# Practical Process for the Air Oxidation of Cresols: Part B. Evaluation of the Laboratory-Scale Oxidation Process

Benita Barton,\* Catherine G. Logie, Barbara M. Schoonees, and Bernard Zeelie

Catalysis Research Unit, Faculty of Applied Science, Port Elizabeth Technikon, Private Bag X6011, Port Elizabeth, South Africa, 6000

## Abstract:

Mechanistic proposals and predictions made in a preceding paper (Part A) were evaluated by carrying out the catalytic air oxidation of *p*-cresol in an alternative solvent system, comprising either a mixture of ethylene glycol and acetic acid (for oxidations under acidic conditions) or ethylene glycol and water (for oxidations under basic conditions). The results obtained in these experiments confirmed that ethylene glycol acts as a nucleophile in these solvent systems, thereby stabilizing the quinomethide intermediate and resulting in highly efficient oxidations in both alkaline and acidic media. 4-Hydroxybenzaldehyde, the desired product, was thus obtained in isolated yields of up to 98% and purities >99%. The inherent drawbacks associated with alkaline methanol and aqueous acetic acid solutions were thus circumvented, and the result is a highly efficient process for the production of 4-hydroxybenzaldehyde.

## Introduction

On the basis of results described in the preceding paper (Part A), it was proposed that the oxidation of *p*-cresol in both aqueous acetic acid and alkaline methanolic media proceeded through the formation of the quinomethide intermediate (see Scheme 4 of Part A). It was thus predicted that the successful oxidation of the cresol to 4-hydroxybenzaldehyde (4-HBA) would depend on the stabilization of the proposed quinomethide intermediate in a form that does not interfere with the oxidation pathway itself. It was discussed that the use of aqueous acetic acid as solvent results in the methide being stabilized as 4-hydroxylbenzyl acetate (4-HBOAc), an intermediate that is not readily oxidized to the desired aldehyde. This acetate requires first hydrolysis to 4-hydroxybenzyl alcohol (4-HB alcohol) thus necessitating the addition of water to the reaction medium) before any significant oxidation can take place. Furthermore, 4-HBOAc was inclined to undergo side reactions, therefore forming unwanted dimers and having a direct influence on the selectivity of the reaction. It has been reported that dimer formation in such solutions may be suppressed by ensuring that the substrate loading is kept below 5% (mass/vol),<sup>1</sup> and this was confirmed by the current authors.

In methanol, on the other hand, the methide is stabilized as 4-hydroxybenzyl methyl ether (4-HB methyl ether), and this is readily oxidized to the required 4-HBA. Methanol was found to effectively compete with other nucleophiles for the quinomethide and so formed the ether derivative readily and in high yield. Furthermore, the reluctance of the ether to undergo addition/ $S_N$  reactions with other intermediate/substrate molecules resulted in the absence of any undesired dimeric byproducts and so allowed for high selectivity to the aldehyde.

While still attempting to maintain the advantages gained by using methanolic solutions in this oxidation process, an alternative solvent system was sought, since the use of alkaline methanol has major drawbacks. First, difficulty is experienced in these reactions in terms of recycling the substrate, intermediates, and products, and, in addition, the alkalinity of the solution presupposes the formation of large quantities of inorganic salts. It has been reported that salt formation may be minimized by isolating the aldehyde product as the salt of the base used because, in certain cases, it is the phenolate salt that is required in further reactions.<sup>2</sup> However, because methanol is a toxic, flammable liquid and has a low flashpoint (11 °C) and a wide flammability limit range (6 to 35% per volume), it remains inherently unsafe to use. It is thus virtually impossible to operate this oxidation on a large scale, unless specialized equipment, designed to overcome such safety issues, are used.

One group of solvents that was thus considered as an alternative that would react via the same mechanism as the alkaline methanolic media (and so ensure high substrate conversions and high selectivities to the desired aldehyde) was the dihydric alcohols such as ethylene glycol (EG), propylene glycol, and the butanediols. Of these, EG has been used in typical examples in at least one patent for the oxidation of cresol in neutral media.<sup>3</sup> Results obtained for the oxidation of 2,4,6-trimethylphenol under pressure and in the presence of PMG catalysts were comparable to the corresponding oxidations in both neutral methanolic and acetic acid solutions. For basic media, EG has been included as a prototypical solvent in a number of patent specifications for the oxidation of p-cresol but was never investigated as a potential solvent in any detail, and never as a cosolvent.<sup>4–7</sup>

Since EG is a much safer solvent to use than methanol, being described as merely harmful (as opposed to toxic),

<sup>\*</sup> To whom correspondence should be addressed. E-mail: barton@yebo.co.za or benita@botsnet.bw.

Fache, E.; Laucher, D.; Constantini, M.; Beclere, M.; Perrin-Janet, F. The Roots of Organic Development. In *Industrial Chemistry Library*; Desmurs, J., Ratton, S., Eds.; Elsevier: Amsterdam, 1996; Vol. 8, pp 380–390.

<sup>(2)</sup> Röhrscheld, F. U.S. Patent 4,748,278, 1988.

<sup>(3)</sup> Diephouse, T. R.; Strom, R. M. U.S. Patent 4,915,875, 1990.

<sup>(4)</sup> Nishizawa, K.; Hamada, K.; Aratani, T. European Patent 0,012,939, 1979.

<sup>(5)</sup> Au, A. T.; Jung, C. W. U.S. Patent 4,453,016, 1984.

<sup>(6)</sup> Schnatterer, A.; Fiege, H. U.S. Patent 4,929,766, 1990 and European Patent 0,330,036, 1989.

