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ARTICLE

Iron-catalysed oxidative cleavage of lignin and β -O-4 lignin model compounds with peroxides in DMSO

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

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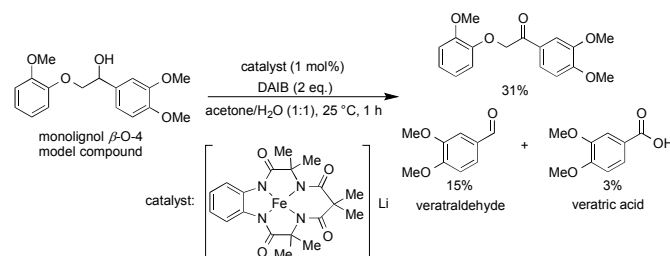
Simple FeCl₃-derived iron catalysts are used for the cleavage of β -O-4 linkages in lignin and lignin model compounds. The degradation of the β -O-4 linkages and the resinol structures in both organosolv and kraft lignin was proven by 2D-NMR (HSQC) experiments, and the oxidative depolymerisation of these lignin sources was confirmed by GPC. Key reactive species facilitating this cleavage are methyl radicals generated from H₂O₂ and DMSO.

1. Introduction

Lignin is the second most abundant polymer on earth after cellulose, and it represents almost one-third of the lignocellulosic biomass.¹ Considering the world's diminishing petroleum reserves, in recent years a strong research emphasis has been devoted to the development of new technologies that allow utilising renewable feedstocks for energy, chemicals and fuels.^{1,2} To this day, however, lignin is still mostly used as a low value energy source in which its caloric value is exploited through incineration.¹ The limited number of processes for the transformation of lignin to higher value products can be attributed to the recalcitrant nature of lignin which makes the valorisation and analytics of the resulting products very challenging.³ Despite these obstacles the number of publications in the field of lignin depolymerisation has doubled within the last five years enforced by increased funding of various institutions.^{1b} The main target in many of these cleavage studies has been the lignin β -O-4 linkage which is the predominant interconnecting bond with 45% to 60% (depending on the wood type).^{3,4} Therefore, lignin model compounds bearing the β -O-4 bond motif have been frequently employed in the search for suitable catalysts for lignin cleavage.⁵

In recent years significant progress has been made in both homogeneous and heterogeneous transition metal-catalysed lignin cleavage reactions, applied on lignin model compounds and/or extracted lignin.⁶⁻⁹ Inspired by these findings we embarked on our search for suitable transition metal catalyst systems. One of the main goals in our studies was to utilise widely abundant non-precious metals, which would potentially be applicable for very large scale processes (lignocellulose is annually extracted on a multi-million ton scale by the paper

industry alone).¹ Along those lines we have recently reported on the oxidative depolymerisation of various lignin sources to dimer- and trimer-size cleavage products with copper and vanadium catalysts.^{8g} Concomitantly, we searched for other metals being applicable in oxidative lignin cleavage reactions. Considering its low price, wide abundance and broad use for oxidations in organic synthesis, iron appeared to be a metal of choice.¹⁰ Iron has already been applied for both reductive¹¹ and oxidative^{12,13} lignin cleavage. These reaction systems, however, required either elevated temperatures (up to 250 °C) and high pressure,¹³ used complex ligands,¹² or employed expensive solvents.¹⁴ Recently, Andrioletti and co-workers have reported the cleavage of a monolignol β -O-4 model compound with Fe(TAML)Li as catalyst and DAIB as oxidant (Scheme 1).¹⁵ The corresponding ketone was obtained as the main product in 31%, while the cleavage products veratraldehyde and veratric acid were formed in 15% and 3% yield, respectively.



Scheme 1 Oxidative cleavage of a monolignol lignin model compound with Fe(TAML)Li as catalyst.¹⁵

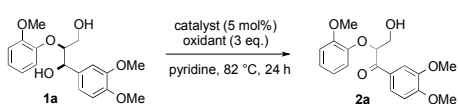
We decided to focus our attention on for iron complexes containing inexpensive nitrogen ligands. Along these lines, a report by Cahiez and co-workers on alkylations of aromatic

Grignard reagents with $[(\text{FeCl}_3)_2(\text{TMEDA})_3]$ as catalyst caught our attention,¹⁶ and we wondered if this type of catalyst would also be suitable for oxidation reactions. Here, we present our findings in the cleavage of differently functionalised lignin model compounds and lignin catalysed by inexpensive FeCl_3 -derived iron complexes.

