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Application of a Mathematical Model by Means of Experimental Design to Alkylation of *o*-Cresol with Cyclohexene

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Abstract

Alkylation of *o*-cresol with cyclohexene in the presence of perchloric acid as catalyst was studied statistically with a three-factored experimental design. Factorial design was employed to study the effects of single factors and the effects of their interactions on the yield of alkylation. Reaction temperature, molar ratio of *o*-cresol to cyclohexene and amount of perchloric acid were considered as the major variables. A mathematical model was derived to calculate the predicted yield of alkylation of *o*-cresol with cyclohexene in the presence of perchloric acid under certain reaction conditions and cyclohexyl *o*-cresol was obtained in high yield. The adequacy of the suggested model was checked up and the discrepancies between the experimental and calculated values did not exceed 1.52%. An optimum yield (89.5%) of the product was obtained under the reaction conditions of a temperature of 140º C; a 6:1 molar ratio of *o*-cresol to cyclohexene and a 5% by weight perchloric acid of *o*-cresol.

Keywords: Alkylation, *o*-Cresol, Factorial design.

I. Introduction

The alkylation of aromatic substrates is important in many sectors of the chemical industry. Alkylation of cresols has earned much interest of the scientists 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[1-6]. Catalytic alkylation of isomeric cresols with different alcohols and esters have been studied by several research groups[7-16]. Reports are also available on the alkylation of isomeric cresols with olefins and styrene in presence of different catalysts[17-22], while alkylation of *o*-cresol with alkenes especially cyclohexene was not studied so much. With the best of our knowledge only alkylation of *o*-, *m*-, and *p*- cresols with cyclohexene in the presence of aluminum cresolates have been studied[23]. We envisioned to studying this classical reaction statistically with the help of experimental design.

The concept of experimental design in synthetic chemistry is very much important to develop a new method, to improve an existing method or to avoid highly expensive experiments. Many books and reviews have been published on experimental design in chemometrics[24-28]. Experimental design is used to synthesize a product in an efficient way. The objectives are first to understand the effect of factors and their interactions and then to form a relationship between response and factors with a minimum number of experiments. Responses are dependent variables while factors are independent ones. In most cases, responses and factors are denoted by y and x ($x_1, x_2, \ldots x_s$), respectively, and $y = f(x_1, x_2, \ldots x_s)$ where, s is the number of factors.

Choosing suitable quantitative factors such as temperature, time, and pH is very important in synthetic chemistry. There are several profile analysis procedures available for estimating main effects of factors and their interaction effects, and so on[29, 30].

In this study, the three-factor two-level Yates Pattern experimental design is used for the analysis of alkylation of *o*-cresol with cyclohexene in presence of perchloric acid[31].

II. Experimental

Chemicals used in this work were purchased from Merck Chemicals Co. and were used without further purification unless stated. Perchloric acid was used as catalyst.

The reactions were carried out in a three necked round bottomed flask fitted with a condenser, a thermometer, a dropping funnel and a stirrer. *o*-Cresol-catalyst mixture was charged into the flask, heated to the temperature of the experiment, the cyclohexene was introduced into the mixture gradually over a certain period of time (time of addition) with constant stirring. The reaction mixture was stirred for another period of time (time of stirring) at the same temperature after the addition of the total amount of cyclohexene. The reaction mass was then cooled to room temperature and neutralized with an equivalent amount of 10% KOH solution. The neutralized reaction mass was then dissolved in benzene or diethyl ether, washed with distilled water several times and dried with anhydrous magnesium sulfate. Unreacted reactants and solvent were distilled off at atmospheric pressure. The product thus obtained was subjected to fractionation by distillation and characterized by physico-chemical and spectral means. A statistical analysis of yields of the experiments was performed to develop a mathematical model.

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III. Results and Discussion

o-Cresol with cyclohexene in the presence of perchloric acid as catalyst gave cyclohexyl *o*-cresol (cyclohexyl group substituted the aromatic ring to the *ortho*- or *para*- positions with respect to the –OH group).

A series of experiments were designed for alkylation of *o*-cresol with cyclohexene in presence of perchloric acid. The design table helped in setting the factors in the experimental runs and calculation of the effects (Yates). In the alkylation of *o*-cresol with cyclohexene temperature, molar ratio of *o*-cresol to cyclohexene and amount of catalyst were considered as the three variables, which were supposed to influence the yield significantly. Obviously, there are some other variables in this experiment such as time of addition, time of stirring, stirring speed, etc. These variables were not included as factors, and they are kept constant at a certain value during the experiment. The various values at which a factor is tested are called levels. The experimental ranges of the variables are listed in Table 1. The yield of product was considered as the critical response of the experimental design.