<sup>(7)</sup> Constantini, M.; Laucher, D.; Fache, E. U.S. Patent 5,354,919c, 1994.

Table 1. Oxidation of	f p-cresol in	1 EG, EG/AcOH,	and AcOH/H <sub>2</sub> O
-----------------------	---------------	----------------	---------------------------

[AcOH]/[EG]/[H <sub>2</sub> O]	conversion	4-HBA	4-HBEG	4-HB acid	4-HBOAc	total
(vol %)	(%)	(%)	(%)	(%)	(%)	(%)
50:0:50 0:100:0 10:90:0 30:70:0	12.33 0.00 89.19 73.94	27.27 0.00 42.77 71.21	0.00 50.33 17.98	4.77 0.00 6.44 3.86	2.26 0.00 0.00 1.02	38.47 <sup><i>a,b</i></sup> 100.00 99.74 94.08 <sup><i>a</i></sup>

<sup>*a*</sup> Low accountability due to the formation of various dimers/oligomers. <sup>*b*</sup> Reaction was continued for 24 h; 4-HBA = selectivity to 4-hydroxybenzaldehyde; 4-HBEG = selectivity to 1; 4-HB acid = selectivity to 4-hydroxybenzoic acid; 4-HBOAc = selectivity to 4-hydroxybenzyl acetate; total = sum of cresol, benzyl acetate, benzyl alcohol, benzaldehyde, benzoic acid and benzyl glycol ether derivatives. <sup>*c*</sup> Note that 4-hydroxybenzyl alcohol is not shown in this table.

having a much increased flashpoint (110 °C) and a smaller flammability limit range (3 to 15% per volume) relative to methanol, a detailed study was conducted with this as the solvent in these oxidations. The oxidation in EG was investigated preliminarily under acidic conditions and extensively under basic conditions by the addition of, for example, acetic acid or aqueous hydroxide, respectively, to the solvent. In these reactions, it is expected (from predictions made in the preceding paper) that the quinomethide intermediate will be stabilized as the corresponding 4-hydroxybenzyl glycol ether 1 (4-HBEG) derivative and that this ether should be readily oxidized to the aldehyde with no dimer formation.



Variables such as water loading, nature of the catalyst, temperature, and others were also investigated in basic EG medium, in much detail. Finally, a formal statistical evaluation and optimization were carried out on the alkaline reaction to obtain an optimal laboratory process. The results of these experiments are disclosed here.

#### **Results and Discussion**

Preliminary Oxidation of *p*-Cresol in Acidic EG Medium. To explore the use of acidic reaction conditions, acetic acid was used as a cosolvent in 10% and 30% concentrations in the EG medium, whilst maintaining a total solvent volume of 100 cm<sup>3</sup>. Thus *p*-cresol (200 mmol) was oxidized with molecular oxygen (40 cm<sup>3</sup> min<sup>-1</sup>) at 100 °C for 18 h, using 5% Pd/C (0.25 g) as the catalyst in these solvent mixtures. The same reaction was also carried out in pure EG and in an aqueous acetic acid alone for comparative purposes. Table 1 is a summary of our findings:

In pure EG, *p*-cresol was not oxidized at all, and 100% of the substrate was recovered after 18 h. However, when acetic acid (10%) was added to the EG, the cresol was oxidized to 4-HB alcohol (not shown in Table 1), 4-HBOAc, 4-HBA, the overoxidized benzoic acid, and, most interestingly (though not unsurprisingly), the ether **1**. At higher acetic acid loadings (30%), small amounts of dimeric materials were also detected. In the absence of EG, the

accountability of the reaction dropped significantly, also due to the formation of dimers (as was reported in the preceding paper).

Some points of interest need to be highlighted here:

(1) In a 50:50 H<sub>2</sub>O/AcOH mixture alone, the conversion of *p*-cresol was 12.33% after 24 h. A sample of this reaction mixture taken at 6 h showed a conversion of 9.43%. In other words, in the additional 18 h, only a further 2.9% of the substrate was converted, indicating that the catalyst experienced significant deactivation in this medium at high (200 mmol) substrate loadings. However, in a mixture of EG and acetic acid, conversions of >70% were obtained in 18 h.

(2) Despite the high substrate conversion in EG/AcOH mixtures, the accountability in terms of the original *p*-cresol charged is high (>94%), implying a lower tendency for the formation of dimers in such media as opposed to aqueous acetic acid media.

(3) A significant amount of the glycol ether **1** is formed in EG/AcOH mixtures. This indicates that EG competes effectively with AcOH for the quinomethide intermediate (as predicted), since, at low acetic acid loadings (10%), none of the benzyl acetate was detected at all, and even at higher loadings (30%), only 1.02% of the acetate was formed. The ability of EG to react with the quinomethide is most likely the reason for the much improved oxidation efficiency as well as the increased selectivity to 4-HBA.

These results suggested that acetic acid may be used as a cosolvent in EG when performing these oxidations, though the loading of this acid should not be too high.

**CAUTION:** Whilst carrying out this investigation, it was brought to our attention by Dow AgroSciences<sup>8</sup> that the acetic acid/EG/Pd/C system may lead to an explosion. It was suggested that interaction between gaseous EG with the dry Pd/C catalyst was responsible for an explosion at a Dow AgroSciences facility, though no concrete evidence was ever obtained. As a result, this work was discontinued immediately. Preliminary reactive chemicals testing by differential scanning calorimetry (DSC) of these reaction mixtures showed no exothermic events at atmospheric pressure, but further investigations would need to be carried out to determine the existence, or otherwise, of any hazards.

