf], compound **3** in Scheme **1**), *N*-butylpyridinium bromide ([Bpyr][Br]) and triflic acid. This reaction likely proceeds through protonation of the ether oxygen, then nucleophilic attack of the bromide onto the methyl group.[24] The relative pK_a values of the species present suggest that hydrogen bromide is generated *in situ* and that the anisole **1** is protonated (at least to some extent) under the reaction conditions used.[*] It is important to note however, that reported pK_a values are in water and that some variation would be expected when the solvent system is changed to the ionic liquid used here. Subsequent nucleophilic attack by bromide results in the loss of methyl bromide from the system.

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†Electronic Supplementary Information (ESI) available: Synthesis of the ionic liquid **3** and reagents **4-10**, raw data for Figures 1-3, rate of reaction data with varying water content for compounds **6-10**, illustration of the protonation equilibrium, mathematical expression for the effect of varying the protonation equilibrium upon the activation parameters, calculations of the *ortho* Hammett *σ* values, representative NMR data before and after methyl ether cleavage demonstrating the formation of the hydroxy intermediate species. See DOI: 10.1039/x0xx00000x

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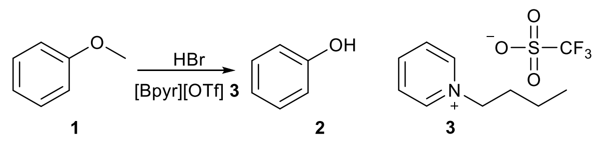

Scheme 1. The reaction of anisole **1** in ionic liquid **3** containing hydrogen bromide.

The ionic liquid **3** was chosen for this analysis because it has been shown previously that this salt is a good solvent for a range of solutes, including complex structures containing different ether functionalities such as lignin.[25] Hydrogen bromide was chosen as the reagent for the compounds used here as it is readily produced *in situ* and previous studies have demonstrated ether cleavage under similar conditions.[5]

Conversion of the anisole **1** to phenol **2** was monitored using ^{1}H NMR spectroscopy and was found to proceed in this ionic liquid mixture with a half life of *ca.* 40 min at 342.6 K.[£] Under equivalent conditions (343 K, 0.5 M hydrogen bromide) no reaction was observed in either aqueous solution or in dimethylsulfoxide solution after 72 h. That is, the ionic liquid facilitates a reaction that is otherwise not possible in these solvents.

Given the lack of reaction in water and the fact that triflate ionic liquids are generally hygroscopic,[26] the reaction was performed in mixtures containing a range of different water contents from 4-25 mol%.[€] A clear decrease in the rate constant was noted with increasing proportion of water in the reaction mixture (Figure 1). At *ca.* 24% by mole water in the reaction mixture, which corresponds to *ca.* 2% water by mass, while progress of the reaction was still able to be monitored, the rate constant was 25-fold less than that observed in the driest mixture considered. This observation demonstrates that small amounts of water (by mass) can significantly affect the reaction and that even when ionic liquid **3** is the predominant species, the reaction is effectively halted.

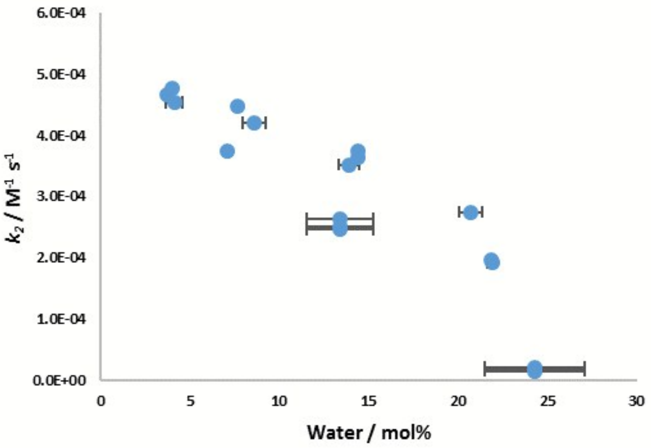

Figure 1. The rate constants of the reaction of anisole **1** in mixtures containing hydrogen bromide in [Bpyr][OTf] **3** with varying water content. The reaction was carried out with *ca.* 15 equivalents of hydrogen bromide at 342.6 K. Uncertainties in water content are half the range of duplicate measurements. Uncertainties in the rate constants come from the fit of the data to the kinetic equation and are negligible compared to the variation between samples; values lie within the size of the marker used.

