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Fine Chemicals from Lignosulfonates. 1. Synthesis of Vanillin by Oxidation of Lignosulfonates

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Abstract:

The oxidation of lignosulfonates (LS) to vanillin by persulphate, oxygen, and a variety of catalytic systems has been investigated. Cobalt and copper catalysts appeared to be the most effective in the oxidation by oxygen. An investigation where multivariate mathematical and statistical design and modelling have been used for the process optimisation has led to the development of a multivariate mathematical model which describes the oxidation process with high predictive capacity. By using this model, an increase of the vanillin yield from 4.1% of the current procedure to 7.2% is obtained, this corresponding to 75% relative improvement of the yield.

Introduction

Vanillin is one of the most important commercial flavours. For a long time it was exclusively produced by oxidation of lignosulfonates[1,2] (LS); more recently a synthetic industrial process has been developed for the production of vanillin starting from guaiacol and glyoxylic acid. Very recently Li and Frost[3] reported a new enzymatic process for the synthesis of vanillin using D-glucose as the carbon source. Borregaard Synthesis is operating a plant synthesising vanillin from guaiacol and glyoxylic acid and is also the only current producer of vanillin by oxidation of LS using a process originally developed by Monsanto.[1] Over the past few years the desire to improve the efficiency of the LS oxidation process has been focused.

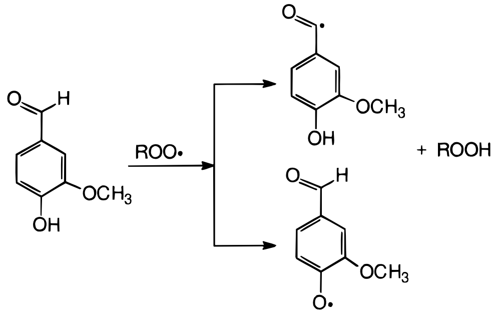
In this paper we report some of the results of our research for this purpose. Two main processes have been developed: (i) the investigation of new catalytic systems for the LS oxidation, (ii) the application of multivariate mathematical and statistical design and modelling for improving the processes.

The general problem of the oxidation of LS to vanillin by oxygen is rather complex for several reasons:

(a) the complex structure of the raw material, lignosulfonate, makes it difficult to rationalise the oxidation mechanism in order to improve the selectivity; a model structure of lignin,[4,5,6,7] from soft wood (Norwegian spruce) is shown in Scheme 1;

(b) the oxidation of LS is associated to complex alkaline hydrolysis steps at high temperatures (170−200 °C);

(c) aromatic aldehydes are particularly sensitive to drastic oxidative conditions; peroxyl radicals, which often are intermediate in the oxidation by oxygen, react fast with vanillin leading to oxidative degradation (eq 1).



(1)

The biosynthesis[4] of lignin proceeds by radical polymerisation of unsaturated alcohols derived from phenylpropane derivatives. The main biosynthetic route involves the enzymatic hydrogen abstraction from coniferyl alcohol (or similar phenylpropane units such as sinapyl alcohol and *p*-coumaryl alcohol) with the formation of a highly resonance-stabilised phenoxylradical (Scheme 2), which then gives origin to a complex polymer structure (Scheme 1).

Borregaard ChemCell is the supplier of the LS (the sulfite-spent liquor) to the Borregaard Synthesis vanillin plant and performs the lignin dissolving process by two main procedures: (i) digestion at 140−145 °C for approximately 6 h (gives LS$_{750}$ and LS$_{850}$) or (ii) digestion at 125−130 °C for approximately 7 h (gives LS$_{1200}$).

The types of LS are defined from which type of cellulose that has been produced. One of the important product

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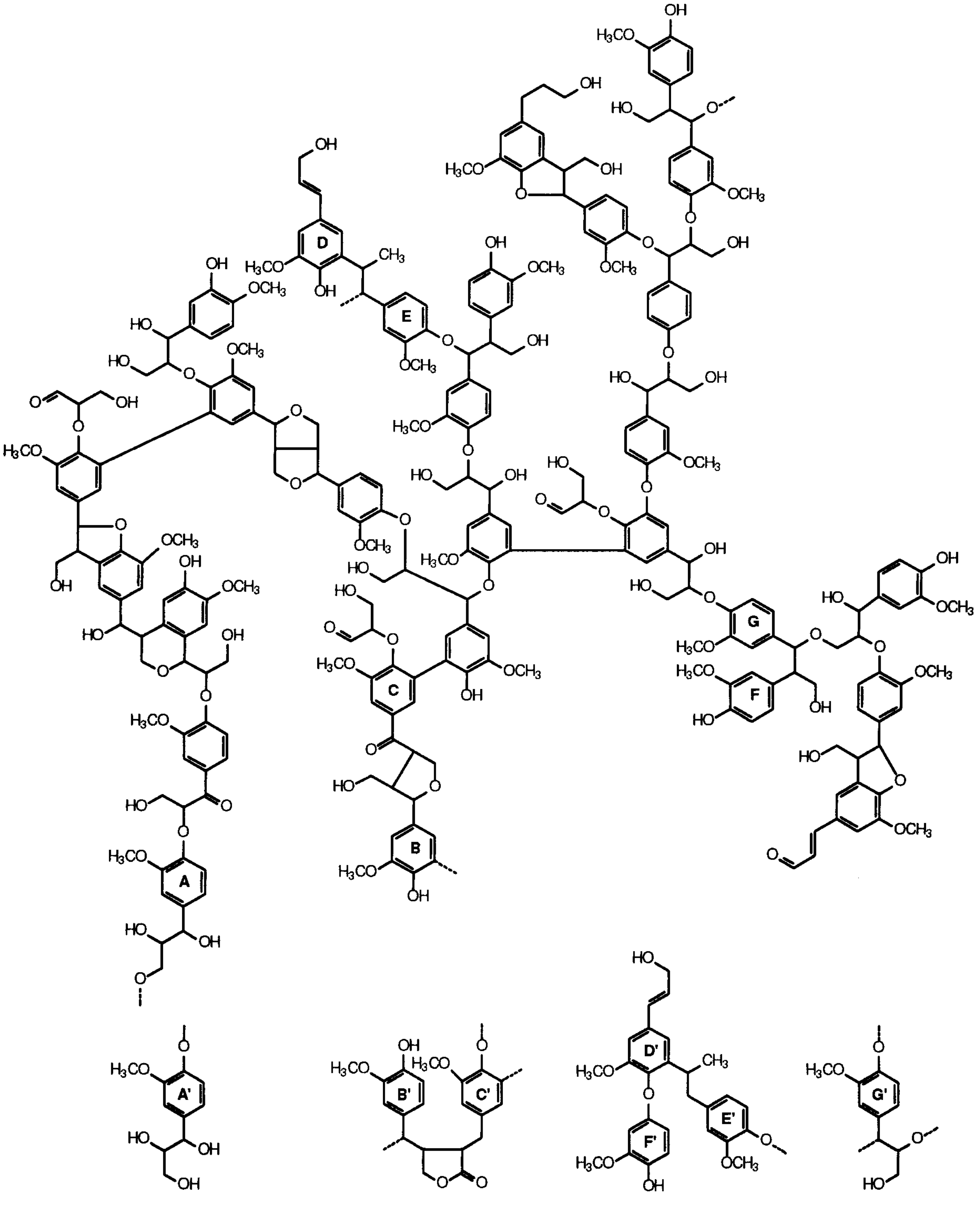
Scheme 1

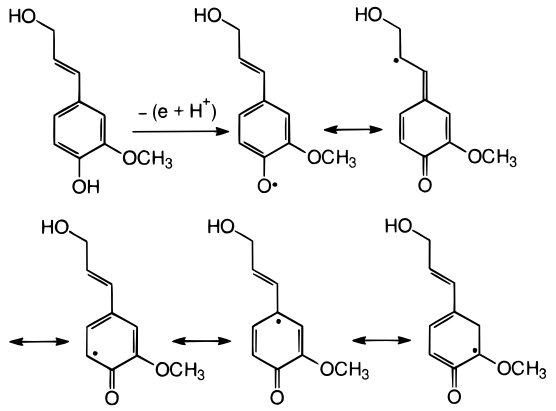


parameters for the cellulose is the viscosity. The viscosity of the cellulose is measured by using a capillary viscose meter of the cellulose dissolved in $Cu(EtNH_2)_2$. Three different LS types have been studied here, LS_{750}, LS_{850}, and LS_{1200}, where the subscript numbers indicate the viscosity numbers measured for the corresponding cellulose. The low viscosity cellulose have been obtained at digestion temperatures in the range 140−145 °C and the high viscosity cellulose are obtained at digestion temperatures in the range 125−130 °C. The variation of the Ca^{2+}/SO_2 ratio in these digestion procedures is also important because a variation of the number of sulphonic groups and the amount of Ca^{2+} will also be found in the different sulphite-spent liquors.