**Oxidation of** *p***-Cresol in Alkaline EG Medium.** In an initial reaction, *p*-cresol (200 mmol) was oxidized, with molecular oxygen (40 cm<sup>3</sup> min<sup>-1</sup>), in alkaline (NaOH, 600 mmol) EG (100 cm<sup>3</sup>) at 100 °C for 18 h in the presence of a CoCl<sub>2</sub>•6H<sub>2</sub>O (0.42 g) catalyst. In the reaction mixture was

<sup>(8)</sup> Personal communication, Dow AgroSciences.

**Scheme 1.** Proposed reaction sequence for the oxidation of p-cresol in alkaline EG<sup>*a*</sup>



<sup>*a*</sup> Products/intermediates shown are obviously in their phenolate salt forms in alkaline medium, prior to workup. These salt forms are not shown here for the sake of simplicity.



*Figure 1.* Product distribution diagram for the initial oxidation of *p*-cresol in alkaline EG medium.

detected 4-HB alcohol, the glycol ether **1**, and the desired product, 4-HBA, and the a reaction sequence was thus proposed (Scheme 1). The product distribution diagram obtained in this initial reaction is shown in Figure 1.

From these preliminary results, it was obvious that the main oxidation intermediates were 4-HB alcohol and 1. Furthermore, no dimeric products were formed at all. The ratio of the benzyl alcohol to the ether 1 during the oxidation process suggests that EG is a stronger nucleophile than water and is thus capable of stabilizing the proposed quinomethide intermediate, preventing dimer formation. Though the conversion of the substrate after 18 h was reasonably high, the yield of 4-HBA was not (<40%), implying that the oxidation of the intermediate ether 1, to afford 4-HBA, was a slow process. A possible reason for this observation is that the high viscosity of the solvent medium prevents the rapid dispersion of molecular O<sub>2</sub>, thus retarding the oxidation rate. It should also be noted that 4-hydroxybenzoic acid, the product that would result upon further oxidation of the aldehyde, was not detected at all during the reaction.

Table 2. Effect of changes in various reaction conditions<sup>a</sup>

	8			
water content (vol %)	conversion (%)	4-HBA (%)	4-HBEG (%)	total (%)
0	95.42	42.11	54.26	99.20
10	97.54	39.92	54.24	99.68
30	80.66	48.84	43.17	98.67
temperature	conversion	4-HBA	4-HBEG	total
(°C)	(%)	(%)	(%)	(%)
80	73.9	44.10	39.78	99.28
100	99.35	74.82	23.47	99.20
120	45.66	89.78	2.17	93.62
base/substrate	conversion	4-HBA	4-HBEG	total
(molar ratio)	(%)	(%)	(%)	(%)
0:1	0.00	0.00	0.00	100.00
0.5:1	94.00	6.77	2.20	13.77
1:1	100.00	25.91	2.19	33.00
2:1	100.00	80.64	3.58	84.49
3:1	97.54	39.92	54.24	96.66
5:1	51.90	9.23	85.13	8.84
	conversion	4-HBA	4-HBEG	total
catalyst	(%)	(%)	(%)	(%)
CoCl <sub>2</sub> •6H <sub>2</sub> O CuCl <sub>2</sub> •2H <sub>2</sub> O	97.54	39.92	54.24	95.68
CLAYCOCU <sup>b</sup>	99.35	74.82	23.47	99.20
$Co_2CuO_4$	98.66	46.94	45.97	94.10
5% Pd/C	55.27	70.42	28.16	100.15
Pb 5% Pd/C	35.82	60.08	36.82	100.42

 $^{a}$  4-HBA = selectivity to 4-hydroxybenzaldehyde; 4-HBEG = selectivity to 1; total = accountability.  $^{b}$  CLAYCOCU = cobalt and copper ion-exchanged montmorillonite K10.

The reaction conditions and effects of changes in these were thus investigated next in an attempt to increase conversions and selectivities to the desired product (Table 2).

Effect of Water: Since the high viscosity of pure EG was deemed to be problematic, water (which is completely miscible with EG) was introduced in quantities of 10% and 30% (v/v), with respect to EG, with the view to reducing the viscosity. (It has been reported that the viscosity of EG drops from 8.7 (when pure) to 2.8 centistokes upon addition of 40% water.<sup>9</sup>) Whilst maintaining the other reaction conditions as in the previous reaction, including using a total solvent volume of 100 cm<sup>3</sup>, the results (Table 2) show that the presence of water had a significant effect on the conversion of the ether **1** to the benzaldehyde and, hence, the selectivity of the reaction. Since at high water concentrations (30%) both the conversion of *p*-cresol and ether **1** were reduced, EG containing 10% (v/v) water was used in further investigations.

Effect of Temperature: Since the boiling point of EG is 197.6 °C, a much wider temperature range is available for oxidations in EG at atmospheric pressures as compared to oxidations in methanol. To determine whether higher reaction temperatures have any significant effect on the rate and extent of oxidation of p-cresol and/or ether 1, oxidations were

<sup>(9)</sup> Sullivan, M. V.; Wolfe, J. K.; Zisman, W. A. Ind. Eng. Chem. 1947, 39 (12), 1607.



Figure 2. Effect of base loading on conversion and selectivity.

performed at three different temperatures, namely 80, 100, and 120 °C, using 10% water/EG media and a cobalt/ copper ion-exchanged Montmorillonite K10 as catalyst (named as CLAYCOCU in this investigation), whilst keeping the other reaction conditions the same as before (Table 2). The results indicate that increasing the reaction temperature results in an increase in substrate conversion up to an apparent maximum, after which the conversion decreases. At the same time, a significant improvement in the conversion of ether 1 and, consequently, the selectivity to 4-HBA, was observed.