The change in observed reactivity could be due to one (or more) of a series of reasons. One possibility is that when the solvent is changed from an ionic liquid to a molecular solvent, the position of the protonation equilibrium changes, altering the concentration of reactive protonated form of the anisole and hence changing the rate accordingly. An additional contribution could be that there are significant changes to the solvation environment of either the transition state or the starting materials (or both) resulting an increase in the reaction rate in the ionic liquid; rate enhancements as a result of each of these types of interactions have been previously described.[12]

In order to further investigate possible microscopic origins of the rate changes, temperature dependent kinetic studies (over the temperature range 318 K to 348 K) were also undertaken at both a high and a low water content. This allowed construction of an Eyring plot (see ESI) for each set of conditions and determination of the activation parameters in each case (Table 1). When the water content of the reaction mixture increased, there was an increase seen in both the enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of activation.[¥] The change in enthalpy of activation is more significant than the change in entropy, corresponding to the observed rate constant decrease on increasing the amount of water.

Table 1 Activation parameters for the reaction of anisole **1** in the ionic liquid **3** containing hydrogen bromide (Scheme 1).

Water Content / mol% [a]	$\Delta H^{\ddagger}$ / kJ mol^{-1} [b]	$\Delta S^{\ddagger}$ / J K^{-1} mol^{-1} [b]
13.4 ± 1.9	67.1 ± 1.4	-185.0 ± 4.1
24.3 ± 2.8	99.5 ± 3.0	-111.6 ± 9.1

[a] Uncertainties quoted are the standard deviation of at least six samples measured in duplicate. [b] Uncertainties quoted are from the fit of the linear regression.

The activation parameters determined incorporate some component from the initial equilibrium (see ESI). Whilst the enthalpy of activation can be determined unequivocally, the entropy of activation cannot. However, it is not anticipated that the change in entropy of activation noted can be accounted for by the change in the position of the initial equilibrium alone (see ESI for full details).

The increase in the enthalpy of activation indicates that there is either a more stabilised starting material or a less stabilised transition state when the proportion of water in the ionic liquid increases. So either (i) the water solvates the anisolium and bromide ions (the 'starting materials' for the rate determining step) *more effectively* than the ionic liquid **3** and this solvation is more significant than that of the transition state or (ii) the water solvates the transition state *less effectively* than the ionic liquid and this solvation is more significant than that of the starting material. The accompanying increase in the entropy of activation is consistent with either (i) an increased interaction between the solvent mixture and the anisolium cation relative to the transition state, or (ii) a reduction in the extent of interaction between the solvent mixture and the transition state (relative to the starting material).

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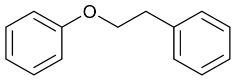
Given the charged nature of the ionic liquid **3** and of the anisolium cation, it seems unlikely that the predominate variation in microscopic interactions is an increase in starting material solvation when the charged ionic liquid solvent is replaced with neutral water; this would support option (ii) above. If, however, the water is more capable of stabilising the charged anisolium (perhaps due to size and more effective solvation), option (i) would be the most likely explanation.

Kamlet-Taft solvent parameters might also provide insight into the differences observed between the two solvent compositions, particularly the ability to solvate the anisolium ion. Whilst not reported for the exact ionic liquid here, the related *N*-octylpyridinium triflate, *N*-methyl-4-methylpyridinium triflate and three isomeric *N*-octylpicolinium triflates all exhibit α values of between 0.48 and 0.51, and β values between 0.29 and 0.33; polarity π^* values are also over a similarly narrow range (0.95-0.99).[28] Even changing the cation to the 1-butyl-3-methylimidazolium system only increases the values of α and β to 0.50 and 0.57, respectively.[27] These values are substantially different to water, which has Kamlet-Taft solvent parameters of 1.12 (α) and 0.14 (β),[28] indicating that it is a stronger hydrogen bond donor and a weaker hydrogen bond acceptor than the ionic liquid **3.** Given the anisolium cation would be expected to be a hydrogen bond donor, this gives greater evidence in support of option (ii) above. Irrespective, enthalpic effects dominate the rate changes observed in these cases.