2. Results and Discussion

To initiate the lignin cleavage studies *erythro* dilignol **1a** was chosen as model substrate as it contained the lignin-relevant β -O-4 linkage and was readily available on a larger scale in diastereomerically pure form.^{5a} The utilised iron complexes were synthesised following a procedure by Cahiez *et al.* (the yields and the spectroscopic data are shown in the ESI†).¹⁶ In the initial phase of the study, the reaction conditions described by us for benzylic oxidations with FeCl_3 as catalyst and *tert*-butyl hydroperoxide (TBHP) as oxidant were applied.¹⁷ Using 5 mol% of FeCl_3 and 3.0 eq. of TBHP in pyridine at 82 °C for 24 h led to 43% conversion of **1a**, and providing ketone **2a** as the main product (Table 1, entry 1). When increasing the catalyst loading to 10 mol% of FeCl_3 (Table 1, entry 2) no significant change was observed. With FeCl_3 -derived iron complexes bearing various nitrogen ligands (Table 1, entries 3 to 7) the conversion increased up to 57% with {Fe-DABCO} being the most active catalyst. Ketone **2a** remained the main product (21% yield). To determine the influence of the catalyst on the progression of the reaction an experiment without catalyst was performed (Table 1, entry 8). This blank reaction revealed that the un-catalysed background oxidation occurred, albeit to only a low degree providing ketone **2a** in 9% yield. When the oxidant was changed to H_2O_2 (Table 1, entry 9) the conversion

Table 1 Iron catalyst screening for the cleavage of *erythro*-dilignol **1a** with pyridine as solvent^a



Entry	Oxidant	Catalyst	Conv. [%] ^b	Yield of 2a [%] ^b
1	TBHP	FeCl_3	43	15
2 ^c	TBHP	FeCl_3	45	20
3	TBHP	{Fe-TMEDA}	48	17
4	TBHP	{Fe-DABCO}	57	21
5	TBHP	{Fe-HMTA}	52	15
6	TBHP	{Fe-PMDTA}	48	18
7	TBHP	{Fe-1,4-dimethylpiperazine}	48	12
8	TBHP	-	9	9
9 ^d	H_2O_2	{Fe-DABCO}	10	5

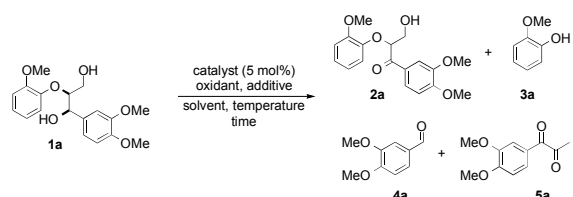
^a Reaction conditions: substrate (0.25 mmol), catalyst (5 mol%), pyridine (1.0 mL), TBHP (3 eq.), 82 °C, 24 h. ^b Conversion determined by HPLC with 3,4-dimethoxybenzyl alcohol as internal standard. ^c Use of 10 mol% of catalyst. ^d Use of H_2O_2 (6 eq.) as oxidant. TMEDA: tetramethylethylenediamine. DABCO: 1,4-diazabicyclo[2.2.2]octane. HMTA: hexamethylenetetramine. PMDTA: pentamethyldiethylenetriamine.

decreased significantly to 10%. Interestingly, in this case the formation of 5% of the cleavage product 3,4-

dimethoxybenzaldehyde (**4a**) as cleavage product was observed.

Intrigued by the latter result, the focus was shifted to the use of H_2O_2 as oxidant. When the solvent was changed from pyridine to DMSO the conversion increased to 41% (Table 2, entry 1). A catalyst screening with the previously employed iron complexes showed that {Fe-DABCO} was again the most active catalyst (see ESI†). When the reaction temperature was raised to 100 °C the conversion of **1a** increased to 84% (Table 2, entry 2). To our delight, aldehyde **4a** was the main product (20% yield), and ketone **2a** was formed in 11% yield. Interestingly, when shortening the reaction time to 6 h at 100 °C the main product was ketone **2a** with a yield of 30%, while aldehyde **4a** was formed in 15% with an overall conversion of 64% (Table 2, entry 3). This indicated that ketone **2a** was formed fast at the beginning of the reaction and then it was slowly consumed with longer reaction times.