Effect of Base Loading: Alkaline alcoholic reaction mixtures for the oxidation of *p*-cresol generally require a base/substrate ratio of at least 2.5:1 for reasonable conversions.<sup>10</sup> The use of excess base, however, implies a large amount of salt waste upon workup. Different base loadings were thus investigated for the oxidation of *p*-cresol in EG containing 10% (v/v) water and using cobalt(II) chloride as catalyst (Table 2). The other reaction conditions were the same as before. Figure 2 is a graphical representation showing the percentage conversion of substrate and selectivity to 4-HBA.

Some aspects regarding the above results deserve further comment.

(1) No reaction occurs in the absence of base.

(2) The conversion of *p*-cresol remains remarkably constant in the region of base/substrate ratios of 0.5:1 to 3:1. The small variations in conversion observed in this region are probably not significant, but the decrease in conversion at a base/substrate ratio of 5:1 is significant and is most likely due to the poor dispersion of oxygen gas in the highly viscous reaction mixture at these high base loadings.

(3) Selectivity to 4-HBA reaches a maximum at a base/ substrate ratio of 2:1. However, at this level, the accountability (Total (%), Table 2) is relatively low (85%). The latter reaches a maximum at a base/substrate loading of 3:1, the increase being mainly the result of the increase in selectivity to ether **1**. (4) The use of a 0.5:1 base/substrate loading resulted in the dimer 4-hydroxybenzyl 4-methylphenyl ether 2 being detected as one of the main products. None of the other



byproducts were characterized, but it is presumed that most of the phenolic material polymerizes in the low base medium. At a 5:1 base/substrate loading, the accountability was even less (approximately 9%). A number of previously undetected byproducts were observed, but again, no attempts were made to characterize these.

Effect of Nature of the Catalyst: The effectivity of several catalysts (Table 2) was evaluated by performing several identical reactions at ambient pressure. NaOH in a base/substrate ratio of 3:1 was used, and 10% H<sub>2</sub>O in EG (total volume of 100 cm<sup>3</sup>) was used as solvent. The other reaction conditions were the same as before. It is clear from these experiments that the palladium-based catalysts did not perform as well as the cobalt-based catalysts in terms of conversion of the substrate, though comparable or better selectivities to 4-HBA were achieved with them. The PGM catalysts did, however, result in excellent accountability and, provided that catalytic activity can be improved, may prove useful in an optimized system. The three cobalt-based catalysts afforded virtually quantitative conversions, but selectivities varied substantially in each case. Here, significant quantities of the ether 1 remained after 18 h, and since 1 is merely an intermediate to 4-HBA, the potential selectivity may be regarded as quite good. Unfortunately, in each of the three copper systems, copper plated out on the stainless steel impeller, indicating that the use of copper as catalyst/ cocatalyst in this oxidation on an industrial scale would not be feasible unless the impeller was enamelled. The origin of the reduction of copper(II) to metallic copper is possibly a result of oxidative dehydrogenation<sup>11</sup> or oxidative cleavage<sup>12</sup> of the ethylene glycol by Cu(II).

Alternative copper-free catalysts were thus sought, and so the solid cobalt-based catalysts cobalt oxide supported on silica, cobalt(II) oxide (CoO), and cobalt(II,III) oxide ( $\sim$ Co<sub>3</sub>O<sub>4</sub>) were used in this investigation. The activities of these catalysts were evaluated by oxidizing *p*-cresol under identical reaction conditions for a period of 6 h while keeping the total metal loading constant throughout. Results obtained are summarized in Table 3.

In comparison with the soluble  $CoCl_2$  as oxidation catalyst (the first entry in Table 3), the solid oxide or supported oxide catalysts gave comparable substrate conversions. However, there may be a significant difference in the ability of the

<sup>(10)</sup> Sharma, S. N.; Chandalia, S. B. J. Chem. Technol. Biotechnol. 1990, 49, 141. Cook, C. D.; Norcross, B. E. J. Am. Chem. Soc. 1956, 78, 3797.

<sup>(11)</sup> Mühler, M. Oxidative Dehydrogenation of Alcohols to Aldehydes, Ketones and Carboxylic Acids. In *Handbook of Heterogeneous Catalysis*; Ertl, G., Knözinger, H., Weitkamp, J., Eds.; VCH Verlagsgesellschaft: Weinheim, 1997; Vol. 5, pp 2274–2284.

 <sup>(12)</sup> Greenspan, F. P.; Woodburn, H. M. J. Am. Chem. Soc. 1954, 76, 6345.
Huyser, E. S.; Rose, L. G. J. Org. Chem. 1972, 37 (6), 851.

Table 3. Use of alternative copper-free catalysts

catalyst	catalyst mass (g)	conversion (%)	4-HBA (%)	4-HBEG (%)	catalyst mass recovered (g)
CoCl <sub>2</sub> •6H <sub>2</sub> O	0.42	60.78	45.82	38.09	
Co oxide/ silica	1.04	49.56	7.53	88.11	0.64
CoO	0.25	66.66	13.97	82.82	0.25
$Co_3O_4$	0.25	47.71	32.47	44.76	0.31

different catalysts to convert the ether **1** to 4-HBA; i.e., both substrate conversion and yield of 4-HBA must be considered when comparing the activity of the different catalysts, not the conversion alone. On this basis, it may be concluded that the soluble CoCl<sub>2</sub> catalyst is more active than any of the solid catalysts. However, since recovery of CoCl<sub>2</sub> is not possible without extensive manipulation of the reaction medium, due to its solubility, it was disregarded as industrially viable. Naturally, the solid catalysts may be recovered by filtration and thus present a better option. However, of the three solid cobaltic catalysts assessed, only the CoO catalyst appeared to be stable as the same mass was recovered from the reaction mixture as that originally charged. The activity of this catalyst was, however, rather poor in comparison.