In order to examine if the ionic liquid effects upon the reaction of ethers extend to more complex systems, both phenethoxybenzene **4** and 1-methoxy-2-phenethoxybenzene **5** were considered. These compounds were examined because they contain phenethyl phenyl ethers, the most common ether linkage present in lignin;[15] if selective ether cleavage could occur between different ether types (such as in species **5**) there is the potential for selective degradation of lignin to generate feedstock chemicals.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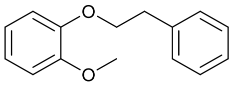
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Initially, the ether **4** (prepared as outlined in the ESI) was studied in a manner analogous to that for the anisole **1** in order to examine if the more sterically hindered ether would react in the same manner. Under the same conditions as the initial studies, the reaction of the ether **4** proceeded more slowly (with a half life of *ca.* 12 h). As was observed for the methyl ether **1**, no reaction was noted in either water or dimethylsulfoxide under the same conditions. Once again, the effect of the water concentration on the rate constant of the process was examined, and the variation of such with water content is shown in Figure 2.

The change in the rate constant of the reaction of the phenyl ether **4** with the water content of the mixture follows a similar trend to the reaction of anisole **1**; as the water content in the ionic liquid increases, the rate of reaction decreases.

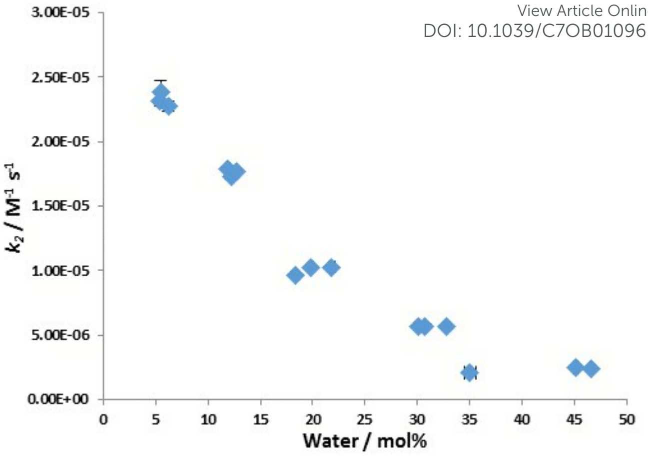

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Figure 2. The rate constants of the reaction of the phenyl ether **4** in mixtures containing hydrogen bromide in [Bpyr][OTf] **3** with varying water content. The reaction was carried out with *ca.* 15 equivalents of hydrogen bromide at 342.6 K. Uncertainties in water content are half the range of duplicate measurements. Uncertainties in the rate constants come from the fit of the data to the kinetic equation and are negligible compared to the variation between samples; values lie within the size of the marker used.

There are two key things to note from this plot. The first point relates to the relative rate of reaction of the two species **1** and **4**; when the methyl group from anisole is replaced with a phenethyl group to give compound **4**, the rate constant of ether cleavage decreases by as much as a factor of 20 for comparable water contents. This difference is likely due to the increased steric bulk of the second aromatic ring, hindering nucleophilic attack of the bromide onto the oxonium ion. The second point of note is that the trend is consistent with the results seen for the reaction for compound **1**; *i.e.* as the water content of the solvent mixture increases, the rate constant of reaction also decreases. Given this trend (Figure 2), it is reasonable to assume that a similar microscopic effect is causing the decrease in rate constant in the case of ether **4** as was seen with compound **1**, though no studies were undertaken to confirm this.

Given the large change in the rate constants for the ether cleavage between the reactions of anisole **1** and compound **4**, methoxy-2-phenethoxybenzene **5** was synthesised (for details, see ESI) to allow direct competition studies. Once again, the rate constant of the reaction for each of the ethers was monitored across a range of different water contents using ^{1}H NMR spectroscopy. It should be noted that the reaction at the methyl ether site was significantly faster than the phenyl ether site (*ca.* 30-50 times faster for reaction at the methyl ether, depending on the water content), simplifying the kinetic analysis dramatically; the reaction at the methyl ether was effectively completed before significant reaction of the phenyl ether was noted. The demethylation reaction was conclusively observed using NMR spectroscopy (*cf.* as observed for compound **1**); representative spectra are displayed in Figure S7. This can be seen in Scheme 2 where the reaction proceeds almost entirely through pathway *a*.

