Dhaka Univ. J. Sci. 58(2): 169-174, 2010 (July)

Benzylation of *p*-Chlorophenol: A Statistical Study

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Received on 02. 02. 2009. Accepted for Publication on 27. 01. 2010.

Abstract

A statistical model has been developed for the benzylation of *p*-chlorophenol with benzyl alcohol in the presence of sulphuric acid as catalyst using Yates pattern experimental design. A set of trials was planned according to a 3 factor 2-level Yates pattern experimental design with 2 replicates and the center point trial with 4 replicates. The critical response was the yield of 2-benzyl-4-chlorophenol. Main effects as well as two-factor interaction effect were statistically significant. A polynomial model was developed and the adequacy of the suggested model was checked up.

Keywords*: p*-Chlorophenol, Benzyl Alcohol, Experimental Design.

I. Introduction

Production and uses of synthetic fuels, lubricating oils, and polymers have been increasing day by day. These compounds undergo thermal, photo and other types of physical and chemical degradation in the presence of heat, light, air, and ozone etc. To protect those against such deterioration, use of antioxidants has become increasingly important. Alkylchlorophenols and their derivatives are effective antioxidants and multifunctional stabilizers in such media[1-7]. Moreover, alkylchlorophenols and their derivatives are also strong herbicides, insecticides and bactericides[7-9].

Chlorophenol has been cycloalkylated with cycloalkenes[10-16], cycloalcohols[17-20] and cycloalkylhalides[21]. Statistical studies have been made on the alkylation of cresols with olefins and alcohols by our research group [22-26]. Reports are also available on the benzylation of chlorophenol and 2,4,6-tribromophenol[27,28]. No attempts have ever been made to investigate benzylation of *p*-chlorophenol with benzyl alcohol in the presence of sulphuric acid.

Present work is the continuation of our investigation in the field of alkylation of chlorophenol and deals with benzylation of *p*-chlorophenol with benzyl alcohol in the presence of sulphuric acid by means of statistical experimental design. Experimental design is used for the synthesis of a product in an efficient way. The aim is first to understand the effect of factors and their interactions and then to develop a relation between response and factors with a minimum number of experiments. Response is dependent variable while factor is independent one [29,30].

Aim of the present investigation is to develop a mathematical model by using a 2^3 factorial design [29].

II. Experimental

Reactions were carried out in a three necked round bottom flask fitted with a condenser, a thermometer, a dropping funnel and a magnetic stirrer. *p*-Chlorophenol- sulphuric acid mixture was heated to the desired temperature and benzyl alcohol was added to it gradually over a certain period of time (addition time) with constant stirring. The reaction mixture was continued to stir at that temperature with an extended period of time (stirring time) and then cooled to room temperature. Reaction mass was dissolved in toluene, neutralized and washed with distilled water several times. Unconverted reactants and solvent were distilled off at atmospheric pressure. Purity of the residual product was checked by TLC and the yield was expressed as percentage of theory. The product was finally distilled and analyzed by spectroscopic (UV-, IR-, ^{1}H NMR-, ^{13}C NMR- and mass-) methods.

III. Results and Discussion

All experiments were planned according to experimental design[29]. Only 2-benzyl-4-chlorophenol was obtained in the reaction of *p*-chlorophenol with benzyl alcohol. The critical response of interest was yield of 2-benzyl-4-chlorophenol (BCP).

The experimental ranges of the variables are listed in Table 1. Three parameters viz. temperature, molar ratio of *p*-chlorophenol to benzyl alcohol and amount of sulphuric acid were considered in the development of the mathematical model of the reaction of *p*-chlorophenol with benzyl alcohol in the presence of sulphuric acid using Yates pattern experimental design. Addition time of benzyl alcohol to *p*-chlorophenol - catalyst mixture was 2h and stirring time after the addition of benzyl alcohol was 1h.

The experimental design used was Yates pattern, 3 factor two level factorial; there were 2^3 i.e. eight trials. Since the basic 2^3 factorial design involves eight trials, each was run in duplicate yielding 16 trials. In order to check the lack of fit due to curvature, additional trial was made at the midpoint level of each factor. The difference between the average center point value and the overall average of the design points indicated the severity of curvature.

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Table. 1. Process variables and Response.

Variable	Range		
	Low (–)	Mid (0)	High (+)
X_1 , Temperature (^{0}C)	70	100	130
X_2 , Molar ratio of *p*-chlorophenol to benzyl alcohol	3:1	4:1	5:1
X_3 , Amount of catalyst, % by wt. of *p*-chlorophenol	3	5.5	8
Y, Response: % yield of BCP.			

Table 2 illustrates the two level 3-factor designs with the factors in coded form. The experimental runs for trial 1 through 8 were run in duplicate; trial 9, the center point trial was run four times, interspersed throughout the experimental run.