Table 2 Screening of reaction conditions for the iron-catalysed cleavage of *erythro*-dilignol **1a**^a



Entry	Oxidant	Catalyst	Additive	Solvent	T [°C]	t [h]	Conv. [%] ^b
1	H_2O_2	{Fe-DABCO}	-	DMSO	82	24	41
2	H_2O_2	{Fe-DABCO}	-	DMSO	100	24	84
3	H_2O_2	{Fe-DABCO}	-	DMSO	100	6	64
4	H_2O_2	{Fe-DABCO}	-	DMSO/ H_2O	82	24	74
5	H_2O_2	{Fe-DABCO}	-	DMSO/ H_2O	100	24	94
6	H_2O_2	{Fe-DABCO}	AcOH	DMSO/ H_2O	100	16	97
7 ^c	H_2O_2	{Fe-DABCO}	AcOH	DMSO/ H_2O	100	16	95
8	H_2O_2	-	AcOH	DMSO	100	16	16
9	H_2O_2	{Fe-DABCO}	AcOH	dioxane	100	16	0
10	H_2O_2	{Fe-DABCO}	AcOH	toluene	100	16	29
11	H_2O_2	{Fe-DABCO}	AcOH	NMP	100	16	10
12	H_2O_2	{Fe-DABCO}	AcOH	DMF	100	16	27
13	H_2O_2	{Fe-DABCO}	AcOH	DMC	100	16	8
14 ^d	H_2O_2	{Fe-DABCO}	AcOH	DMSO/ H_2O	100	16	88
15 ^e	H_2O_2	{Fe-DABCO}	AcOH	DMSO/ H_2O	100	16	86
16 ^{e,f}	H_2O_2	FeCl_3 + DABCO	AcOH	DMSO/ H_2O	100	16	77
17 ^e	H_2O_2	FeCl_3	AcOH	DMSO/ H_2O	100	16	81
18 ^e	H_2O_2	$\text{Fe}(\text{acac})_3$	AcOH	DMSO/ H_2O	100	16	76
19 ^e	H_2O_2	CuBr_2	AcOH	DMSO/ H_2O	100	16	52
20 ^e	H_2O_2	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$	AcOH	DMSO/ H_2O	100	16	25
21 ^e	H_2O_2	$\text{Co}(\text{OAc})_3 \cdot 4\text{H}_2\text{O}$	AcOH	DMSO/ H_2O	100	16	10
22	TBHP	{Fe-DABCO}	AcOH	DMSO/ H_2O	100	16	68

^a Reaction conditions: substrate (0.25 mmol), catalyst (5 mol%), DMSO/ H_2O (0.5 mL/0.5 mL), AcOH (0.5 eq.), H_2O_2 (6 eq.). ^b Conversion determined by HPLC analysis. ^c Reaction performed on a 1 mmol scale, conversion determined by column chromatography. ^d Use of 2.5 mol% catalyst. ^e Use of 10 mol% catalyst. ^f Use of 15 mol% of DABCO.

Changing to a 1:1 mixture of DMSO and water (Table 2, entry 4) increased the conversion of **1a** from 41% to 74%. This result can be explained by a better solubility of the iron complex in this solvent mixture. When the reaction temperature was raised to 100 °C the conversion increased further to 94% (Table 2, entry 5). Aldehyde **4a** was thus obtained in 24% yield, and ketone **2a** in 12% yield.¹⁸