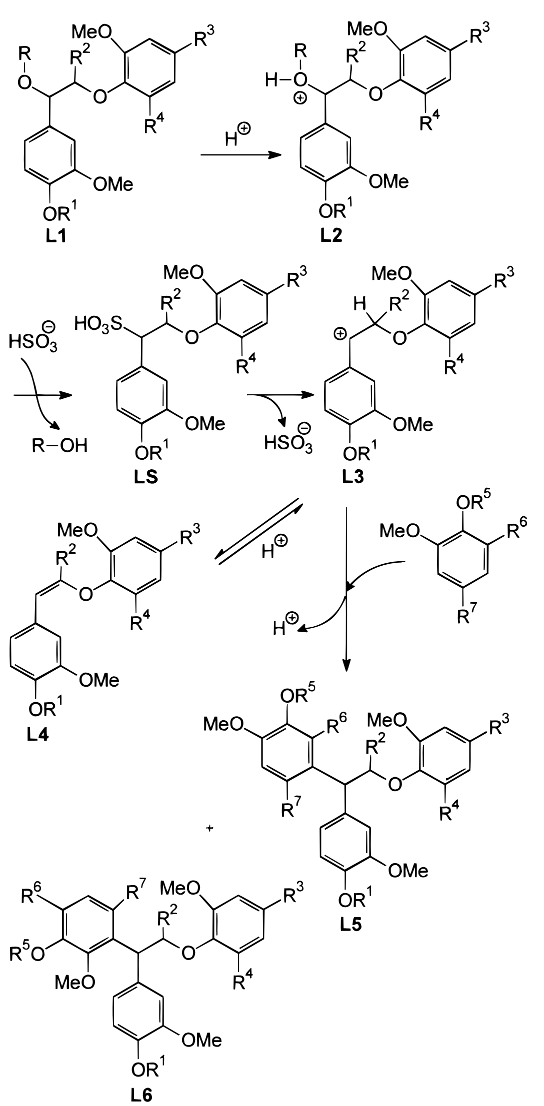
The chemical reactions that occur in the acid sulphite pulping process can be schematically described by Scheme 3.

The first interaction concerns the protonation of the benzyl ether of the lignin fragment **L1**; the protonated ether **L2** is then attacked by the nucleophilic HSO_3^-, leading to the formation of the lignosulfonate fragment (**LS**), which is soluble in water and is separated from cellulose fibres. The digestion process can also lead to condensation reactions in

Scheme 2



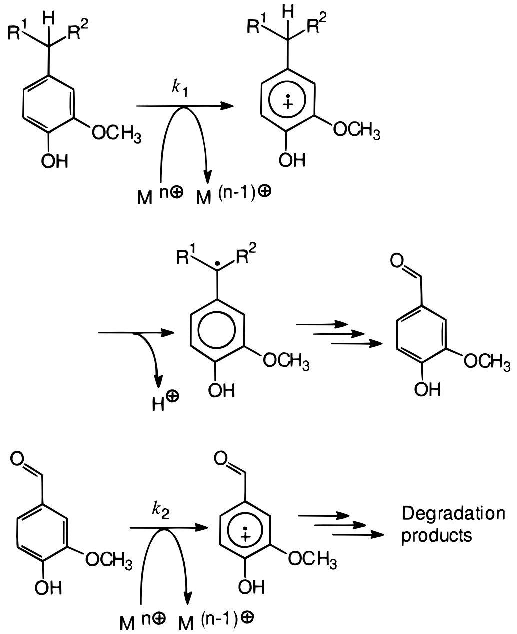
Scheme 3



L1 **L2** **LS** **L3** **L4** **L5** **L6**

addition to sulphonation. These reactions are related tointermediate benzylic carbonium ions (**L3**), which can form a double bond (**L4**) by proton elimination or can participate in Friedel–Crafts alkylation on activated aromatic rings, leading to the condensation products **L5** and **L6** (Scheme 3).

Scheme 4



The different cellulose processes which vary the digestion temperature and time and the amounts and the ratios of Ca^{2+}/SO_2 give rise to different cellulose qualities and thus also different sulphite-spent liquors (LS), which then give different yields of vanillin in the oxidation process. The LS types, LS_{750} and LS_{850}, obtained from cellulose processes using a high digestion temperature give a yield of vanillin in the range 4.0–4.2% when using LS_{750} and 4.2–4.5% when using LS_{850}. Lignosulfonates type LS_{1200} obtained from processes with a lower digestion temperature give significantly higher yields of vanillin (5.8–6.2%).

New Catalytic Approaches for the Oxidation of Lignosulfonates. The fast oxidation of vanillin by oxygen under free radical chain conditions (eq 1) suggested that an electron-transfer mechanism could be effective for the oxidation of LS to vanillin and it likely occurs also in the current procedure,[1,8–16] involving Cu(II) catalysis and NaOH. The rationale for this assumption is related to the increase of the redox potential by passing from LS to vanillin, due to the electron-withdrawing character of the aldehyde group ($k_1 > k_2$ in Scheme 4).[17,18]

Byproducts, always present in the traditional process, such as vanillin acid (eq 2), dehydrovanillin (eq 3), vanillyl (eq 4), clearly arise by further free radical oxidation of vanillin according to eq 1.

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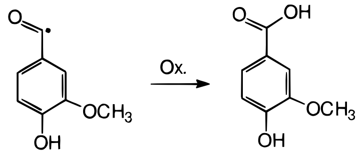
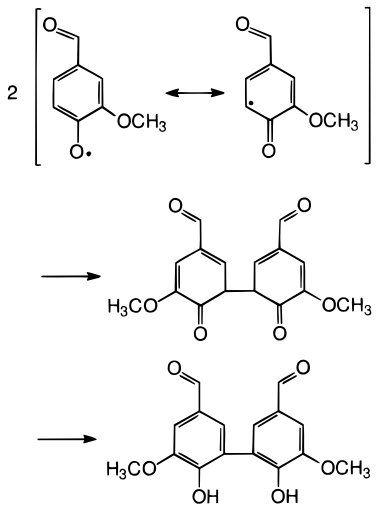


(2)



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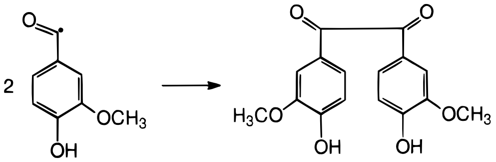


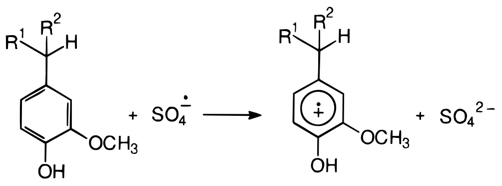
(4)

Following this general assumption we have investigated several routes for the oxidation of LS, which could involve electron-transfer mechanism.