Table 1. Experimental variables and their levels.

Variable	Range		
	Low (-)	Mid (0)	High (+)
x_1; Temperature (^oC)	60	100	140
x_2; Molar ratio of *o*-cresol to cyclohexene	4:1	5:1	6:1
x_3; Amount of catalyst, % by wt. of *o*-cresol	1	3	5
Response: y-yield of cyclohexyl *o*-cresol			

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

Table 2. Experimental design.

Trial	Replicates	Design		
		Temperature, x_1	Molar ratio of *o*-cresol to cyclohexene, x_2	Amount of catalyst, % by wt. of *o*-cresol, x_3
1	2	-	-	-
2	2	+	-	-
3	2	-	+	-
4	2	+	+	-
5	2	-	-	+
6	2	+	-	+
7	2	_	+	+
8	2	+	+	+
9	4	0	0	0

The results of the experiments of alkylation of *o*-cresol with cyclohexene in presence of perchloric acid are listed in Table 3.

Table 3. Results of three-factor experiment

Trial	Yield			Range	Variance
	y_1	y_2	$\bar{y}$		
1	40.6	41.8	41.2	1	0.72
2	60.4	62.0	61.2	2	1.28
3	46.9	48.7	47.8	2	1.62
4	73.3	75.5	74.4	2	2.42
5	44.1	45.5	44.8	1	0.98
6	67.4	69.8	68.6	2	2.88
7	66.3	68.5	67.4	2	2.42
8	88.2	90.8	89.5	3	3.38
	59.8	61.5			
9			60.9	2	1.05
	60.3	62.0			

The average yield, $\bar{y}$ for each trial, 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[32] and summarized in Table 3.

$$Variance = S^2 = \frac{(y_1 - \bar{y})^2 + (y_2 - \bar{y})^2 + ... \\ .....+ (y_n + \bar{y})^2}{n-1} \quad ....(1)$$

where, y = response value, $\bar{y}$ = average or mean response values and n = number of observations.

The variances calculated for each trial with Eq. (1) were then used in the calculation of a weighted average of the individual variances for each trial.

Pooled variance was calculated by the following equation:

$$Pooled\ \text{var}iance = S^2{}_{pooled} = \frac{(n_1-1)(S_1^2) + (n_2-1)(S_2^2) + ... + (n_k-1)(S_k^2)}{(n_1-1) + (n_2-1) + ... + (n_k-1)}$$

$$= \frac{0.72+1.28+1.62+2.42+0.98+2.88+2.42 \\ +3.38+3.15}{1+1+1+1+1+1+1+1+3} = \frac{18.85}{11} = 1.71363 \quad ...(2)$$

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

$$= \overline{Standard\ deviation}_{pooled} = \sqrt{S^2{}_{Pooled}}$$

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

Table 4 illustrates the two-level three-factor designs with the factors in coded form.

Table 4. Computational matrix for three-factor experiments.

Trial	Mean	Design			Computation				Response
		x_1	x_2	x_3	x_{12}	x_{13}	x_{23}	x_{123}	$\bar{y}$
1	+	-	-	-	+	+	+	-	41.2
2	+	+	-	-	-	-	+	+	61.2
3	+	-	+	-	-	+	-	+	47.8
4	+	+	+	-	+	-	-	-	74.4
5	+	-	-	+	+	-	-	+	44.8
6	+	+	-	+	-	+	-	-	68.6
7	+	-	+	+	-	-	+	-	67.4
8	+	+	+	+	+	+	+	+	89.5
Sum +'s	494.9	293.7	279.1	270.3	249.9	247.1	259.3	243.3	
Sum -'s	0	201.2	215.8	224.6	245.0	247.8	235.6	251.6	
Sum	494.9	494.9	494.9	494.9	494.9	494.9	494.9	494.9	
Difference	494.9	92.5	63.3	45.7	4.9	-0.7	23.7	-8.3	
Effect	61.86	23.12*	15.82*	11.42*	1.22	-0.17	5.92*	-2.07*	
Curvature = 61.86 - 60.9 = 0.96									