The results of these experiments are listed in Table 3. The average yield $\overline{Y}$, the range and the variance were calculated for each trial. The variance, which was an estimate of dispersion of data, was calculated by the following formula:

$$\text{Variance} = S^2 = \frac{(Y_1 - \overline{Y})^2 + (Y_2 - \overline{Y})^2 + \ldots\ldots\ldots\ldots\ldots + (Y_n - \overline{Y})^2}{n-1}$$

where, Y = response value, $\overline{Y}$ = average or mean of response values, n = number of observations.

For example, for trial 1,

$$\text{variance} = S_1^2 = \frac{(64.2 - 64.7)^2 + (65.2 - 64.7)^2}{2-1} = 0.25$$

$+ 0.25 = 0.50$

and for trial 9,

$$\text{variance} = S_9^2 = \frac{(80.1-80.8)^2 + (80.6-80.8)^2 + (81.0-80.8)^2 + (81.5-80.8)^2}{4-1}$$

$= 0.35$

The variances calculated for each trial were then used in the calculation of a weighted average of the individual variances for each trial.

$$\text{Pooled variance} = S^2_{\text{pooled}} = \frac{(n_1-1)(S_1^2) + (n_2-1)(S_2^2) + \ldots\ldots\ldots + (n_K-1)(S_K^2)}{(n_1-1) + (n_2-1) + \ldots\ldots\ldots + (n_K-1)}$$

$$= \frac{0.50+0.72+0.50+0.98+0.72+0.98+0.72+1.28+3\times0.35}{1+1+1+1+1+1+1+1+3} = 0.68$$

The pooled standard deviation is the square root of the pooled variance:

$$\text{Standard deviation}_{\text{pooled}} = \sqrt{S^2_{\text{Pooled}}} = \sqrt{0.68} = 0.82$$

Table. 2. Experimental Design.

Trial No.	Replicates	Design		
		Temperature,X_1	Molar ratio, X_2	Amount of catalyst, X_3
1	2	–	–	–
2	2	+	–	–
3	2	–	+	–
4	2	+	+	–
5	2	–	–	+
6	2	+	–	+
7	2	–	+	+
8	2	+	+	+
9	4	0	0	0

Table. 3. Results of three-factor experiment.

Trial No.	Results				
	Yield			Range	Variance
	Y_1	Y_2	$\bar{Y}$		
1	64.2	65.2	64.7	1	0.50
2	75.3	76.5	75.9	1	0.72
3	74.7	75.7	75.2	1	0.50
4	87.4	88.8	88.1	1	0.98
5	76.4	77.6	77.0	1	0.72
6	86.1	87.5	86.8	1	0.98
7	85.6	86.8	86.2	1	0.72
8	97.1	98.7	97.9	2	1.28
9	80.1 81.0	80.6 81.5	80.8	1	0.35

The pooled standard deviation used to calculate the minimum observed effect that was statistically significant.

The computation analysis for this experiment is shown in Table 4. The design matrix was supplemented with a computation matrix, which was used to detect any interaction effects.

This computation matrix was generated by simple algebraic multiplication of the coded factor levels. In trial 1, X_1 was minus, X_2 was minus, therefore, X_1X_2 was plus; in trial 2, X_1 was plus, X_2 was minus, therefore X_1X_2 was minus. The column at the far right of the table was the average yield for each trial. The sum +'s row was generated by totaling the response values on each row with a plus for each column. In the similar manner the sum –'s row was generated. The sum of these two rows should equal the sum of all the average responses and was included as a check on the calculations. The difference row represented the difference between the responses in the four trials when the factor was at a high level and the responses in the four trials when the factor was at a low level. The effect was then calculated by dividing the difference by the number of plus signs in the column.

In the first column, labeled mean, the effect row value was the mean or average of all data points. The average of the center point runs, Trial 9, was then subtracted from the mean effect to give a measure of curvature.

The minimum significant factor effect [MIN] and the minimum significant curvature effect [MINC] were again derived from t-test significance criteria. The relationships are:

$$[\text{MIN}] = \text{t.s}\sqrt{\frac{2}{m.k}}$$

$$[\text{MINC}] = \text{t.s}\sqrt{\frac{1}{m.k}+\frac{1}{c}}$$

where, t = appropriate value from "t- table" , s = pooled standard deviation, m = number of plus signs in column, k = number of replicates in each trial, c = number of center points.

The t value of 2.20 was from the Students' "t" table for the 95% confidence level and 11 degrees of freedom[30]. The degrees of freedom resulted from eight trials with two replicates and one trial with four replicates.