Mechanistically, a Fenton-type initiation process was assumed where the combination of the iron catalyst and the oxidant led to the formation of a hydroxyl radical by an electron-transfer pathway. Furthermore, a key role was attributed to the solvent, DMSO. As reported in the literature the reaction of a hydroxyl radical with DMSO leads to the formation of methanesulfonic acid along with a methyl radical.¹⁹ We thus hypothesised that this methyl radical was also a reactive species in the newly devised reaction system. Methyl radicals generated in this manner have been employed in organic synthesis, for example for the methylation of 1,3,5-trinitrobenzene and *p*-benzoquinone as described by Bertilsson *et al.*²⁰ But to the best of our knowledge this methodology has never been employed in the context of lignin degradation. The formation of hydroxyl radicals in Fenton-type reactions is favoured at an acidic pH.²¹ Therefore, several acids were screened as additive to increase the formation of methyl radicals (see ESI†). Gratifyingly, the addition of 0.5 eq. of acetic acid (AcOH) led to a higher conversion (97%) of **1a**, and the reaction time could be shortened to 16 h (Table 2, entry 6). Furthermore, the yield of aldehyde **3a** increased to 32% while affording ketone **2a** in 15%. To facilitate the product isolation and characterisation, the reaction was performed on a 1 mmol scale. Then, column chromatography allowed a clean product separation (Table 2, entry 7). In this manner, guaiacol (**3a**) was isolated as the main product in 42% yield. It was concomitantly formed in the cleavage of dilignol **1a** to 3,4-dimethoxybenzaldehyde (**4a**), which was obtained in 35% yield. Furthermore, ketone **2a** and di-ketone **5a** were formed in 16% and 5% yield, respectively. Another control experiment with DMSO as solvent showed that in the absence of catalyst 16% of **1a** was converted and only trace amounts of the previous products were observed (Table 2, entry 8). To gain further evidence about the crucial role of DMSO in this reaction system numerous solvents were screened under the previously employed reaction conditions (Table 2, entries 9-13). As hypothesised, the conversions decreased considerably.

Both an increase (10 mol%) and a decrease (2.5 mol%) of the catalyst loading led to slightly lower conversions of **1a** (86% and 88%, respectively, Table 2, entries 14 and 15). When FeCl₃ and DABCO were added individually instead of the preformed complex, the conversion of **1a** decreased to 77% (Table 2, entry 16). The pure iron salts FeCl₃ and Fe(acac)₃ were also less active with conversions of 81% and 76%, respectively, as both salts displayed poorer solubility than the preformed iron complexes (Table 2, entries 17 and 18). Other transition metal salts showed lower activities (Table 2, entries 19 to 21) for this reaction system. Since Swern and co-workers have described the generation of methyl radicals with DMSO in

the presence of TBHP, we also tested the optimized reaction conditions using TBHP as oxidant (Table 2, entry 22).^{19c} The reaction led to a conversion of 68%, but ketone **2a** was identified as the major product in 42% yield. The cleavage product aldehyde **4a** was formed in less than 5% yield.

Evidence that the reaction did indeed involve radicals was obtained by introducing (2,2,6,6-tetramethylpiperidin-1-yl)-oxyl (TEMPO) as a radical scavenging agent. TEMPO was either added directly at the beginning of the reaction or after a reaction time of 0.5 h or 1 h. In all three cases the total reaction time was 16 h while employing the optimised reaction conditions (see Table 2, entry 7). When TEMPO was added after a reaction time of 0.5 h or 1 h the conversion of **1a** was almost identical with 48% and 50%, respectively. However, upon addition of TEMPO directly at the beginning of the reaction no conversion occurred. This indicated that the reaction proceeds most likely through a radical pathway. Furthermore, the decisive radical species seemed to be formed quickly which allowed the reaction to progress to almost 50% conversion even when the radical species are quenched after 0.5 h.

In order to determine active radical species in this reaction, *N*-tert-butyl-*a*-phenylnitron (6) (PBN) was used as radical spin trap (Figure 1).²²

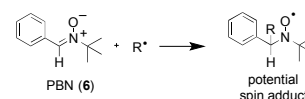


Fig. 1 Spin trapping reaction of PBN (6).

The detection of the methyl adduct of PBN by EPR spectroscopy confirmed the presence of the methyl radical at the beginning of the reaction. More surprisingly, two other species were detected as well (see Figure 2 and ESI† for detail). The first one was identified as the hydrogen adduct of PBN. Its presence, however, does not necessarily imply the formation of the hydrogen radical and is most likely due to a one-electron reduction of PBN coupled with a proton transfer.²³ The second species is an unknown radical displaying hyperfine coupling constants ($a_N = 47.5$ MHz, $a_H = 116$ MHz) which are not compatible with a PBN derivative and that could be indicative of a partial iron-catalysed decomposition of DABCO.