Figure 3 illustrates the change in rate constant for reaction at each site in the species **5** on changing the water content of

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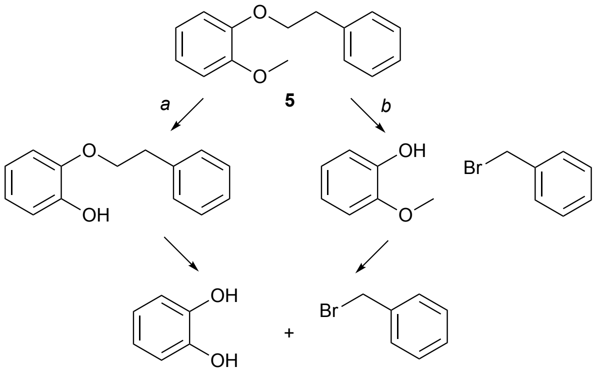
the reaction mixture. The first point to note is that the general trend seen previously, namely decrease in each of the rate constants with increasing water concentration was again noted here, implying that similar microscopic interactions are once again important.



Scheme 2. The two potential paths for reaction of the ether **5** in mixtures containing hydrogen bromide. Due to the large difference in the rate of reaction between the methyl and phenethyl ethers, the reaction proceeds almost entirely *via* pathway *a*.

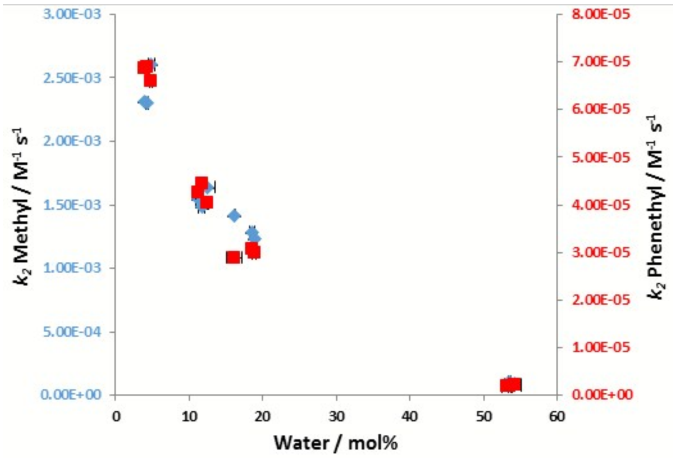


Figure 3. The rate constants of the reaction of the diether **5** in mixtures containing hydrogen bromide in [Bpyr][OTf] **3** with varying water content. Rate constants for reaction at the methyl ether site are illustrated in blue and refer to the left axis while rate constants for the phenyl ether is shown in red and uses the right axis. The reaction was carried out with *ca.* 15 equivalents of hydrogen bromide at 342.6 K. Uncertainties in water content are half the range of duplicate measurements. Uncertainties in the rate constants come from the fit of the data to the kinetic equation and are negligible compared to the variation between samples; values lie within the size of the marker used.

A significant difference between the diether case **5** and each of the monoethers **1** and **4**, however, is that the rate constants for each of the reactions are larger when the two functional groups are combined in the same compound; this is seen across the full range of water contents examined. The rate constants for ether cleavage in compound **5** are between 2- and 6-fold larger across the range of water contents considered when compared to compounds **1** and **4**, where cleavage of each ether type was considered individually.

One possible explanation of this rate enhancement might be the electronic effects of an additional ether (or alcohol, in the case of the partially degraded starting material). The extra oxygen containing functional group, however, might be expected to stabilise the protonated form of the anisole **3**; the result would be a more stable starting material for the rate limiting step, which would be expected to cause a decrease in the rate of reaction. Similarly, it is unlikely that steric effects would cause a rate increase. This suggests that perhaps enhanced protonation of the ether functionalities in compound **5**, perhaps through a bifurcated hydrogen bond (Figure 4), is responsible for these observations.

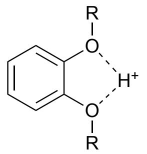
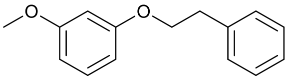


Figure 4. The proposed structure for the bifurcated hydrogen bond that causes the rate acceleration seen in the *ortho* substituted compound **5.**

After observing the increase in the rate constants for ether cleavage in the *ortho* substituted case **5**, both the *meta* (compound **6**) and the *para* (compound **7**) substituted substrates were synthesised (for details, see ESI) to further examine the contributions of electronic effects to the reaction and any importance of the sites being adjacent (*i.e.* the extent to which a bifurcated hydrogen bond is significant). The reactions were carried out under the same conditions as previously and, once more, the progress of the processes followed using ^{1}H NMR spectroscopy to obtain the rate constants shown in Table 2. Once again, kinetic analyses were straightforward given the large differences in the observed rate constants for the two processes. Also included in Table 2 are the relative rates of reaction at the different sites in diethers **5-7**.



