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A Statistical Approach to Alkylation of *p*-Cresol with Cyclopentanol

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A statistical analysis for the yield of alkylation of *p*-cresol with cyclopentanol in presence of perchloric acid was performed. Design of experiment technique was employed to study the influence of individual effects of the variables and their interactions on yields of alkylation. The effects of temperature, molar ratio of *p*-cresol to cyclopentanol and amount of perchloric acid were found to be significant. Finally, a mathematical model was developed to predict the theoretical yield of alkylation of *p*-cresol with cyclopentanol in presence of perchloric acid as a catalyst under any reaction conditiopn.

Key Words: Alkylation, *p*-Cresol, Design of experiment.

INTRODUCTION

The concept of design of experiment (DOE) in synthetic chemistry is very much important to develop new methods or to improve existing methods. Design of experiment is an invaluable tool in identifying critical parameters and optimizing chemical processes. Thus, design of experiment is used to synthesize a product in an efficient way. The objectives are to understand first the effect of the factors and their interactions and then to model the relationship between response y and factors (x_1, x_2. . . , x_s) with a minimum number of experiments. Many books and reviews have been published on design of experiment[1-5]. Recently, many research groups also have reported the application of DOE to optimize chemical reactions[6-10].

Alkylation of cresols with olefins and alcohols are industrially important since alkylated cresols may be used as raw materials for the production of resins, durable surface coatings, varnishes, printing inks, surface active agents, antioxidants, fungicides, petroleum additives and multifunctional stabilizers for fuels, lubricating oils and polymeric materials[11-17]. Isomeric cresols have been alkylated with different alcohols, olefins and esters by several research groups[18-26]. This study focuses on alkylation of *p*-cresol with cyclopentanol in presence of perchloric acid and analysis of the results with 3-factor 2-level design of experiment.

EXPERIMENTAL

Alkylation of *p*-cresol with cyclopentanol under different reaction conditions was carried out in presence of perchloric acid. The residual product was finally distilled and characterized by IR and ^{1}H NMR spectroscopy. The yields were analyzed by factorial design method.

RESULTS AND DISCUSSION

Alkylation of *p*-cresol with cyclopentanol in presence of perchloric acid as catalyst yields 2-cyclopentyl-4-methylphenol. It is assumed that effects of the following five variables *e.g.* temperature, molar ratio of *p*-cresol to cyclopentanol, amount of perchloric acid, time of addition of cyclopentanol and time of stirring might be significant. Recently, our group screened out the parameters by Plackett-Burman experimental design and showed that three variables *viz.* temperature, molar ratio of reactants and amount of catalyst are significant for alkylation of *m*-cresol with cyclohexene[27]. Hence these three parameters were also considered in this study.

The experimental variables and their ranges are listed in Table-1. The effects of the factors are examined at two levels; a high level (designated by '+') and a low level (designated by '–'). The critical response of interest was yield of 2-benzyl-4-methylphenol. Time of addition of cyclopentanol to cresol-catalyst mixture and time of stirring after adding cyclopentanol were kept constant at 2 and 1 h, respectively.

TABLE-1
EXPERIMENTAL LEVELS OF INDEPENDENT VARIABLES AND RESPONSE

Variable	Low (-)	Mid (0)	High (+)
Temperature (ºC), X_1	60	80	100
Molar ratio of *p*-cresol to cyclopentanol, X_2	3:1	4:1	5:1
Amount of perchloric acid, % by wt. of *p*-cresol, X_3	1	3	5

Response, Y: Yield of 2-cyclopentyl-4-methylphenol.

The experimental design used was Yates pattern, 3 factor two level factorial; therefore, 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 centre point value and the overall average of the design points indicated the severity of curvature.

Table-2 illustrates two level 3-factor design with the factors in coded form. The experimental runs for trial 1 through 8 were run in duplicate; trial 9, the centre point trial was run four times, interspersed throughout the experimental run. The average yield $\overline{Y}$, the range and the variance were calculated for each trial. The variance, which is an estimate of dispersion of data, was calculated by the following formula:

TABLE-2
FACTORIAL DESIGN: EXPERIMENTAL MATRIX AND RESULTS

Trial	Mean	Design			Computation				Response Y
		X_1	X_2	X_3	X_1X_2	X_1X_3	X_2X_3	$X_1X_2X_3$	
1	+	–	–	–	+	+	+	–	29.8
2	+	+	–	–	–	–	+	+	69.7
3	+	–	+	–	–	+	–	+	40.9
4	+	+	+	–	+	–	–	–	79.8
5	+	–	–	+	+	–	–	+	36.1
6	+	+	–	+	–	+	–	–	74.4
7	+	–	+	+	–	–	+	–	47.3
8	+	+	+	+	+	+	+	+	84.0
Sum +'s	462.0	307.9	252.0	241.8	229.7	229.1	230.8	230.7	
Sum -'s	0	154.1	210.0	220.2	232.3	232.9	231.2	231.3	
Sum	462.0	462.0	462.0	462.0	462.0	462.0	462.0	462.0	
Difference	462.0	153.8	42.0	20.6	-2.6	-3.8	-0.4	-0.6	
Effect	57.75	38.45*	10.5*	5.15*	-0.65	-0.95	0.1	-0.15	

Curvature = 57.75-58.60 = -0.85; where 58.60 is the average yield of center point, trial 9.