1. Oxidation by Persulphate. A first attempt concerned the use of persulphate as oxidant, in combination or not with metal salt catalysis. The thermal or catalytic decomposition of persulphate generates the radical anion $SO_4^{-\bullet}$ (eqs 5 and 6), which is able to directly oxidise aromatic rings by electron transfer (eq 7).[17,18]

$$S_2O_8^{2-} \longrightarrow 2\,SO_4^{\bullet -} \tag{5}$$

$$S_2O_8^{2-} + M^{n+} \longrightarrow SO_4^{\bullet -} + SO_4^{2-} + M^{(n+1)+} \tag{6}$$



(7)

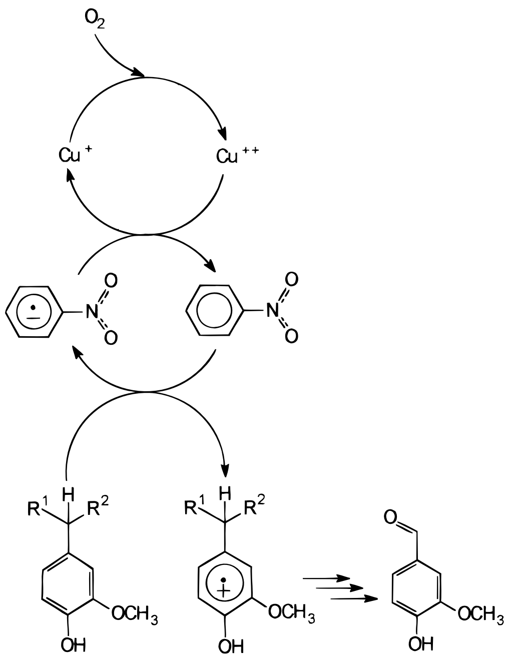
$M = Fe^{2+},\ Cu^{+},\ Ag^{+},\ Co^{2+}$

Moreover the radical anion $SO_4^{-\bullet}$ is also able to oxidise metal salt to higher oxidation states (eq 8), which can be responsible for electron-transfer oxidation.

$$Cu^{2+} + SO_4^{\bullet -} \longrightarrow Cu^{3+} + SO_4^{2-} \tag{8}$$

The main difficulty, encountered by this approach, is concerned with the reaction temperature because the overall reaction is a combination of hydrolysis and oxidation of LS.

Scheme 5



The hydrolysis requires a high temperature (160−200 °C), which is not suitable for the oxidation by persulphate. On the other hand, at a lower temperature (100−110 °C) (atmosphere pressure in the absence of oxygen) vanillin was formed, but the conversions were low, most probably due to only partial hydrolysis of LS.

Some results are reported in Table 1. Further investigations by this approach were not carried out, also considering the cost of persulphate, although it was possible to consider a two-step process: (i) LS is first hydrolyzed at a high temperature (160−200 °C); (ii) the hydrolyzed solution could be oxidised by persulphate at a lower temperature.

2. Oxidation by Nitrobenzene. The selectivity in vanillin is significantly higher by oxidation of LS by nitrobenzene,[19−22] compared to other known methods, where a vanillin yield of approximately 20% has been reported. However the amount of nitrobenzene, required by this procedure is to high for the industrial application. We have tried to make the overall process catalytic in nitrobenzene by combining the oxidation of LS by nitrobenzene and oxygen catalysed by Cu(II) salt in order to obtain the catalytic cycle reported in Scheme 5.

The highest vanillin yield we obtained with the combined method of Cu(II)/nitrobenzene is reported in entry 1 of Table 2. Moreover, Table 2 lists results for experiments using only Cu(II) as catalyst and the combined method with 1,3,5-trinitrobenzene/Cu(II) as catalysts. The courses of the reactions for these experiments are graphically represented in Figure 1.

As the yields decrease, after a maximum, the pH of the reaction medium also decreases meaning that the degradation reactions lead to acidic products (eq 2).

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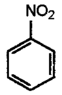
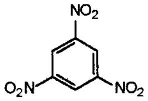
Table 1. **Experiments carried out under atmospheric pressure with sodium persulphate as oxidising agent**[a]

no.	lignin LS-LTP [g]	oxidation agent type	oxidation agent [g]	catalyst	pH	Rx time [h]	isolated yield [g]	GC area % of vanillin	yield % of vanillin of lignin
1	13.51	$Na_2S_2O_8$ (s)	10.0	–	<7	4:00	0.0400	16.25	0.048
2	5.40	$Na_2S_2O_8$ (aq)	4.05	$CuSO_4$	<7	4:00	0.0475	10.69	0.094
3	5.40	$Na_2S_2O_8$ (aq)	4.04	–	<7	4:00	0.0446	7.03	0.058
4	5.40	$Na_2S_2O_8$ (aq)	4.07	$AgNO_3$	<7	3:30	0.0624	7.91	0.091
5	5.40	$Na_2S_2O_8$ (aq)	4.00	–	>7	3:00	0.0365	1.16	0.008
6	5.40	$Na_2S_2O_8$ (aq)	4.04	$CuSO_4/AgNO_3$	>7	3:00	0.0470	2.91	0.025
8	5.40	O_2 (g)		$CuSO_4/AgNO_3$	>7	5:15	0.1179	16.53	0.361
9	5.40	$Na_2S_2O_8$ (aq)	4.07	$Co(OOCCH_3)_2$	>7	4:30	0.0421	17.40	0.136
10	5.40	$Na_2S_2O_8$ (s)	4.07	–	>7	4:15	0.0311	2.92	0.017

[a] The reaction mixtures were added NaOH (100 mL, 2 M), and extracted with 2-propanol (100 mL + 50 mL), acidified with sulphuric acid (pH 2–3), filtered, and extracted with toluene (100 mL × 2). The toluene extract was analysed on GC.

Table 2. **Experiments carried out in the laboratory reactor**[a]

	catalyst type	catalyst amount	maximum vanillin yield observed
1	$CuSO_4 \cdot 5H_2O$	1.08 g	5.92
		2 mL	
2	$CuSO_4 \cdot 5H_2O$	1.00 g	5.31
3	$CuSO_4 \cdot 5H_2O$	1.12 g	4.14
		4.16 g	

[a] Procedure: Lignosulfonate of type LS_{1200} (110.6 g) is mixed with NaOH (18 g dissolved in 16 mL of water). In experiments 1 and 2 the reaction mixture was preheated in 15 min under pressure (15 atm) before the catalysts were added. In experiment 3 the catalyst was charged together with the lignosulfonate and NaOH. The reaction temperature was 190 °C in all of the experiments.

The plots of Figure 1 show that the combined catalysis nitrobenzene/Cu(II) gives 11.5% higher relative yields in a shorter time compared with the use of only Cu(II) catalysis under the same conditions, but the yields are lower compared to the oxidation by a large excess of nitrobenzene.[19–22] By using a more powerful oxidant 1,3,5-trinitrobenzene, yields are somewhat lower. All of the experiments have shown that the efficiency of the catalysts is considerably increased by using a preheating methodology, that is, the reaction mixture is heated at the reaction temperature for 15–20 min (180–190 °C) in the absence of the catalyst, which is then added under pressure; most of the vanillin (81% in the experiment 1 of Table 2) is formed after the addition of the catalyst.

The higher yields of vanillin in the oxidation by a large excess of nitrobenzene can be related, in our opinion, always to oxidation by electron-transfer processes (eq 9), which avoid the degradation of vanillin by free-radical processes, which generally occur to some extent in the presence of oxygen.