Further experiments using varying amounts of these solid catalysts showed that the amount of catalyst has only a small effect on substrate conversion and 4-HBA yield. This seems to suggest that factors other than the available catalytic surface area are responsible for oxidation efficiency.

The results described thus far illustrate that EG may possibly be used as solvent for the oxidation of *p*-cresol under alkaline conditions. However, it is also clear that there are a number of reaction variables that appear to have a significant effect upon the outcome of such oxidations. Investigation of the effects of reaction variables may become quite involved and time-consuming when there is more than one variable affecting the outcome of experimental procedures. Various techniques have been developed to assist experimenters when studying the effects of reaction variables. Of these techniques, the best insight into a system is most frequently gained by employing statistical design methods,<sup>13</sup> and these were employed next to optimize the yield of 4-HBA in these reactions, using the CoO or  $\sim$ Co<sub>3</sub>O<sub>4</sub> solid catalysts, since these appeared to be the most viable for a large-scale process.

**Optimization of** *p***-Cresol Oxidation in Alkaline EG.** Four variables were identified that probably affect the yield of 4-HBA in this process, namely temperature, base loading, water loading, and substrate loading. (Preliminary results had shown that an oxygen flow rate kept between 20 and 60 cm<sup>3</sup> min<sup>-1</sup> did not significantly affect the results of the reaction. Thus a rate of 40 cm<sup>3</sup> min<sup>-1</sup> was selected for these experi-

Table 4. Experimental domain

			va	variable level				
code	variable	unit	low (-1)	centre (0)	high (+1)			
T B	temperature base loading	°C ratio to substra	80 2 te	85 3	90 4			
W S	water loading substrate loading	% g	10 15	15 20	20 25			
	Fixed Variables							
	variable		unit	le	evel			
cobalt(II,III) oxide (Fluk total solvent volume oxygen flow rate stirring rate time		ka)	g cm <sup>3</sup> cm <sup>3</sup> min <sup>-1</sup> rpm h	0. 10 40 12	.50 00 0.00 000 2			

ments, and in addition, adequate agitation (1000 rpm) was applied to ensure efficient mass transfer between the solid, liquid, and gas phases. The total solvent volume was kept constant at 100 cm<sup>3</sup>, and 0.5 g of  $Co_3O_4$  solid catalyst was employed in each case.)

Table 4 lists the full experimental domain selected for the response surface experimental design. A reduced central composite design was used for the evaluation of the four experimental variables selected. Although such a design does not necessarily have the same predictive power as a full, rotatable central composite design, its use results in a significant saving in experimental runs.<sup>13</sup> The response variables selected for the optimization procedure were selectivity to the aldehyde (4-HBA (%), Table 5) and the sum of the selectivities to the aldehyde and the ether 1 (Sum, Table 5) after 12 h. From experience gained with this oxidation system, long reaction times appeared to be required for maximum aldehyde selectivity. The selection of a reaction time of 12 h enabled both a reasonable yield of oxidation products and the opportunity to try and reduce reaction times. Table 5 illustrates the experimental design used and lists the experimental responses obtained.

The second-order response surface models derived (using StatEase's Design Expert version 5.0.9) for the selectivity to 4-HBA and the sum of selectivities to 4-HBA and ether 1 are given in eqs 1 and 2, respectively. In these models,  $x_1$  was the coded level for the amount of base,  $x_2$ , the level for temperature,  $x_3$ , the level for amount of water, and  $x_4$ , the level for the amount of substrate charged.

$$4-\text{HBA} = 39.34 + 4.20x_1 + 3.36x_2 + 2.36x_3 - 7.62x_4 - 10.55x_1^2 + 0.81x_2^2 + 0.22x_3^2 + 1.34x_4^2 - 0.02x_1x_2 + 2.98x_1x_3 + 4.04x_1x_4 - 0.76x_2x_3 - 5.17x_2x_4 + 1.46x_3x_4 \quad (1)$$

$$Sum = 73.39 + 10.00x_1 + 3.68x_2 - 0.09x_3 - 5.12x_4 - 17.07x_1^2 + 1.41x_2^2 - 0.34x_3^2 + 0.51x_4^2 + 5.30x_1x_2 + 2.77x_1x_3 + 7.64x_1x_4 + 0.80x_2x_3 - 12.09x_2x_4 - 0.27x_3x_4 (2)$$

An analysis of variance (ANOVA) for the individual response surface models for the selectivity to 4-HBA and

<sup>(13)</sup> Box, G. E. P.; Draper, N. R. Emperical Model-building and Response Surfaces; Wiley: New York, 1987; Chapter 13. Davies, L. Efficiency in Research, Development and Production: The Statistical Design and Analysis of Chemical Experiments; Royal Society of Chemistry: 1993.