Degrees of freedom = 8(2 – 1) + 1(4 – 1) = 11

The calculations for the minimum significant effects were as follows:

$$[\text{MIN}] = 2.20 \times 0.82 \times \sqrt{\frac{2}{4\times 2}} = 0.90$$

$$[\text{MINC}] = 2.20 \times 0.82 \times \sqrt{\frac{1}{8\times 2}+\frac{1}{4}} = 1.0$$

Applying these criteria to the calculated effects, it was seen that the effects of temperature (X_1), molar ratio of *p*-chlorophenol to benzyl alcohol (X_2), amount of sulphuric acid (X_3) and interaction between temperature and molar ratio of *p*-chlorophenol to benzyl alcohol (X_1X_2) were significant. There was no significant curvature effect. These results were expressed as a mathematical model using a first order polynomial. The values for the c*o*-efficient were one half the factor effects listed in Table 4 since these were based upon coded levels +1 and –1 that differed by two units.

$$Y = 81.48 + 5.7X_1 + 5.38X_2 + 5.5X_3 + 0.45X_1X_2$$

In this equation, the factors were expressed in coded units. These were converted into real units by substituting:

for temperature T (^{0}C), $X_1 = \dfrac{T - \dfrac{130+70}{2}}{\dfrac{130-70}{2}} = \dfrac{T-100}{30}$

for molar ratio (m:1), $X_2 = \dfrac{m - \dfrac{5+3}{2}}{\dfrac{5-3}{2}} = \dfrac{m-4}{1}$

Table. 4. Computation matrix for three factor experiment.

Trial	Mean	Design			Computation				Response
		X_1	X_2	X_3	X_1X_2	X_1X_3	X_2X_3	$X_1X_2X_3$	
1	+	–	–	–	+	+	+	–	64.7
2	+	+	–	–	–	–	+	+	75.9
3	+	–	+	–	–	+	–	+	75.2
4	+	+	+	–	+	–	–	–	88.1
5	+	–	–	+	+	–	–	+	77.0
6	+	+	–	+	–	+	–	–	86.8
7	+	–	+	+	–	–	+	–	86.2
8	+	+	+	+	+	+	+	+	97.9
Sum +'s	651.8	348.7	347.4	347.9	327.7	324.6	324.7	326	
Sum –'s	0.0	303.1	304.4	303.9	324.1	327.2	327.1	325.8	
Sum	651.8	651.8	651.8	651.8	651.8	651.8	651.8	651.8	
Diff.	651.8	+45.6	+43.0	+44.0	+3.6	-2.6	-2.4	+0.2	
Effect	81.48	+11.4*	+10.75 *	+11.0*	+0.9*	-0.65	-0.6	+0.05	
Curvature = 81.48-80.8 = 0.68									

for the amount of catalyst (y), $X_3 = \dfrac{y - \dfrac{8+3}{2}}{\dfrac{8-3}{2}} = \dfrac{y - 5.5}{2.5}$

These substitutions yielded the following final expression:
Y = 34.86 + 0.13T + 3.88m + 2.2y +0.015Tm.

Table 5 gives a comparison of the experimentally determined yield of BCP (each value is the average of two replications) with the predicted yield from the derived equation.

The discrepancies between the experimental and predicted values did not exceed 1.0 %.

Table. 5. Comparison of experimental and predicted yields.

Trial	% yield of BCP		Percentage deviation
	Experimental	Predicted	
1	64.7	65.35	-1.0
2	75.9	75.85	0.07
3	75.2	75.21	-0.01
4	88.1	87.51	0.67
5	77.0	76.35	0.84
6	86.8	86.85	-0.06
7	86.2	86.21	-0.01
8	97.9	98.51	-0.62

The ^{1}H NMR spectrum of the product showed peaks whose chemical shifts of the protons have been recorded in Table 6.

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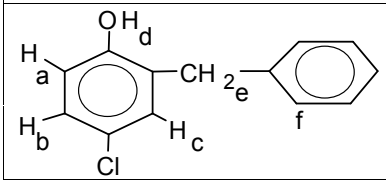
Table. 6. Signals of the protons in the ^{1}H NMR spectrum of BCP.

BCP	Protons	Chemical shift in δ ppm
	a, b, c, f	7.2
	d	4.8
	e	3.9

Positions of the characteristic absorption of the product in the IR-spectrum were as follows:

3540 cm^{-1}	–OH group
3060 cm^{-1}	Saturated C—H stretching
1600 cm^{-1}	Aromatic ring C = C stretching
817 and 878 -890 cm^{-1}	1, 2, 4 – trisubstituted aromatic ring
653 cm^{-1}	Chlorine atom

The product showed strong absorption at λ_{max} = 254.6 nm in 0.01M methanol solution in the UV- spectrum.
^{13}C NMR ($CDCl_3$): δ 130.97- 115.71, 36.33
Mass (m/z): 218.7 (M^+)

IV. Conclusion

A 2^3 Yates pattern factorial design gave a mathematical model for the reaction. The difference between the experimental and predicted yields was negligible. The highest experimentally found yield was 97.9%. The experimental settings were temperature 130^{0}C, molar ratio of benzyl alcohol to *p*-chlorophenol 5:1, conc. of sulphuric acid 94%, amount of the acid 8% by wt. of p-chlorophenol, addition time 2h and stirring time 1 h. The predicted yield was found to be 98.51% which indicated the power of statistical experimental design methodology.

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