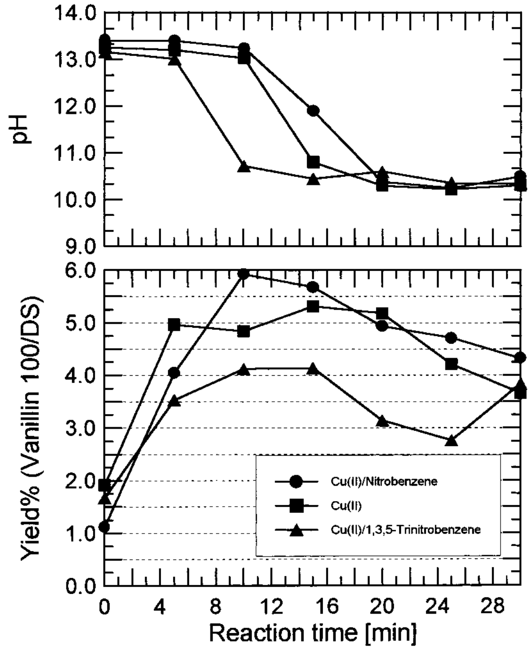
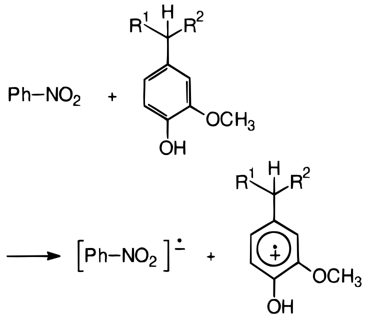


Figure 1. **Course of the hydrolysis–oxidation of LS_{1200} using (●) Cu(II)/Nitrobenzene, (■) Cu(II), or (▲) Cu(II)/1,3,5-Trinitrobenzene as catalytic systems. The experiments were carried out in the pilot plant using 600 gram LS_{1200} with 15 min preheating of the reaction mixture before the catalyst is added.**



(9)

3. Oxidation of LS by Oxygen and Metal Salt Catalysis. The effectiveness of the metal salts could be related to high oxidation potentials, which more easily would allow electron-transfer processes from aromatic rings according to the Scheme 4, but at the same time a high oxidation potential makes the regeneration of the metal salt into the higher oxidation state to obtain a catalytic cycle more difficult. In

Table 3. **Experimental conditions for metal salt catalyst tests**[a]

no.	catalyst/[mol]	amount of NaOH/[g]	temperature [°C]
1	Ce(IV)/0.04813	384	190
2	Cu(II)/0.0654	384	190
3	Ce(IV)/0.02406 + Cu(II)/0.02406	384	190
4	Co(II)/0.04813	384	190
5	Cu(II)/0.1259	480	185
6	Co(II)/0.1358	480	185

[a] Experiments carried out in pilot plant scale, using 600 g of LS_{1200}. The reaction mixture was preheated in 15 min under pressure (11−12 atm) before the catalyst was added as a water solution under pressure.

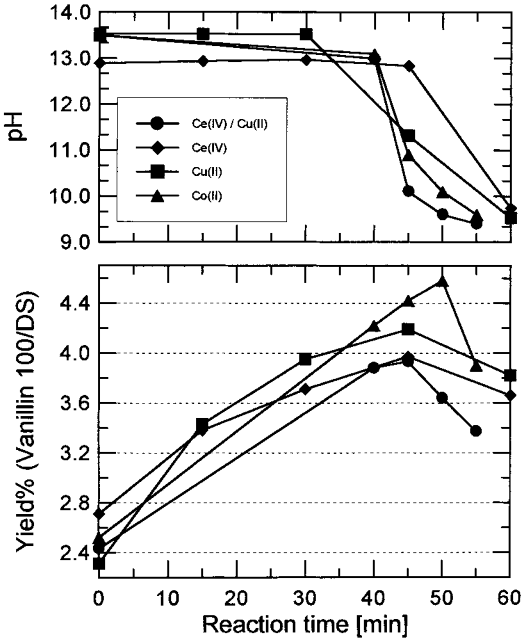


Figure 2. **Course of the hydrolysis-oxidation of LS_{750} using (●) Ce(IV)/Cu(II), (◆) Ce(IV), (■) Cu(II), and (▲) Co(II) as catalyst. The experiments were carried out in the pilot plant using 600 gram LS_{750} with 15 min preheating of the reaction mixture before the catalyst is added.**

addition to the Cu(II) catalysis, developed in the Monsanto process,[8−16] we have investigated as catalyst Ce(III)/Ce(IV) and Co(II)/Co(III) salts, well known[24] for the effectiveness of electron-transfer from aromatic substrates.

To compare the efficiency of the three catalysts, some representative experiments were carried out under the conditions reported in Table 3. The reactions were performed with a preheating to 190 °C under elevated pressure (~12 atm) for 15 min to perform basic hydrolysis of LS without oxidative conditions. Then the catalyst was added under pressure, and bubbling of air through the reaction mixture, still under elevated pressure, was started. The results of experiments 1−4 are graphically reported in Figure 2.

The graphs of Figure 2 shows that the optimal reaction time is 45−50 min (in addition to the preheating time of 15 min) when carried out at 190 °C when the same amount of NaOH is used. The efficiency of the catalysts is Co(II) > Cu(II) > Ce(IV) > Ce(IV)/Cu(II).

The experiments 5 and 6 of Table 3 were carried out when an optimisation procedure for the oxidation of LS_{750} was established, as it will be discussed afterwards.

The efficiency of the Cu(II) and Co(II) catalysts is quite similar; however, the oxidation is somewhat faster by the Cu(II) catalyst: when using Cu(II), the maximum yield of vanillin was 5.9% and was obtained after 70 min, and when using Co(II) as catalyst, a maximum vanillin yield of 5.8% was obtained after 90 min, both experiments being carried out at a reaction temperature of 185 °C.

It appears from the results that Co(II) can substitute for Cu(II) as catalyst, while Ce(IV) shows a lower efficiency in the oxidation of LS, that is likely related to the higher difficulty to reoxidise Ce(III) to Ce(IV).

Screening and Optimisation of the Current Oxidation Procedure

(A) Oxidation of LS from High-Temperature Digestion Process (LS_{750} and LS_{850}). Statistical experimental design[23−25] and modelling using multiple linear regression[26] and the partial least-squares regression[24] was used to obtain an overview of the influence of the experimental, controllable variables in the current procedure for the basic hydrolysis−oxidation of LS.

Since the current vanillin process has been run for nearly 30 years with concomitant process evolution and optimisation studies, an overwhelming amount of process and experimental data were available. These data were, however, not consistent for modelling purpose, mostly due to changes in LS qualities and changes in the hydrolysis−oxidation unit of the plant. However, in the screening phase of the present study, some of these process and experimental data material were used as a support for selecting variables and experimental levels for a screening study. Hence, the experimental variables the reaction temperature (x_1), the reaction time (x_2), the amount of air (x_3), the amount of $CuSO_4$ (x_4), the amount of NaOH (x_5), and the amount of lignosulfonate (x_6) were all expected to affect the vanillin yields and were thus investigated in a 2^{6-2} fractional factorial design.

The experimental levels for these variables (Table 4) were based on the existing standard oxidation procedure. Other variables, such as reaction pressure and stirrer speed, were also considered to influence the reaction, but it was decided to perform the experiments at fixed levels for these variables based on observations from earlier studies using LS_{750}. An empirical model, eq 10, was derived from the design matrix and the analytical results (vanillin yield) given in Table 4.

$$y_i = \beta_0 + \sum_{k=1}^{K}\beta_k x_k + \sum^{K}\sum_{k\neq l}^{K}\beta_{kl}x_k x_l + \sum^{K}\sum_{k\neq l\neq m}^{K}\sum^{K}\beta_{klm}x_k x_l x_m + \epsilon_i \qquad (10)$$

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Table 4. **Screening design 2^{6-2} using lignosulfonate type LS_{750}**

no.	x_1	x_2	x_3	x_4	x_5	x_6	response[b] y
	exptl variables[a]						
1	−1	−1	−1	−1	−1	−1	5.22
2	+1	−1	−1	−1	+1	−1	4.78
3	−1	+1	−1	−1	+1	+1	5.50
4	+1	+1	−1	−1	−1	+1	4.57
5	−1	−1	+1	−1	+1	+1	4.96
6	+1	−1	+1	−1	−1	+1	4.80
7	−1	+1	+1	−1	−1	−1	5.12
8	+1	+1	+1	−1	+1	−1	5.05
9	−1	−1	−1	+1	−1	+1	5.04
10	+1	−1	−1	+1	+1	+1	5.47
11	−1	+1	−1	+1	+1	−1	5.16
12	+1	+1	−1	+1	−1	−1	5.59
13	−1	−1	+1	+1	+1	−1	4.69
14	+1	−1	+1	+1	−1	−1	4.89
15	−1	+1	+1	+1	−1	+1	5.73
16	+1	+1	+1	+1	+1	+1	5.29
17	0	0	0	0	0	0	4.93
18	0	0	0	0	0	0	5.10
19	0	0	0	0	0	0	4.96

[a] Experimental variables: x_k [−1, +1] x_1, reaction temperature [165, 185] °C; x_2, reaction time [45, 75] min; x_3, amount of air [−1, +1] $m^3\ min^{-1}$; x_4, $CuSO_4$ [2.20, 4.40] g; x_5, amount of NaOH [422, 462] g; x_6, amount of lignosulfonate [580, 660] g. [b] Responses measured by HPLC and related to dry substanse (DS) (i.e., LS) of the reaction mixture *y* (vanillin/DS)%. Generators for the experimental design: $x_5 = x_1 \cdot x_2 \cdot x_3$ and $x_6 = x_2 \cdot x_3 \cdot x_4$.