After having gained a more detailed understanding of the reactive species involved in this reaction, the optimised reaction conditions were tested with other β -O-4 lignin model compounds. Table 3 shows the yields of the corresponding methoxyphenol and benzaldehyde derivatives, which were the main products in each reaction (for a complete list of all isolated products, see ESI†). The conversions for all of the employed model compounds were always between 95% and 97%. Compared to dilignol **1a** its *threo* diastereomer **1b** (Table 3, entry 2) afforded guaiacol (**3a**) and veratraldehyde (**4a**) in slightly higher yields with 47% and 46%, respectively. With *erythro* dilignol **1c**, bearing a phenolic hydroxyl group, fewer products could be isolated and identified (Table 3, entry 3). Again, guaiacol (**3a**) was the main product but with a lower

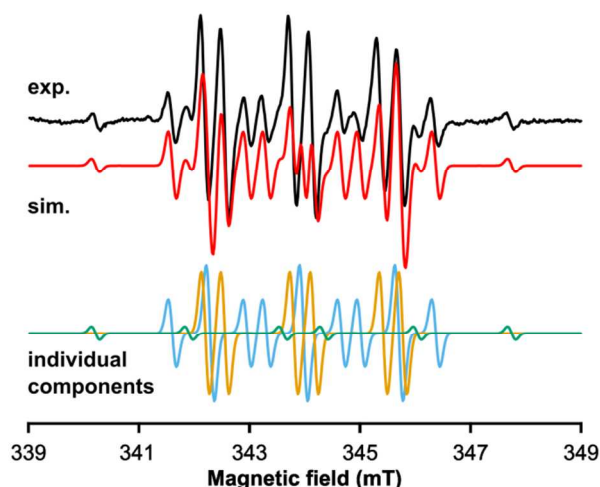


Fig. 2 Experimental (top, black) and simulated (middle, red) EPR spectra of a fresh mixture of **1a**, {Fe-DABCO}, H₂O₂, AcOH and PBN in DMSO/H₂O; Isolated components of the simulated spectrum (bottom): CH₃-PBN. (45%, a_N = 45.2 MHz, a_H = 9.5 MHz, orange), H-PBN. (55%, a_N = 47.9 MHz, a_{2H} = 19.1 MHz, blue), unknown (5%, a_N = 47.5 MHz, a_H = 116 MHz, green).

yield of 27%. Surprisingly, we were unable to isolate vanillin, which should be formed concomitantly with **3a**. We assume that vanillin was formed and then underwent further degradation reactions. The cleavage of monolignol **1d**, which lacks the primary hydroxyl group, proceeded smoothly and with good selectivity (Table 3, entry 4), showing that the second hydroxyl group does not play a key role in the cleavage

mechanism. Indeed, guaiacol (**3a**) and veratraldehyde (**4a**) were obtained in 52% and 39% yield, respectively. When the steric hindrance was increased, either at the arene with the aryl ether linkage (Table 3, entry 5) or at the arene adjacent to the benzylic alcohol (Table 3, entry 6), the yields for the corresponding methoxyphenol and benzaldehyde derivatives decreased significantly. Hence, **1e** afforded 2,6-dimethoxyphenol (**3b**) in 23% and veratraldehyde (**4a**) in 28% yield. For dilignol **1f** guaiacol (**3a**) was obtained in 15% yield and trimethoxy benzaldehyde (**4b**) in 12% yield. These results suggest that this reaction system is most likely best suited for lignin sources which contain low amounts of synapyl alcohol derived building blocks and have a low amount of phenolic moieties.

Next, we wanted to test whether these model-based results would translate to polymeric lignin. For this purpose, two organosolv beech lignin sources (**7** and **8**), which were extracted and supplied by two different entities (for the pretreatment conditions see ESI[†]), were applied. Kraft lignin **9** was purchased from Sigma Aldrich (#370959). 2D-NMR (HSQC) allowed monitoring the cleavage of the characteristic interconnecting bonds within lignin. The spectral data were interpreted in accordance to the detailed work by Sun and co-workers.²⁴ The degree of depolymerisation for the corresponding lignin sources was determined by calibrated GPC.