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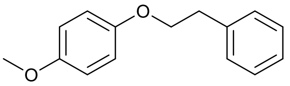

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Table 2 The rate of constants reaction between one of the ethers **5-7** and hydrogen bromide dissolved in [Bpyr][OTf] **3** with *ca.* 5% by mole water at the sites specified, along with ratio of these rate constants. The reaction was carried out with *ca.* 15 equivalents of hydrogen bromide at 342.6 K.

Substrate	k_2 methyl ether / x 10^{-4} M^{-1} $s^{-1\,a}$	k_2 phenethyl ether reaction / x 10^{-4} M^{-1} $s^{-1\,a}$	k_2 methyl ether / k_2 phenethyl ether ^{b}
1	4.66 ± 0.12	-	-
4	-	0.233 ± 0.056	-
5	24.06 ± 0.15	0.679 ± 0.016	34.6 ± 0.8
6	4.76 ± 0.13	0.230 ± 0.002	20.5 ± 0.6
7	13.69 ± 0.28	0.775 ± 0.010	17.4 ± 0.4

[a] Uncertainties quoted are the standard deviation of three replicate experiments. [b] Uncertainties quoted are compounded from the relative errors of the rate constants used.

When considering these data, it is important to highlight the different electronic effects of oxygen functionalities depending on their position on the aromatic ring. In the *para*

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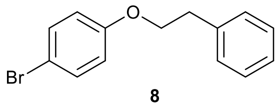
position, resonance electron donating effects dominate, whilst in the *meta* position inductive electron withdrawing effects dominate.[29] Typically substituents at the *ortho* position are not considered in such analyses because their position adjacent to the site of substitution leads to steric and through-space electronic interactions (field effects) which vary with the nature of the process being considered.[30] However, in the *ortho* position oxygen containing functionalities might be expected to be net electron donating, similar to if they were in the *para* position.

Immediately apparent from these data is that the rate constants for the *meta* substituted diether **6** are almost the same as for the monoether cases **1** and **4**. This suggests that any electronic effects of the oxygenated substituent in this position are negligible. The *para* case **7** is of interest as rate enhancements relative to the monoether cases are again noted. This observation suggests some component of the rate enhancement in the *ortho* case is due to the electron donating nature of the substituent; while the greater rate enhancement in the *ortho* case compared to the *para* case is consistent with the formation of the bifurcated hydrogen bond (Figure 4) proposed earlier. Of interest though is the relative rate enhancement, which can be seen in the final column of Table 2.

The increase in the rate constant for the methyl ether cleavage relative to the phenethyl ether case is substantially higher for the *ortho* substituted case **5** than for either of the other diethers **6** and **7**. It might be reasonably assumed that any electronic effects on each process, including increasing the extent of protonation through bifurcated hydrogen bond formation, would be similar so it does not seem likely that the cleavage of the methyl ether is enhanced relative to that of the phenyl ether. Rather, these data suggest that another factor is reducing the rate constant of the phenethyl ether cleavage. One explanation could be reduction in the extent of protonation through subsequent reaction of the hydroxy substituent. However none of the expected notable changes in the aromatic region of the ^{1}H NMR spectra were seen. Alternatively, the reaction at the phenethyl ether might simply be more susceptible to steric effects of an *ortho* substituent than the methyl ether.

In an effort to further examine electronic effects on the rate of reaction at the phenethyl ether site, compounds **8-10** were also synthesised (for details, see ESI). These compounds were chosen to examine the rate of phenethyl ether cleavage in systems with substituents of differing electronic character. Compound **10** was particularly included to examine if substitution at the *ortho* position would cause the same rate constant increase in a system without the possibility for a bifurcated hydrogen bond.

Data for the rate of reaction for compounds **8-10** were obtained in the same manner as the other compounds studied here and graphs similar to Figures 1-3 were obtained (see ESI for more details). Rate data for each of the compounds **4-10** at approximately the same water content were used to construct a Hammett plot (Figure 5) in order to examine if a trend could be seen in respect to the electronic nature of the substituent.