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

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

The variance calculated for each trial was then used in the calculation of a weighted average of the individual variances for each trial. Pooled variance was calculated as follows:

Pooled variance = S^2_{pooled}

$$= \frac{(n_1 - 1)(S_1^2) + (n_2 - 1)(S_2^2) + \ldots\ldots\ldots\ldots + (n_K - 1)(S_K^2)}{(n_1 - 1) + (n_2 - 1) + \ldots\ldots\ldots + (n_K - 1)}$$

$$= \frac{0.32 + 0.98 + 0.72 + 2.00 + 0.61 + 1.62 + 0.72 + 2.42 + 3 \times 0.567}{1+1+1+1+1+1+1+1+3}$$

$$= 1.0082$$

According to definition, the pooled standard deviation is the square root of the pooled variance.

Therefore, standard deviation$_{pooled}$ = $\sqrt{S^2_{Pooled}}$

$$= \sqrt{1.0082} = 1.0041$$

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

The computation analysis for this experiment is also shown in Table-2. The design matrix was supplemented with a computation matrix, which was used to

detect any interaction effect. This computation matrix was generated by simple algebric multiplication of the coded factor levels. Colums X_1, X_2 and X_3 represent the factor effect. Columns X_1X_2, X_1X_3 and X_2X_3 represent two factor interactions while column $X_1X_2X_3$ depicts three factor interactions. Column Y of Table-2 is the average yield for each trial. The sum +'s and sum –'s row was calculated. The sum of these two rows should be equal to the sum of all the average responses and was used 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 of Table-2, labeled mean, the effect row value was the mean or average of all data points. The average of the centre point runs 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 calculated as follows:

$$[MIN] = t.s\sqrt{\frac{2}{m.k}} = 1.1045$$

$$[MINC] = t.s\sqrt{\frac{1}{m.k}+\frac{1}{c}} = 1.2349$$

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 and c = number of centre points.

The t value of 2.20 is from the student's 't' table for the 95 % confidence level and 11 degrees of freedom[28]. The degrees of freedom result from eight trials with two replicates and one trial with four replicates, *i.e.*

$$\text{Degrees of freedom} = 8(2\text{-}1) + 1(4\text{-}1) = 11$$

Factors and their interactions with 'Effect' (absolute value) exceeding [MIN] have significant effects on alkylation of *p*-cresol with cyclopentanol. Table-2 shows that effects of temperature (X_1), molar ratio of *p*-cresol to cyclopentanol (X_2) and amount of perchloric acid (X_3) were significant and there was no significant interaction. There was also no significant curvature effect.

These results can be expressed as a mathematical model using a first order polynomial. The values for the co-efficient were one half the factor effects listed in Table-2, since these were based upon coded levels +1 and -1 that differed by two units.

$$Y = 57.75 + 19.225X_1 + 5.25X_2 + 2.575X_3$$

The factors in the above equation are expressed in coded units and can be converted into real units by substituting X_1, X_2 and X_3 as follows:

$$X_{1s} = \frac{T - \frac{100+60}{2}}{\frac{100-60}{2}} = \frac{T-80}{20}; X_2 = \frac{m - \frac{5+3}{2}}{\frac{5-3}{2}} = m\text{-}4; X_3 = \frac{y - \frac{5+1}{2}}{\frac{5-1}{2}} = \frac{y-3}{2}$$

The substitutions give the following final expression:

$$Y = 57.75 + 19.225\left(\frac{T-80}{20}\right) + 3.95\left(\frac{m-3.5}{0.5}\right) + 5.25\,(m\text{-}4) + 2.575\left(\frac{y-3}{2}\right)$$

$$= -44.1325 + 0.96275\,T + 5.25m + 1.2875y$$

This equation represents the final mathematical model that can be used to predict the yield of of alkylation of *p*-cresol with cyclopentanol in presence of perchloric acid under certain reaction conditions.

For example, in case of trial 1, temperature (T) = 60 ºC, molar ratio of *p*-cresol to cyclopentanol (m:1) = 3:1 and the amount of catalyst (y) = 1 % by wt. of *p*-cresol. Therefore, predicted yield calculated with derived model is:

$Y_{(cal.)} = - 44.1325 + 0.96275 \times 60 + 5.25 \times 3 + 1.2875 \times 1 = 30.67$

Experimental average yield of trial 1 was, $Y_{(exp.)} = 29.80$

These data reveals a good agreement between the calculated yield and experimental yield. Thus, the developed mathematical model can be used to predict the yield of alkylation of *p*-cresol with cyclopentanol in presence of perchloric acid under certain reaction condition.

Conclusion

By applying the techniques of experimental design, significant factors affecting alkylation of *p*-cresol with cyclopentanol in presence of perchloric acid was identified. The effects of temperature, molar ratio of *p*-cresol to cyclopentanol and amount of perchloric acid on yields of alkylation were significant. Finally, a mathematical model was developed for alkylation of *p*-cresol with cyclopentanol in presence of perchloric acid. The experimental yield showed a good agreement with the calculated yield obtained from the mathematical model developed in this study.

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