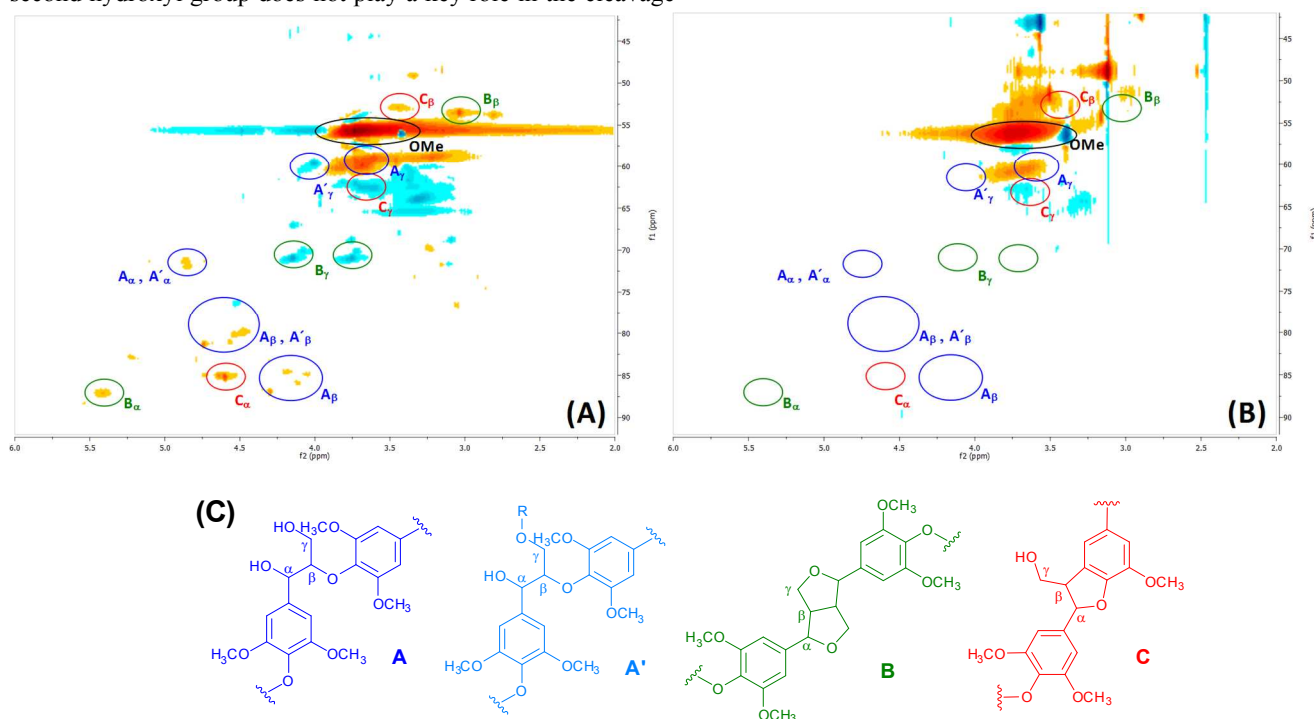


Fig. 3 2D-NMR HSQC spectrum (in DMSO-*d*₆) of organosolv lignin sample **8**; (A) before and (B) after 8 h reaction time; (C) exemplary structures for the β-O-4' aryl ether linkages (A, A'), resinol linkages (B) and phenylcoumaran linkages (C); for additional information on lignin samples **7** and **9** see ESI[†].