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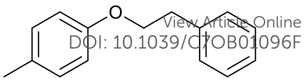

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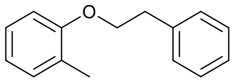

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It should be noted that due to the presence of both through space electronic (field) and steric effects, Hammett σ values are typically not reported for *ortho* substituents. In the case of Figure 5, potential σ values for compounds **5** and **10** were calculated using the procedure outlined by Fujita and Nishioka[30] (For further details about the calculations used see ESI). The implications of using these data will be discussed further below.

Considering initially only the data for the species with well defined Hammett σ values,[₦] it can seen that there is a correlation with the electronic nature of the substituent on the reagents **4, 6-9**. Notable here is that the Hammett susceptibility constant (the gradient of the plot) is -1.31 ± 0.16. The fact that the magnitude is greater than one is consistent with a larger effect of the substituent on the rate constant than for the dissociation of benzoic acid from which the reference σ values are obtained.[31] However, the sign of the gradient is key; the negative value of the substituent constant shows that the process is favoured by electron donating groups and disfavoured by electron withdrawing groups. As was argued above, this is inconsistent with the key effect being on the rate determining step, where electron donating groups which would be expected to stabilise the protonated starting material and result in a decrease in the rate constant.[§]

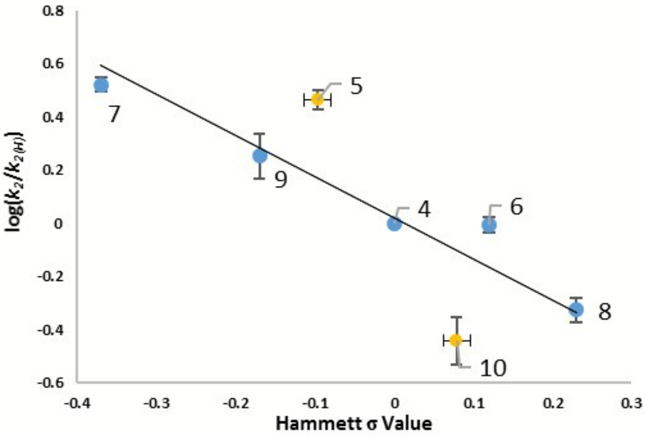

Figure 5. A Hammett plot for the reaction between hydrogen bromide and each of a series of substituted phenethyl ethers **4-10**. Uncertainties in rate are from triplicate experiments compounded by division while uncertainties in the σ value for compounds **5** and **10** are the ranges generated during calculation of the *ortho* σ parameter using the chosen model reaction.

An alternative explanation for the negative susceptibility constant for this process relates to the position of the equilibrium between the starting ethers and their protonated forms (see ESI for illustration of this equilibrium). While an

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electron donating group would be expected to stabilise the protonated intermediate, slowing down the nucleophilic attack of the bromide, it would also shift the position of the initial equilibrium towards the product.[¶] The Hammett correlation suggests that this second effect dominates, though the magnitude being 'only' 1.31 ± 0.16 (*cf.* 2-3.5 for equilibria with negative charge development on an oxygen centre[32,$]) implies that effects on the rate determining step also contribute.

Irrespective, an important outcome here is that the extent of protonation of the ether moiety is key in determining the change in observed rate constant. This extent of protonation is demonstrated in terms of electronic effects and also likely contributes to the effect of the ionic liquid on the reaction. Considering this protonation also leads into a brief final discussion of the effect of *ortho* substituents.

As mentioned above, Hammett values for *ortho* substituents are typically not used given that it is difficult to take into account field and steric effects. The values used to present the data in Figure 5 are calculated based on reported data for a similar reaction (in this case the acid dissociation of an aryl ammonium cation, see ESI for other assessed model reactions and discussion about the differences between them). Immediately apparent is that the methyl substituted case **10** has a smaller rate of reaction than might be expected based on the correlation of the other data, whilst the methoxy case **4**[¢] has a rate constant that is larger. The former effect is consistent with a negative steric effect of the methyl group; if this is taken into account and the Hammett σ value adjusted, the rate constant enhancement in the methoxy case **4** becomes even more marked (the Hammett σ value for methoxy becomes less negative). This clearly supports the argument above that there is another effect of the *ortho* methoxy group, with formation of a bridged protonated species most likely.