Table 5. Experimental	design	and	responses
-----------------------	--------	-----	-----------

run		variable settings <sup>a</sup>				experimental responses	
no.	B (ratio)	<i>T</i> (°C)	W(%)	<i>S</i> (g)	4-HBA (%)	sum (%)	
1	+1 (4.0)	+1 (90.0)	+1(20.0)	-1 (15.0)	49.31	91.39	
2	+1(4.0)	+1(90.0)	-1(10.0)	-1(15.0)	44.99	82.57	
3	+1(4.0)	-1(80.0)	+1(20.0)	+1(25.0)	39.92	76.34	
4	-1(2.0)	+1(90.0)	-1(10.0)	+1(25.0)	14.11	23.70	
5	+1 (4.0)	-1 (80.0)	-1(10.0)	+1(25.0)	26.72	71.88	
6	-1(2.0)	-1 (80.0)	+1(20.0)	-1(15.0)	27.49	48.00	
7	-1(2.0)	+1 (90.0)	+1(20.0)	+1(25.0)	12.32	20.29	
8	-1(2.0)	-1(80.0)	-1(10.0)	-1(15.0)	32.04	53.54	
9	-1.7(1.3)	0 (85.0)	0 (15.0)	0 (20.0)	2.87	7.46	
10	+1.7(4.7)	0 (85.0)	0 (15.0)	0 (20.0)	17.00	41.10	
11	0 (3.0)	-1.7 (76.6)	0 (15.0)	0 (20.0)	36.42	70.38	
12	0 (3.0)	+1.7(93.4)	0 (15.0)	0 (20.0)	47.73	82.75	
13	0 (3.0)	0 (85.0)	-1.7 (6.6)	0 (20.0)	34.12	73.22	
14	0 (3.0)	0 (85.0)	+1.7(23.4)	0 (20.0)	46.65	69.98	
15	0 (3.0)	0 (85.0)	0 (15.0)	-1.7 (11.6)	56.38	82.61	
16	0 (3.0)	0 (85.0)	0 (15.0)	+1.7(28.4)	30.76	65.39	
17	0 (3.0)	0 (85.0)	0 (15.0)	0 (20.0)	42.24	81.76	
18	0 (3.0)	0 (85.0)	0 (15.0)	0 (20.0)	41.70	71.44	
19	0 (3.0)	0 (85.0)	0 (15.0)	0 (20.0)	36.99	67.13	
20	0 (3.0)	0 (85.0)	0 (15.0)	0 (20.0)	36.09	67.65	
21	0 (3.0)	0 (85.0)	0 (15.0)	0 (20.0)	38.68	78.78	

<sup>a</sup> Natural values given in parentheses.

for the sum of the selectivities to 4-HBA and ether 1 was then carried out. From the results obtained for the former, it was clear that substrate loading had the largest effect on the selectivity to 4-HBA: the higher the substrate loading, the lower this selectivity became. The effect of an increase in base loading was to increase the selectivity, while the effects of temperature and water loading were somewhat less significant. There were also two significant twofactor interactions, namely between base loading and substrate loading and between temperature and substrate loading. The origin of the first of these two interactions is possibly due to the formation of the sodium salt of *p*-cresol (which probably becomes more complete with increasing base loading). The interaction between temperature and substrate loading is not clear. Furthermore, the ANOVA for the model for selectivity to 4-HBA showed that there was not a significant lack-of-fit for this model. This was also confirmed by the normal probability plot of the residuals (Figure 3) and the plot of the residuals versus predicted response (Figure 4), both of which showed none of the deviations expected for poor models (normal probability plots should give a straight line in view of the fact that random experimental error is always normally distributed, while a plot of residuals versus predicted response should show a random scatter of points equally distributed about the zero line).<sup>13</sup> It was thus possible to use trends from this model to optimize the reaction in terms of selectivity to 4-HBA.

The same variables identified for the selectivity to 4-HBA were again significant for the sum of the selectivities to 4-HBA and ether 1. In this case, however, base loading had the largest influence and is probably a reflection of the initial oxidation of p-cresol to the ether 1 which now becomes included in the experimental response. The interaction between substrate loading and temperature was also more



Figure 3. Normal probability plot of residuals.

significant than before. As for the model for the selectivity to 4-HBA, the fitted response surface model for the sum of selectivities to 4-HBA and ether **1** did not show any significant lack-of-fit. In fact, the ANOVA showed a particularly good fit. Once again, the normal probability plot of the residuals (Figure 5) and the plot of residuals versus predicted response (Figure 6) showed no abnormalities.

Since both models derived above were shown to be valid within the experimental domain investigated, they were then used to optimize the reaction conditions. We first noted that the stationary points on each of the two experimentally determined response surfaces fell outside the experimental domain investigated. The stationary points were obtained by



Figure 4. Residuals versus predicted response.

finding the partial derivative with respect to each reaction variable for each model and solving for each unknown variable setting at the point where the change in experimental response was zero (i.e.,  $\delta(\text{response})/\delta x_i = 0$ ). The first procedure resulted in two sets of four simultaneous equations (eqs 3a-d and 4a-d for the selectivity to 4-HBA and sum of selectivities to 4-HBA and ether 1, respectively).

$$4.20 - 21.10x_1 - 0.022x_2 + 2.98x_3 + 4.04x_4 = 0 \quad (3a)$$

$$3.36 - 0.022x_1 + 1.62x_2 - 0.77x_3 - 5.17x_4 = 0 \quad (3b)$$

$$2.36 + 2.98x_1 - 0.77x_2 + 0.44x_3 + 1.46x_4 = 0 \qquad (3c)$$

$$-7.62 + 4.04x_1 - 5.17x_2 + 1.46x_3 + 2.68x_4 = 0 \quad (3d)$$

$$10.00 - 34.14x_1 + 5.30x_2 + 2.7/x_3 + 7.46x_4 = 0 \quad (4a)$$

 $(A\mathbf{h})$ 

$$3.68 + 5.30x_1 + 2.82x_2 + 0.80x_3 - 12.09x_4 = 0 \quad (4b)$$

$$-0.089 + 2.77x_1 + 0.08x_2 - 0.08x_3 - 0.27x_4 - 0 \quad (4c)$$

$$-5.12 + 2.64x_1 - 12.09x_2 - 0.27x_3 + 1.02x_4 = 0 \quad (4d)$$

Solving for  $x_1$  to  $x_4$  by matrix algebra and decoding gave the respective stationary points as shown in Table 6:

 $3.68 \pm 5.30r \pm 2.82r$ 

These values clearly fall outside the experimental domain indicating that:

(1) the experimentally determined response surface contains a rising ridge in a direction defined by one or more of the reaction variables; this conclusion is also supported by the observation that the quadratic coefficients in the response surface models determined previously (eqs 1 and 2) have differing signs;

(2) stationary points determined above do not show the position of a maximum response but rather a stationary point with no real chemical meaning; and

(3) the response surface models cannot be used directly for the determination of optimum conditions; however, trends displayed by these models, particularly within the experimental domain investigated, may indicate the direction in which to move to approach optimum conditions.



Figure 5. Normal probability plot of residuals.



Predicted

Figure 6. Residuals versus predicted response.

Table 6. Stationary points for response surface design

	natural value of variable at stationary point				
variable	4-HBA	sum			
temperature base loading water loading substrate loading	63.25 °C 1.08 -28.66% 22.96 g	83.46 °C 2.45 22.20% 22.53 g			

To establish the direction of the experimental optimum, a graphical interpretation of the two response surface models was conducted. Contour and their associated three-dimensional (3D) diagrams for the variation in experimental response as a function of two variables at a time (the other two variables being constant at these respective midpoint values) were plotted. For the sake of brevity, only the



*Figure 7.* 3D Plot showing the effect of a change in base and substrate loading on the selectivity to 4-HBA.

3D representation for the effect of a change in substrate and base loading on the selectivity to 4-HBA is shown here (Figure 7).

The rising ridge referred to previously can clearly be seen in this 3D plot (as well as in all those contour and 3D plots not shown here). These diagrams also hinted that the amount of base required in order to maintain reasonably high experimental responses would vary with the other variable settings. For example, at low substrate loadings (approximately 12.0 g), the base/substrate ratio should be almost equal to the midpoint value of 3:1, while, for higher substrate loadings, the base/substrate ratio should be increased slightly. Similar effects were observed for the base/substrate ratio for increasing water concentrations and increasing temperatures. Interestingly, these effects appeared to be more pronounced for the sum of selectivities to 4-HBA and ether 1 than for the selectivity to 4-HBA alone. This could possibly be a manifestation of the fact that 4-HBA is formed via ether 1, which has already been converted into the sodium salt. Slight variations in base loading with varying settings of the other experimental variables then probably reflect the amount of excess base required to keep the ether 1 and/or the resultant 4-HBA in the phenolate form.

From these optimization strategies, it could be predicted that the working temperature should be set as high as possible (whilst bearing in mind both safety concerns and the possibility of side-product formation at increased temperatures). The optimal base loading was predicted to be approximately 3.3:1 (relative to the substrate), while the water loading did not influence the reaction significantly (though a higher water loading would probably be more desirable due to the associated lower medium viscosities and

Table 7. Conditions for confirmatory experiments<sup>a</sup>

expt no.	base/substrate loading	temp (°C)	H <sub>2</sub> O loading (% v/v)	substrate loading (g)	reaction time (h)
1	3.3	110	15	20	14
2	3.3	110	15	20	16
3	3.3	100	15	20	16
4	3.3	110	30	20	16
5	3.3	110	15	25	16
$6^b$	3.3	110	15	20	16

<sup>a</sup> Catalyst: cobalt(II,III) oxide. <sup>b</sup> Catalyst: cobalt(II) oxide.

Table 8. Results of confirmatory experiments

expt no.	conversion (%)	4-HBA (%)	4-HBEG (%)	total (%)
1 2 3	100.00 100.00	95.56 98.05 74.07	2.02 0.85 20.48	101.19 98.17 05.10
5 4 5	99.57 92.84	96.31 50.22	20.48 2.92 44.30	99.46 97.25
6	99.79	91.63	5.62	97.47

the beneficial impact it would have on the solvent cost). Furthermore, it was predicted that the substrate loading should be as high as possible. However, in this case, cycle times should be borne in mind, since the lower the substrate loading, the shorter would be the cycle time.

Using these predictions, a range of confirmatory experiments was carried out in order to assess their accuracy. The reaction conditions used in these experiments, and their associated results, are summarized in Tables 7 and 8, respectively.

These results (Table 8) confirm most of the predictions made in the optimization strategy. The selectivity to 4-HBA was clearly favoured by the use of higher temperatures. A base/substrate ratio of 3.3:1 also appeared to be the optimum level for lower substrate loadings. It would, however, be of interest to observe the effect of a slightly increased base loading on the outcome of experiment 4, where the substrate loading was increased from 20 to 25 g. The use of a higher substrate loading resulted in a lower conversion and selectivity. This may, however, possibly be countered by the use of longer reaction times and, as mentioned above, a slightly higher base loading. Increasing the water loading from 15% to 30% (v/v) had virtually no effect on the conversion of p-cresol and selectivity to 4-HBA, as predicted. However, as stated previously, the use of higher water loadings is preferable from an economic point of view.

The product distribution diagram for a typical oxidation of p-cresol using the optimized reaction conditions is illustrated in Figure 8.