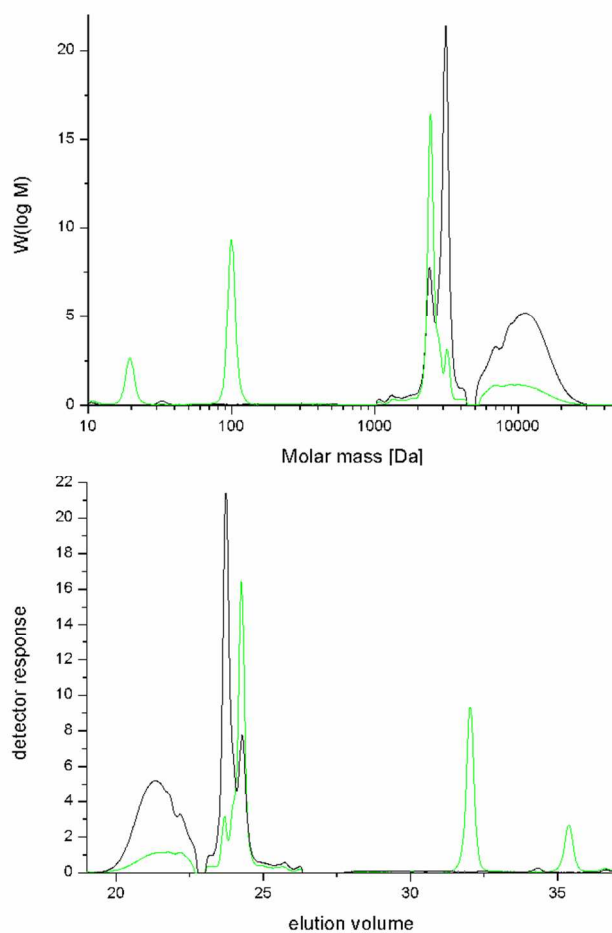
Table 3 Iron-catalysed cleavage of β -O-4 lignin model compounds^a

Entry	Substrate	Conversion [%]	Methoxyphenol derivatives	Benzaldehyde derivatives
1		95 ^b	 3a (42%)	 4a (35%)
2		97	 3a (47%)	 4a (46%)
3		95	 3a (27%)	-
4		97	 3a (52%)	 4a (39%)
5		96	 3b (23%)	 4a (28%)
6		95	 3a (15%)	 4b (12%)

^a Reaction conditions: substrate (0.5 mmol), catalyst (5 mol%), DMSO/H₂O (1.0 mL/1.0 mL), AcOH (0.5 eq.), H₂O₂ (6 eq.), conversion and yields determined after column chromatography.
^b reaction performed on a 1 mmol scale.

Figure 3 shows the 2D-NMR spectra of organosolv lignin **8** before the reaction (A, left side) and after the degradation study (B, right side) with 5 wt% of {Fe-DABCO} at 100 °C and a reaction time of 8 h. It can be clearly seen that the reaction system degraded the β -O-4 linkages **A** and **A'** quantitatively as their characteristic signals in the HSQC disappeared entirely. In addition, the corresponding signals for the resinol structure **B** vanished likewise. For the phenylcoumaran substructure **C** the α -signal completely disappeared, while the β - and γ -signals were still present but with a significantly reduced signal intensity. To verify the general applicability of the newly devised catalyst system the reaction conditions were applied for the cleavage of organosolv lignin **7** and kraft lignin **9** (the HSQC spectra of both lignin sources before and after the reaction are shown in the ESI†). In both samples a complete degradation of the resinol structures **B** and of the β -O-4 linkages **A** and **A'** was observed after 16 h. The spectroscopic data for the phenylcoumaran linkages **C** were in accordance to the previously obtained results with organosolv lignin **8**.

Next, it was attempted to determine the degree of depolymerisation, and possible re-polymerisation of lignin treated under the aforementioned reaction conditions, by GPC analysis. The mass values that are shown in the following discussion are based on an external calibration with polystyrenesulfonate standards and are subject to the standard mass deviation that these calibrations encompass. Figure 4 shows the mass distribution and the elugram for organosolv lignin **8**. Before the treatment (black line) the mass maximum is around 3200 Dalton with another broad signal being observed in the range of 5000 to 10000 Dalton. After 8 h under the

**Fig. 4** GPC measurements for organosolv lignin sample **8**; lignin sample before treatment (black), after treatment for 8 h under the standard conditions (green). Top: mass distributions; bottom: elugram.

standard reaction conditions (green line), the high mass signal (5000-10000) was still present. The mass maximum, however, had shifted from 3200 Dalton to around 2500 Dalton. This indicates that a certain degree of depolymerisation had occurred. In addition, two signals with very high elution volumes were recorded. These suggest the formation of low molecular weight products. Unfortunately, they could not be assigned to reasonable mass values as their elution volume was outside the calibration boundary. It should also be noted that due to the work up all volatile monomeric products with boiling points similar to DMSO had probably been removed. Importantly, no re-polymerisation to higher mass values had occurred. Similar results were also obtained for the depolymerisation of organosolv lignin **7** and kraft lignin **9** (see ESI†).