Table 5. **Regression model derived from screening design studying oxidation of LS_{750}**

effect[a]	effect value	SEM	*P*	confidence interval
β_0	5.097	0.030	4.67×10^{-7}	±0.097
β_1	−0.058	0.031	0.161	±0.099
β_2	0.127	0.031	0.027	±0.099
β_3	−0.047	0.031	0.228	±0.099
β_4	0.110	0.031	0.039	±0.099
β_5	−0.004	0.031	0.917	±0.099
β_6	0.051	0.031	0.203	±0.099
β_{12+35}	−0.058	0.029	0.144	±0.094
β_{13+25}	0.002	0.029	0.945	±0.094
β_{14+56}	0.123	0.029	0.025	±0.094
$\beta_{15+23+46}$	0.086	0.029	0.062	±0.094
β_{16+45}	−0.068	0.029	0.105	±0.094
β_{24+36}	0.067	0.029	0.108	±0.094
β_{34+26}	−0.029	0.029	0.399	±0.094
β_{124}	−0.013	0.028	0.681	±0.088
β_{134}	−0.117	0.028	0.024	±0.088

[a] The subscript numbers indicate the variable numbers or cross product between them. Hence, e.g., 16 means 1 × 6. 0 = the mean yield, 1 = the reaction temperature, 2 = the reaction time, 3 = the amount of air, 4 = the amount of $CuSO_4$, 5 = the amount of NaOH, and 6 = the amount of LS. Statistical product: $Q^2 = 0.1441$, $R^2 = 0.9699$, RSD = 0.1324 at a confindence level of 95%.

The main effects, the two- and three-factor interactions with their confounded two-variable interaction pattern and their corresponding estimated coefficient values are reported in Table 5.

These coefficient values were analysed by the cumulative normal probability (CND)[25] shown in Figure 3.

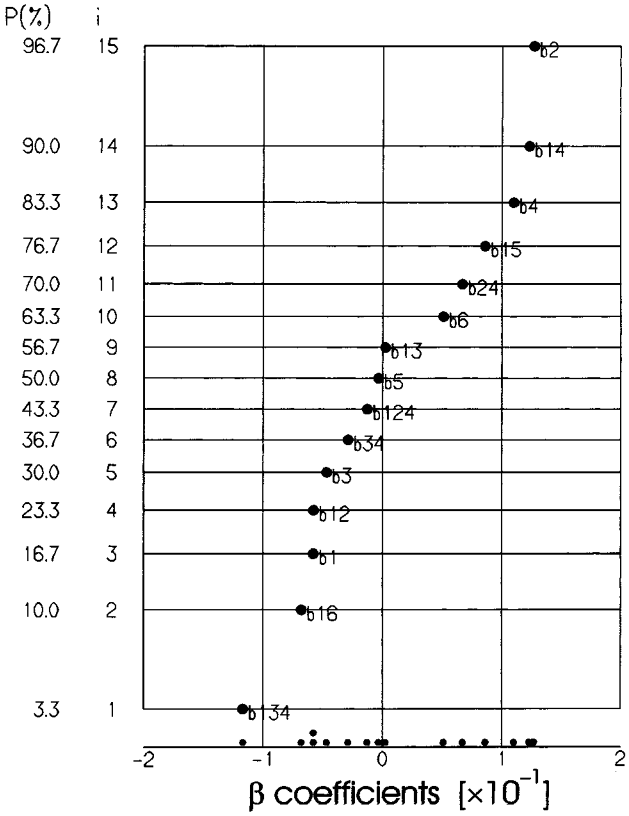

Figure 3. **Cumulative normal distribution plot of the regression coefficients estimated for the screening design $2.^{6-2}$**

The CND plot (Figure 3) shows that the regression coefficients β_{134}, β_{16+45}, β_1, β_{12+35}, and β_3 (with negative values), and β_4, β_{14+56}, and β_2 (with positive values) were the effects with the largest influence on the response (*y*) of eq 10. Statistical analysis of the estimated model parameters, the β's, (Table 5) shows, however, that many of these are not statistically significant. An assessment of the confounded two-factor interactions β_{12+35}, β_{14+56}, and β_{16+45} indicates that the most probable two factor interactions are: β_{12} (reaction temperature × reaction time), β_{14} (reaction temperature × amount of Cu), and β_{45} (amount of Cu × amount of NaOH). This interpretation is build upon *a priori* knowledge concerning the hydrolysis−oxidation reaction, where variations on the amount of sodium hydroxide, the reaction temperature, and the reaction time influence the outcome of vanillin. The determined screening model was then used to estimate some simple response surfaces,[26] graphically represented in Figure 4, which were used as a support for selecting new experimental levels for a response surface modelling experiment, which also included quadratic terms in the predictive model.

The experimental variables the reaction temperature (x_1), the reaction time (x_2), the amount of Cu(II) (x_4), and the amount of NaOH (x_5) were thus selected for further pilot plant optimisation studies in the experimental domain predicted to be promising by eq 10 that is graphically represented in Figure 4. The variables were renumbered for the new experimental design, such that the amount of NaOH became x_1, the amount of Cu(II) became x_2, the reaction temperature became x_3, and finally the reaction time became x_4.

The variables x_1−x_3 were used in a central composite design.[30] For each experiment five samplings were performed, namely, at 30, 60, 70, 80, and 100 min. Including the centre experiments, the experimental design becomes

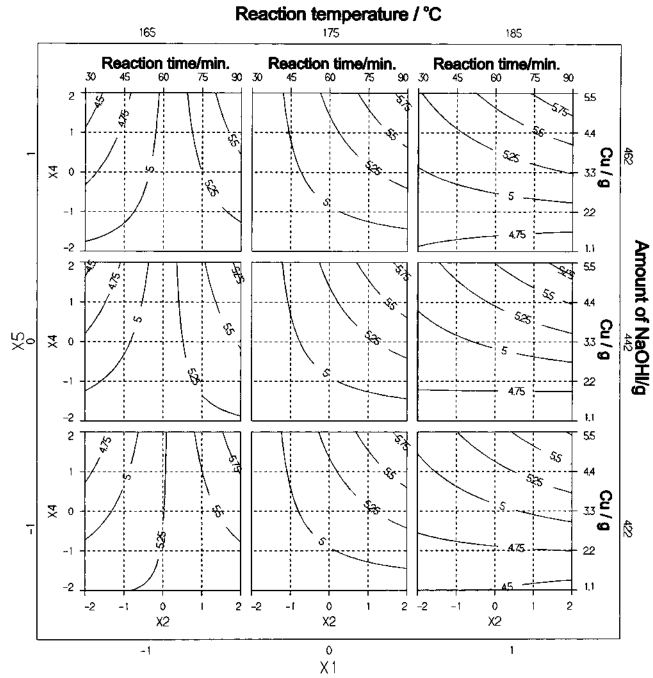

Figure 4. Response surface representation of the screening model for the hydrolysis−oxidation process of lignosulfonate LS_{750}.