Isolation of 4-HBA as the Sodium Salt: Isolation of the sodium salt of 4-HBA was investigated by adding varying amounts of water to the filtered reaction mixture (to remove the catalyst) and cooling to -18 °C for 12 h. A small seed crystal was added to each reaction mixture before cooling. The crystallized product was filtered under vacuum and



*Figure 8.* Product distribution diagram for the optimized system.

vacuum-dried for 2 h at room temperature. Isolated yields and purities calculated in each case showed that water should be present in at least a 1:1 ratio with EG for successful isolation of the product. Less water afforded an impure isolated product in lower yields, while higher water loadings also reduced the purity of the isolated product to some extent. The use of the minimum amount of water during isolation is desired, since the excess water will require removal prior to recycling of the solvent, substrate, intermediates, and residual product.

Catalyst Recycling: From an economic and environmental point of view, it is important that the catalyst of choice can be reused. To establish the stability of the Co(II,III) oxide catalyst, it was used and reused in five identical, consecutive reactions. After each reaction, water (70 cm<sup>3</sup>) was added to the reactor, the reaction mixture was cooled, and the catalyst was removed by centrifugation. The centrifuge tube containing the catalyst was rinsed with water (10 cm<sup>3</sup>) to remove excess reaction mixture, and fresh solvent (EG containing 15% (v/v) water, total volume of 100 cm<sup>3</sup>) was used to transfer the catalyst back to the reactor. Results showed that the Co(II,III) oxide catalyst could be recycled successfully for at least five consecutive reactions without a significant change in p-cresol conversion and 4-HBA selectivity. (It should also be noted that no catalyst activation procedure was employed prior to its recycle in each case.) This is an important consideration, since the observed stability of the catalyst may allow for the process to be run on a continuous, or semicontinuous, basis.

**Recycling the Reaction Medium:** After isolation of the sodium salt of 4-HBA, the reaction mixture was heated to 100 °C to remove water. To the residue was added 15% (v/v) water, and the mixture was analyzed and found to contain 4.08% of 4-HBA, 16.35% of 1, 0.59% of the benzyl alcohol, and 4.35% of the substrate. *p*-Cresol (200 mmol), NaOH (155 mmol), and Co(II,III) oxide (1.0 g) were then added to this mixture, and the oxidation procedure was carried out as usual. The reaction was allowed to proceed for 11.5 h, and analyses showed that the reaction mixture has the potential to be successfully reused at least once without significant

change in the outcome of the reaction (conversion 97.34%, selectivity to 4-HBA 85.21%, and selectivity to 1 20.58%, which compares favourably with the original experiment). (The somewhat higher selectivity to 4-HBA is most likely the result of residual 4-HBA recycled back to the reactor.) Byproducts resulting from the possible oxidation of EG were not determined.

## Conclusion

The results described here confirm suggestions made in a previous paper that the outcome of the liquid-phase oxidation of p-cresol will be influenced by the nature of the reaction solvent and particularly the ability of the reaction solvent to stabilize the primary quinomethide oxidation intermediate. In mixtures of EG and acetic acid, O-(4hydroxybenzyl)ethylene glycol 1 was formed in significantly larger amounts than 4-hydroxybenzyl acetate, even in the absence of additional water (which would suppress the formation of the acetate); this observation suggests that ethylene glycol is a better nucleophile for the quinomethide intermediate than acetic acid. In alkaline ethylene glycol solutions, the quantities of observed O-(4-hydroxybenzyl)ethylene glycol are considerably higher than the corresponding 4-hydroxybenzyl methyl ether formed during oxidations of *p*-cresol in alkaline methanolic solutions; this observation is probably a reflection of the fact that ethylene glycol is a slightly better nucleophile than methanol towards the quinomethide intermediate and that the resultant glycol ether is oxidized with somewhat greater difficulty than the corresponding methyl ether; this probably accounts for the longer reaction times required for oxidations in ethylene glycol to reach high levels of 4-hydroxybenzaldehyde formation.

Oxidations of alkylphenols in ethylene glycol media, in the presence of either base or carboxylic acid, may be carried out to high conversions while still maintaining high 4-hydroxybenzaldehyde selectivities. Oxidations in alkaline ethylene glycol solutions may, for example, be carried out virtually to complete conversion without the formation of 4-hydroxybenzoic acid.

One of the most important advantages of this novel oxidation of alkylphenols, particularly p-cresol, is the ease of product isolation and the ability to recycle the catalyst, unreacted substrate, partially oxidized substrate, and incompletely separated reaction product with relative ease and without affecting the efficiency of the oxidation system. Only limited work has been carried out in this regard, but the results obtained show that the product may be removed from oxidation mixtures by crystallization following the addition of water to the reaction mixture. The product so-isolated is the sodium salt of 4-hydroxybenzaldehyde and may be used, as such, for further transformations or may be converted to the free phenolic compound by acid neutralization. Mother liquor from the crystallization process containing unreacted substrate, partially oxidized substrate, and residual 4-hydroxybenzaldehyde may be concentrated by removal of excess water and returned to the oxidation reactor. The ability to recycle substrate, partially oxidized substrate, and product

opens the way for high overall reaction yields which is considerably more difficult to achieve in methanol. In addition, it is conceivable that a continuous or semicontinuous process may be developed as a result of the ease of recycling.

# **Experimental Section**

Please refer to the preceding paper (Part A) for the reaction/reactor setup in these oxidations.

# Acknowledgment

We thank the National Research Foundation, the Port Elizabeth Technikon, and Dow AgroSciences for their continued support, financial and otherwise.

Received for review August 12, 2004. OP049844J