3. Conclusions

FeCl₃-derived iron catalysts in combination with peroxides in DMSO degrade lignin and lignin β -O-4 model compounds. In studies with the latter it was shown that methyl radicals

generated from DMSO were a key reactive species leading to the cleavage of the β -O-4 linkage. As a result, methoxyphenol and benzaldehyde derivatives were obtained as the main products from various lignin model compounds. The same reaction system could be applied for the cleavage of lignin samples. Independent of the lignin pretreatment conditions, all the β -O-4 linkages and resinol structures were degraded. GPC analysis revealed a shift of the mass maximum in the lignin samples to lower masses and provided evidence for the formation of low molecular products.

Experimental Section

General procedure for the catalytic cleavage of lignin β -O-4 model compounds:

The model compound (0.250 mmol, 1.0 eq.) and the respective iron catalyst were introduced into a 25 mL round bottom flask equipped with a magnetic stirrer. The solvent (1 mL) was subsequently added, followed by the addition of either H₂O₂ (50 wt% in H₂O) or TBHP (70 wt% in H₂O) as oxidant and acetic acid as additive (0.5 eq.). The flask was then equipped with a reflux condenser, heated to the desired reaction temperature and stirred for the respective reaction time. Upon completion, the reaction mixture was cooled to room temperature and quenched with an aqueous HCl solution (c = 1 M, 20 mL). A standard solution of 3,4-dimethoxybenzylalcohol in methanol (1.000 mL, c = 0.2 mol/L) was added with an Eppendorf-pipette. The resulting aqueous phase was extracted with dichloromethane (3 x 20 mL). Next, the combined organic phases were washed with brine (2 x 50 mL) and water (50 mL), dried over MgSO₄, filtered and the solvent was removed under reduced pressure. A minimum of 2 samples containing 2-3 mg of the residue were prepared and dissolved in a mixture of 0.5 mL acetonitrile and 0.5 mL ethyl acetate. After all the products had gone into solution they were filtered into HPLC vials and subsequently measured by HPLC.

General procedure for the catalytic cleavage of lignin samples 7-9:

A 25 mL round bottom flask was charged with 100 mg of the corresponding lignin sample **7**, **8**, or **9** and {Fe-DABCO} (5 mg, 5 wt%). Subsequently, 2 mL of DMSO or DMSO-*d*₆ (for the HSQC experiments) was added followed by the addition of H₂O₂ (50 wt% in H₂O, 150 mg, 125 μ L) and AcOH (10 mg, 9.5 μ L, 10 wt%). The flask was equipped with a reflux condenser and stirred at 100 °C for the desired reaction time. Upon completion, the reaction was cooled to room temperature. In the case of the HSQC experiments the solution was directly filtered into a NMR tube. For the GPC experiments the solvent was evaporated under high vacuum yielding a solid brown residue.

Acknowledgements

This research was supported by the Cluster of Excellence "Tailor Made Fuels from Biomass" (TMFB) funded by the Excellent Initiative of the German federal and state governments. J. M. is grateful to the NRW Graduate School BrenaRo for a predoctoral stipend. We thank Dr. N. Anders (RWTH Aachen University) for the GPC measurements, Dr. C. Rauber (RWTH Aachen University) for helpful discussions during the NMR investigations and Dr. R. Rinaldi (MPI fur Kohlenforschung, Mulheim a.d.R.), Prof. Dr. A. Spie, Prof. Dr. M. Wessling, S. Stiefel, and S. Roth (all RWTH Aachen University) for supplying organosolv lignin **7**. We acknowledge T. Lorenz for his synthetic contributions.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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