Table 6. Central composite design for pilot plant experiments using LS_{750}

exptl variables[a]				response[b] y				
				reaction time t [min]				
no.	x_1	x_2	x_3	30	60	70	80	100
1	−1	−1	−1	2.19	4.69	4.96	5.20	4.91
2	+1	−1	−1	2.90	4.33	4.73	4.95	4.68
3	−1	+1	−1	2.88	4.83	4.98	4.91	4.46
4	+1	+1	−1	2.37	4.52	4.85	5.06	5.09
5	−1	−1	+1	3.20	4.91	5.21	5.16	4.98
6	+1	−1	+1	3.08	4.85	5.07	5.22	4.95
7	−1	+1	+1	2.54	4.71	5.11	5.20	4.84
8	+1	+1	+1	3.03	4.68	4.95	5.02	4.98
9	− 2	0	0	3.05	4.95	5.09	5.23	4.77
10	+ 2	0	0	2.80	4.48	5.20	5.27	5.07
11	0	−2	0	3.04	3.98	4.75	4.86	5.05
12	0	+ 2	0	2.90	4.82	5.13	5.27	4.84
13	0	0	−2	2.71	4.45	4.80	4.82	4.65
14	0	0	+ 2	3.42	4.41	4.84	5.05	4.95
15	0	0	0	3.51	4.89	5.17	5.29	5.16
16	0	0	0	2.89	4.63	4.89	5.27	5.25
17	0	0	0	3.22	4.95	5.14	5.18	5.18
18	0	0	0	2.91	4.89	5.41	5.39	4.76

[a] Experimental variables: x_k [−2, −1, 0, +1, +2]: x_1, the amount of NaOH [440, 450, 460, 470, 480] g; x_2, the amount of Cu [2.0, 4.0, 6.0, 8.0, 10.0] g, and x_3, the reaction temperature [160, 170, 180, 190, 200] °C. Current procedure: LS (660 g) in a 23−25% water solution is added NaOH (440 g) and Cu (2.3 g) and oxidised at $T = 175$ °C. [b] Responses: y_1 (Vanillin/DS)%.

$(2^3 + 2 \times 3 + 3) \times 5^1$. Each of the withdrawn samples was analysed on HPLC to determine the amount of vanillin. The selected experimental levels for the variables x_1−x_3, the experimental plan with adjacent results for the determined yields, are reported in Table 6.

From these data an empirical model that included the main effects, the two-variable interaction, and the quadratic effect (eq 11) was estimated using the partial least-squares method.

Table 7. Regression model derived from the response surface design studying oxidation of LS_{750}

effects	effect values	SEM	P	confidence intervall
β_0	5.077	0.047	0.00	±0.093
β_1	−0.010	0.025	7.00×10^{-1}	±0.049
β_2	0.025	0.024	3.01×10^{-1}	±0.047
β_3	0.093	0.024	1.75×10^{-4}	±0.047
β_4	0.560	0.023	2.32×10^{-37}	±0.046
β_{11}	−0.019	0.020	3.40×10^{-1}	±0.039
β_{22}	−0.049	0.018	6.00×10^{-3}	±0.035
β_{33}	−0.062	0.018	6.79×10^{-4}	±0.035
β_{44}	−0.416	0.021	2.30×10^{-31}	±0.042
β_{12}	0.018	0.031	5.58×10^{-1}	±0.061
β_{13}	0.012	0.031	6.86×10^{-1}	±0.061
β_{14}	0.007	0.023	7.55×10^{-1}	±0.045
β_{23}	−0.037	0.034	2.81×10^{-1}	±0.067
β_{24}	0.007	0.022	7.70×10^{-1}	±0.045
β_{34}	?0.034	0.022	1.29×10^{-1}	±0.045

[a] Subscripts corresponding to the variable numbers. 1 = amount of NaOH, 2 = the amount of Cu(II), 3 = the reaction temperature, and finally 4 = the reaction time. The regression coefficients β_k's for the model is estimated by using the partial least-squares regression (PLSR) method. A PLS model of $a = 2$ principal components were obtained, with $Q^2 = 0.882$, $R^2 = 0.951$, and RSD = 0.207 indicating a model with high predictive capability.

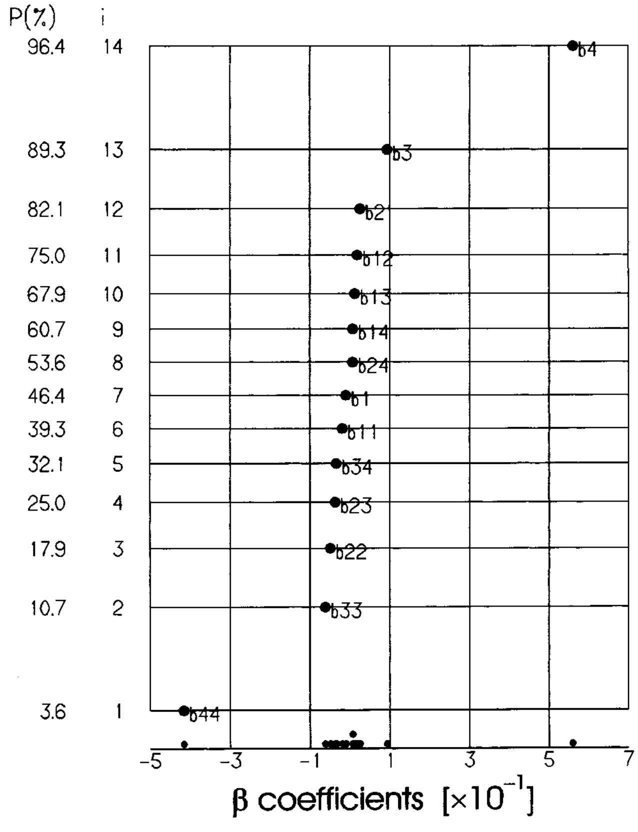

Figure 5. Cumulative normal probability plot of the estimated regression coefficients for the response surface model which describes the formation of vanillin in the hydrolysis−oxidation of LS_{750}.

$$y_i + \beta_0 + \sum_{k=1}^{K}\beta_k x_k + \sum_{k=1}^{K}\beta_{kk} x_k^2 + \sum^{K}\sum_{k\neq 1}^{K}\beta_{kl} x_k x_l + \epsilon_i \qquad (11)$$

The estimated regression coefficients are reported in Table 7, and plotted in a CND plot (Figure 5) to determine the

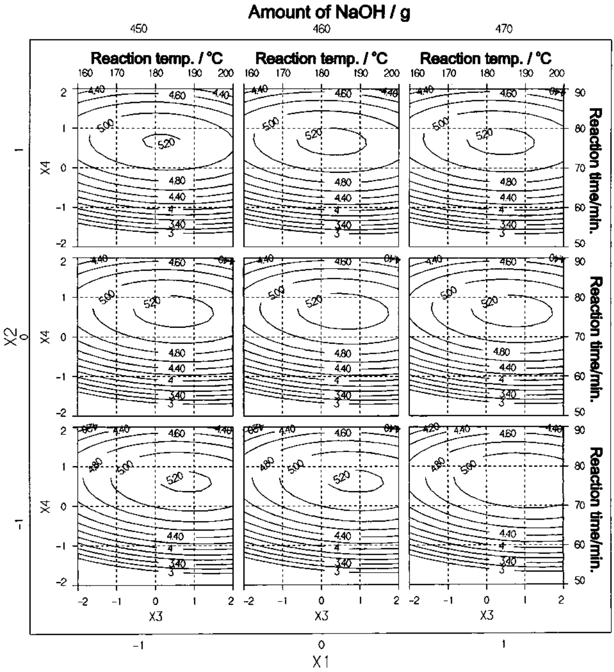

Figure 6. **Response surface projections of a model that also includes quadratic terms. The contour lines show the yield of vanillin when the four experimental variables *the amount of sodium hydroxide* (x_1), *the amount of Cu(II)* (x_2), *the reaction temperature* (x_3), and *the reaction time* (x_4) are varied. To read the plot, the large frame shows the variation in *the amount of sodium hydroxide* (x_1) and *the amount of Cu(II)* (x_2). In this frame nine subplots showing the contour lines of the response surface when the experimental variables *the reaction temperature* (x_3) and *the reaction time* (x_4) are varied.**

significant influencing variables. A statistical analysis (Table 7) of the regression coefficients shows a similar selection as the CND plot of Figure 5. The significant model parameters were: β_4, β_3, β_2, (β_{22}), β_{33}, and β_{44}. The final model is graphically represented as a response surface projection plot given in Figure 6.

Three optimisation experiments, based on Figure 6, were carried out in the pilot plant reactors. Varying the amount of catalyst Cu(II) as graphed in Figure 7 shows an improved yield of vanillin.