Experimental

Anisole **1** was commercially available and was purified immediately prior to use according to literature procedure.[33] Triflic acid was purchased from Sigma-Aldrich and used without further purification. The ionic liquid **3** was prepared from its bromide precursor, which itself was prepared through alkylation of the parent heterocycle.[34] The substrates **4-10** were prepared based on literature methods.[35, 36] 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 **1**, **4-10**, *ca*. 15 mM) and [Bpyr][Br] (>10 equivalents) in [Bpyr][OTf] **3**. Where applicable, water was also added to the mixture to get the desired mole fraction. 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. Activation parameters were calculated using the bimolecular form of the Eyring equation[37] (for further information see ESI).

For kinetic measurements with half lives shorter than 3 h, the reaction was maintained at a constant temperature 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 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 reactions of compounds **5-7**, a mixture of both techniques was used; the rate of reaction was measured for the cleavage of the methyl ether with the sample in the spectrometer prior to the rate of reaction for the phenethyl ether cleavage being measured using the water bath technique described above.

Conclusions

This work has examined the reaction of a range of different, but structurally similar, ethers in an ionic liquid **3**. The reaction between these ethers was not seen to progress in the molecular solvents considered under these conditions but the presence of the ionic liquid has enabled this reaction to progress in an efficient manner. It was seen that the microscopic origin of the rate enhancement seen here was a decrease in the degree of stabilisation between the ionic liquid and the transition state with increasing water content noting also the possibility of affecting the extent to which the ether was protonated. Irrespective, the ionic liquid facilitates the ether cleavage process.

The reaction of the different ether types is significantly affected by steric effects, as was shown by the 20-fold rate constant difference between compounds **1** and **4**. This difference immediately introduces the possibility of exploiting this kinetic selectivity in such systems. Examination of the electronic effects suggested that affecting the position of the initial protonation equilibrium was key; this was supported by results with *ortho* substituted phenyl ethers where the formation of a proton bridged complex can accelerate this reaction further. Both these steric and electronic characteristics offer the potential to build in selectivity to a process through kinetic resolution.

A combination of the features above – namely the selectivity and the enhanced rates relative to molecular solvents – along with the demonstrated solubility of complex materials in such ionic liquids leads to further opportunity. There is the potential to consider more complex ethers such as lignin and their degradation in a controlled fashion.

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Notes and references

* The pK_a values in water are; triflic acid: -14, hydrogen bromide: -9, anisolium: -6.5.[38] Whilst these values are in water, they give an indication of the relative stabilities of the acid forms and combined with the reaction conditions (>ten-fold excess of hydrogen bromide) suggest that there is protonation of anisole **1**.

£ Along with resulting in a rate of reaction that was convenient to observe, this temperature (which corresponds to *ca*. 70°C) was also practical for carrying out the reaction both in the laboratory and directly in the NMR spectrometer.

€ Due to the hygroscopic nature of the ionic liquid, samples with water content <4% by mole were not obtained.

¥ It is worth noting that changing the temperature might vary the position of the protonation equilibrium and therefore the activation parameters determined. The observed data correlated with the bimolecular Eyring Equation, suggesting any temperature dependence was negligible.

₦ Hammett sigma values are determined in molecular solvents, from the dissociation of benzoic acids.[31] There is the possibility that they could change in the ionic liquid used here, however this would likely affect the magnitude of the values not the order of the values for the different substituents. Thus the gradient of the Hammett plot may change with adjusted σ values but it is not believed that the change could be significant enough to change the argument presented in this work. It should also be noted that previous analyses using Hammett sigma data (including those with changes in the nature of the transition state[39,40]).

§ For an example of a closely related reaction (involving substrates positively charged adjacent to a benzene ring undergoing substitution β to the aromatic system) and the Hammett analyses, particularly noting the positive susceptibility constant, see Westaway and Poirier.[41]

¶ This effect is seen in negative values of Hammett susceptibility constants in analyses of the equilibrium constants for many processes involving formation of cationic species including, for example, the protonation of amines.[32]

$ The authors are unaware of any reported data involving Hammett susceptibility constants assessing electronic effects on equilibria involving the protonation of oxygen.

¢ It should be noted that the substituent present when the phenethyl ether is cleaved is hydroxy, given the methyl ether has already reacted. This does not affect the discussions given the similarity in electronic effects of these groups.

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