Using the same type of raw material, the optimised oxidation procedure gives a vanillin yield of 5.7% against a yield of 4.1% with the current procedure which corresponds to a relative improvement of 37%. The yield obtained in the optimisation experiments is however 0.5%, corresponding to 9.6% relative higher yield than predicted by the response surface model represented in Figure 6. This observation is most probably due to the natural variation in the LS_{750} raw material. Similar variation in the vanillin yield is frequently observed also in plant scale reactors.

(B) Oxidation of LS from High-Temperature Digestion Process (LS_{750} and LS_{850}) with Copper Oxide as Catalyst. The copper (II) catalyst, which is used in the vanillin plant, is charged to the hydrolysis−oxidation reactors as a water solution of copper sulphate. When the oxidation reaction is completed, the copper is recovered as sludge of inorganic and organic substances, from which the copper is extracted by using ammonia and precipitated as copper (II) oxide.

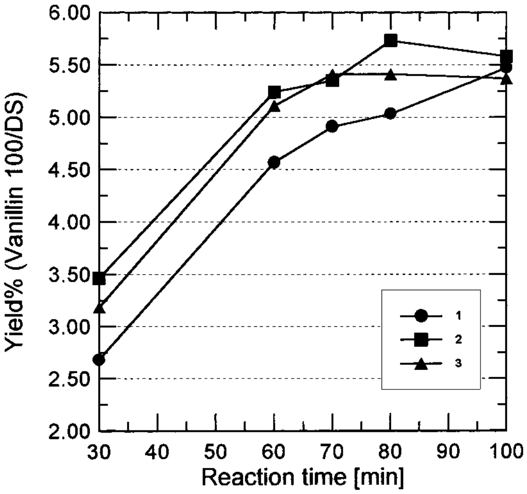

Figure 7. **Course of the optimisation reactions for LS_{750} with conditions predicted from the model derived from the experiments in the response surface design. The conditions for the different experiments performed in the pilot plant reactors are for the three experiments: 2630 mL of an approximately 24% lignosulfonate solution (660 gram LS) is diluted with 740 mL water, 465 g sodium hydroxide as 50% solution and copper as $CuSO_4$ solution of approximately 16% are added. The different amounts of copper were: (●) 5 g Cu, (■) 6 g Cu, and (▲) 7 g Cu. All experiments were performed at a temperature of 182−185 °C.**

Table 8. **Experimental design with adjacent experimental results[a]**

	exptl variables[b]		responses, y^c					
			reaction times, t [min]					
no.	x_1	x_2	30	40	50	60	70	80
1	−1	−1	2.53	3.70	4.07	4.23	4.38	4.61
2	0	−1	2.95	3.94	4.42	4.77	4.91	4.95
3	+1	−1	3.05	3.97	4.40	4.68	4.83	4.87
4	−1	0	2.93	3.55	3.91	4.06	3.98	4.29
5	0	0	3.05	3.48	4.00	4.21	4.21	4.10
6	+1	0	3.39	3.78	4.10	4.24	4.40	4.40
7	−1	+1	2.45	3.54	3.84	4.59	4.30	4.28
8	0	+1	3.29	4.12	4.77	4.91	5.09	5.42
9	+1	+1	3.71	4.59	5.14	5.44	5.36	5.71

[a] Experiments carried out using LS_{750}. [b] Experimental variables: x_k [−1, 0, +1] x_1, the amount of Cu(II) [2, 4, 6] g; x_2, the amount of NaOH [420, 440, 460] g of 660 g LS−HTP1 was used in each of the experiments. [c] Responses measured by HPLC and related to dry substance (LS) of the reaction mixture y (Vanillin/DS).

In the present study we wanted also to explore if the recovered copper oxide could be recycled in the vanillin plant as solid copper (II) oxide. Thus, by using the gained knowledge of how to oxidise LS_{750}/LS_{850}, a new experimental design vary the amount of copper and sodium hydroxide was performed in the pilot plant reactors. The experimental design with adjacent experimental results is given in Table 8, from which the response surface model of eq 12 was derived based on these results.

$$y_i + \beta_0 + \sum_{k=1}^{K}\beta_k x_k + \sum_{k=1}^{K}\beta_{kk}x_k^2 + \sum^{K}\sum_{k\neq 1}^{K}\beta_{kl}x_kx_l + \epsilon_i \qquad (12)$$

This model was used to calculate the response surface projection reported in Figure 8, which shows an interesting

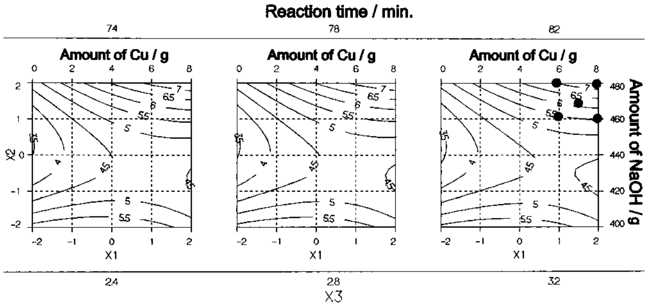

Figure 8. **Contour projection lines show the yield of vanillin when the three experimental variables *the amount of Cu* (x_1), *the amount of sodium hydroxide* (x_2), and *the reaction time* (x_3) are varied. In the present experimental study was recovered and recycled Cu used as catalyst. The copper was charged to the reaction mixture as a "slurry" of CuO. To read the plot, the large frame shows the variation in *the reaction time* (x_3). In this frame three subplot showing the contour lines of the response surface when the experimental variables *the amount of Cu(II)* (x_1) and *the amount of sodium hydroxide* (x_2) are varied. The five points indicated in the subplot given at time 82 min were selected to be carried out as new optimising experiments.**

Table 9. **Optimising experiments using LS_{750} with conditions and adjacent measured experimental results**

	exptl conditions[a]		response/% vanillin/LS[b]					
			reaction time/[min]					
no.	Cu	NaOH	65	75	80	85	90	100
1	6 g	460 g	5.49	5.64	5.54	5.56	5.52	5.31
2	8 g	460 g	5.23	5.53	5.67	5.57	5.59	5.49
3	6 g	480 g	5.06	5.93	6.55	5.66	6.35	6.31
4	8 g	480 g	6.20	6.45	6.41	7.22	6.75	6.46
5	7 g	470 g	5.24	5.32	5.68	5.58	5.43	5.21

[a] The amounts of water, lignosulfonate is as described in experimental. The hydrolysis−oxidation experiments are performed at 185 °C. [b] Percent vanillin is correlated to the amount of dry substance found in the sample.

region of high vanillin yield when both the amounts of Cu(II) and NaOH are increased, whereas the experimental conditions is given in Table 9. The results from these follow-up experiments are reported in Table 9 and Figure 9.

The obtained model has shown an excellent predictive capacity, as illustrated by the comparison of the estimated response surface in Figure 8 with the experimental results of Figure 9. The best yield of vanillin was obtained using the conditions for experiment entry 4 of Table 9, in which $y_{exp} = 7.2\%$ and the yield predicted by the model is exactly the same, $y_{pred} = 7.2\%$. This result represents a 75% relative improvement compared to the standard Borregaard procedure developed from the Monsanto process.[1]

(C) Oxidation of LS from Low-Temperature Digestion Process (LS_{1200}). A model similar to (A) has been developed in the pilot plant reactors, and the obtained response surface model is graphically represented in Figure 10. Optimisation experiments, based on this response surface (Figure 10) were performed. The interpretation of this model is very different from the obtained model for LS_{750}/LS_{850}. A general description of the model is:

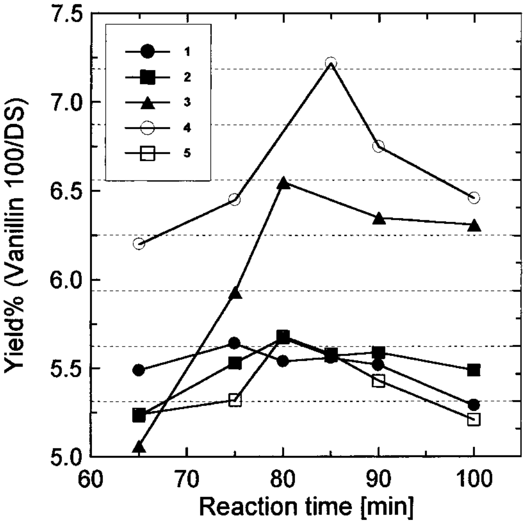

Figure 9. **The course of the optimisation reactions with conditions predicted from the model derived from the response surface design. The conditions for the different experiments performed in the pilot plant reactors are for all experiments 2630 mL of an approximately 24% lignosulfonate solution (660 g LS) which is diluted with 740 mL water and sodium hydroxide as 50% solution and the copper catalyst as recovered copper oxide. The graph shows: (●) 6 g Cu and 460 g NaOH, (■) 8 g Cu and 460 g NaOH, (▲) 6 g Cu and 480 g NaOH, (○) 8 g Cu and 480 g NaOH, and (□) 7 g Cu and 470 g NaOH. All experiments were performed at 185 °C.**

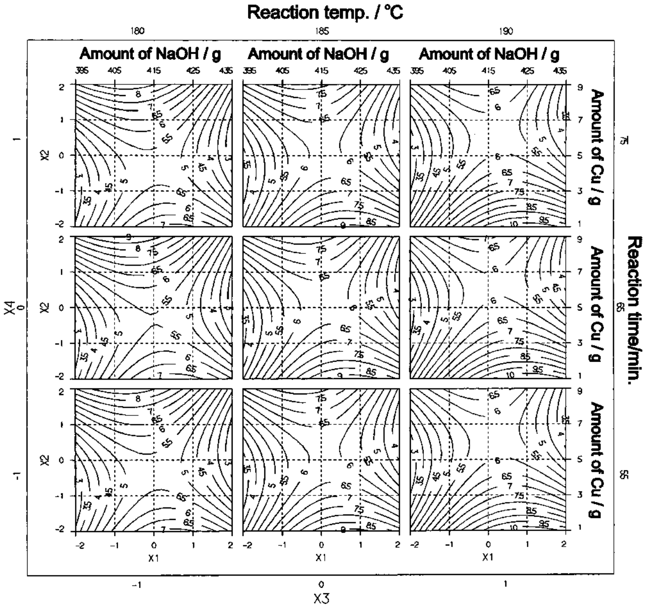

Figure 10. **Response surface projections of a model that also includes quadratic terms. The contour lines show the yield of vanillin when the four experimental variables *the amount of sodium hydroxide* (x_1), *the amount of Cu(II)* (x_2), *the reaction temperature* (x_3), and *the reaction time* (x_4) are varied. To read the plot, the large frame shows the variation in *the reaction temperature* (x_3), and *the reaction time* (x_4). In this frame nine subplots showing the contour lines of the response surface when the experimental variables *the amount of sodium hydroxide* (x_1) and *the amount of Cu(II)* (x_2) are varied.**

(i) The reaction temperature should be 185−195 °C (may be even better with a higher temperature).

(ii) The reaction time should be 65−75 min.

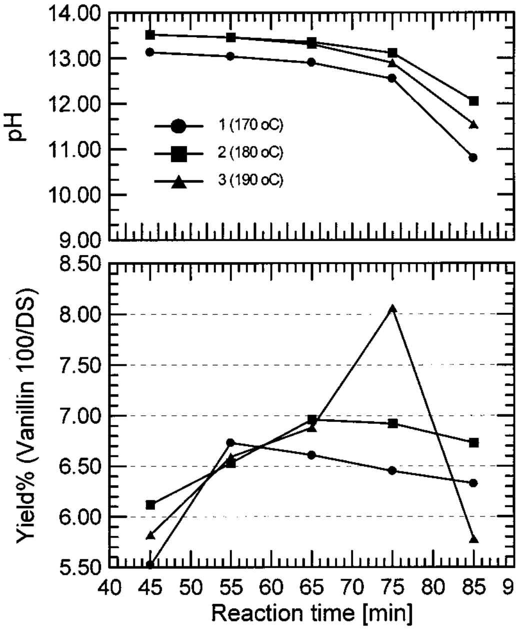

Figure 11. **The course of the optimisation reactions for LS_{1200} with conditions predicted from the model derived from the response surface design. The conditions for the different experiments performed in the pilot plant reactors are for all experiments 2630 mL of approximately 24% lignosulfonate solution (660 g LS) diluted with 740 mL water and 425 g sodium hydroxide added as 50% solution and the copper catalyst (1.2 g Cu) added as $CuSO_4$ solution. The different reaction temperatures were (●) 170 °C, (■) 180 °C, and (▲) 190 °C.**

(iii) The amount of NaOH should not be kept at the current level.

(iv) The amount of Cu should be reduced about 45−50% compared with the current level.

Thus, on the basis of these considerations some optimisation experiments were performed in the pilot plant. The conditions and the course of reactions are shown in Figure 11. A vanillin yield of 8% was obtained in the optimisation experiments (Figure 11) against 6% yield with the current procedure, an relative improvement of 35%.

Conclusion

The assumption that electron-transfer processes can play an important role in the hydrolysis−oxidation of lignosulfonates (LS) to vanillin has led to the development of new procedures and a new effective catalyst. The application of statistical experimental design and mathematical modelling has allowed a great improvement of the vanillin yields compared to those of the original Monsanto process. Even with a simplified methodology in the variable selection by using the normal probability plots, models with high predictive ability have been established. During the study, the yield showed approximately 75% relative improvement for the procedure using LS from high-temperature digestion cellulose processes (LS_{750} and LS_{850}) and approximately 35% relative increase of the vanillin yield for the procedure using LS from a low-temperature digestion cellulose process (LS_{1200}).

Experimental Section

General Oxidation Procedure in the Pilot Plant Reactor. The reactor is charged with a lignosulfonate (LS) solution of types LS_{750}, LS_{850}, or LS_{1200} (660 g LS, or 2630 mL of an approximately 24% LS solution), copper sulphate solution (corresponding to 2.3 g Cu, that is, 50 mL of $CuSO_4$ solution with a concentration of 16.3%), sodium hydroxide (430 g NaOH, that is, 580 mL of a 50% NaOH solution), and water (740 mL). The pressure was then set at $p = 11$ atm with a stirrer speed of 850 rpm. Several samplings were performed, typically in the range 50−110 min. The samples were analysed with the standard method on HPLC.

General Oxidation Procedure in the Laboratory Scale Reactor: The reactor is charged with a LS solution of types LS_{750}, LS_{850}, or LS_{1200} (25 g LS = 110.6 g LS solution, 22.6% dry substance), the catalyst $CuSO_4 \cdot 5H_2O$ (0.35 g = 0.09 g Cu), sodium hydroxide (16 g), and water (16 mL). The pressure was then set at $p = 11-12$ atm with a stirrer speed of 850 rpm. The temperature was successively augmented to 180 °C, with a constant and high flow of oxygen throughout the experimental run. Several samplings were performed, typically in the range 30−110 min. The samples were analysed with the standard method on HPLC.

Sample Preparation. The reactor sample is shaken and centrifuged for about 10 min. The centrifuged sample (approximately 0.2 g) exactly weighed on an analytical balance in a measurement flask (50 mL) is diluted to the mark with a solution consisting of methanol (800 mL), water (1200 mL), and glacial acetic acid (12 mL).

Analytical Method on HPLC for Determination of Vanillin. The analysis is performed on a HPLC instrument equipped with a reversed phase column (C-18) and an UV detector ($\lambda = 280$ nm). The flow is 1.5 mL/min with an eluting solution constisting of methanol (420 mL, HPLC analytical grade), glacial acetic acid (6 mL), and water (HPLC analytical grade) until a volume of 1000 mL is reached. The analysis is performed with standards of vanillin, vanillic acid, and acetovanillone.

Determination of Dry Substance in the Reactor Sample. On a filter paper (ϕ 9 cm) is placed a piece of Al folio, and a sample of the centrifuged reaction mixture (exactly measured approximately 1 g) is deposited on the filter when placed on an analytical balance. The Al folio with the filter paper is dried at 135 °C for 1 h.

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