The experimental design used was Yates pattern, three-factor two-level factorial; therefore, there were 2^3, i.e. eight trials. Since the basic 2^3 factorial design involved 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. The computation analysis for this experiment is also shown in Table 4. According to definition, a main effect is the difference between the average response at the high level and the average response at the low level of a factor. Using the design Table 4, the effects of the factors are calculated as sum of the product between the sign of the corresponding factor in the design matrix and the response, divided by *N*/2. 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. The column at the far right of the table was the average yield for each trial. The sum +'s was calculated by the summation of the response values on each row with a plus sign for each column. In the similar manner the sum −'s was calculated. The sum of +'s and −'s should be equal for all factors and interactions and was used to check the calculations and design. The difference row represented the difference between the responses in the four trials when the factor was at a high level and that at a low level. The effect was then calculated by dividing the difference with the number of plus signs in the column. In the first column of Table 4, labeled mean, the effect was the mean of all data points. The average of the centre point runs, Trial 9, was then subtracted from 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 according to the following equations:

$$[MIN] = t.s\sqrt{\frac{2}{m.k}} \quad \text{... (3)}$$

$$[MINC] = t.s\sqrt{\frac{1}{m.k} + \frac{1}{c}} \quad \text{... (4)}$$

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 center points.

The t value of 2.20 was taken from the students' "t" table for the 95% confidence level and 11 degrees of freedom[32].

The degree 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.

By substituting the values in Eqs. (3) and (4) we have

$$[MIN] = 2.20 \times 1.30905\sqrt{\frac{2}{4\times 2}} = 1.4399$$

$$[MINC] = 2.20\times 1.30905\sqrt{\frac{1}{8\times 2} + \frac{1}{4}} = 1.6099$$

By comparing the [MIN] and [MINC] values and effects calculated by experimental design (Table 4) the significant factors and the interaction effects of the factors that influence the yields were determined. It was revealed that the effects of temperature (x_1), molar ratio of *o*-cresol to cyclohexene (x_2), amount of perchloric acid (x_3), interaction between molar ratio of *o*-cresol to cyclohexene and amount of perchloric acid (x_{23}), and temperature, molar ratio of *o*-cresol to cyclohexene and amount of perchloric acid (x_{123}) were significant. There was no significant curvature effect. These results can be expressed as a mathematical model using a first order polynomial. The values for the coefficients are one half of the factor effects listed in the Table 4, since these are based on coded levels +1 and −1 that differed by two units. Therefore, the following mathematical model in which factors are in the coded form can be developed:

$$y = 61.86 + 11.56x_1 + 7.91x_2 + 5.71x_3 + 2.96x_2x_3 - 1.04x_1x_2x_3 \quad \text{... (5)}$$

The coded units in Eq. (5) can be converted into real units by substituting their values.

For temperature,

$$x_1 = \frac{T(^0C) - \frac{140+60}{2}}{\frac{140-60}{2}} = \frac{T(^0C) - 100}{40}$$

For molar ratio, $x_2 = \dfrac{m - \frac{6+4}{2}}{\frac{6-4}{2}} = \dfrac{m-5}{1}$

For amount of catalyst,

$$x_3 = \frac{w - \frac{5+1}{2}}{\frac{5-1}{2}} = \frac{w-3}{2}$$

where, T = temperature (°C); m = molar ratio of *o*-cresol to cyclohexene and w = amount of perchloric acid, % by wt. of *o*-cresol.

The substitutions of x_1, x_2, x_3, x_{23}, and x_{123} values in Eq. (5) yield the final mathematical model:

$$y = 61.86 + 11.56\left(\frac{T-100}{40}\right) + 7.91\left(\frac{m-5}{1}\right) + 5.71\left(\frac{w-3}{2}\right) + 2.96\left(\frac{m-5}{1}\right)\left(\frac{w-3}{2}\right) - 1.04\left(\frac{T-100}{40}\right)\left(\frac{m-5}{1}\right)\left(\frac{w-3}{2}\right)$$

$$y = 26.54 + 0.094T - 0.43m - 11.04w + 0.039Tm + 2.78mw + 0.065Tw - 0.013Tmw$$

For Trial 1, yield calculated from the derived model

$$\begin{aligned} y_{(calculated)} = {} & 26.54 + 0.094\times 60 - 0.43\times 4 \\ & - 11.04\times 1 + 0.039\times 60\times 4 + 2.78\times 4\times 1 \\ & + 0.065\times 60\times 1 - 0.013\times 60\times 4\times 1. \\ & = 40.68. \end{aligned}$$

Table 5 summarizes the experimental and predicted yields of alkylation of *o*-cresol with cyclohexene in presence of perchloric acid under various experimental conditions.

The experimental yield and calculated yield showed a good agreement. Thus the application of statistical design provided a convenient set of experimental conditions for the synthesis of cyclohexyl *o*-cresol.

The UV spectrum of cyclohexyl *o*-cresol showed strong absorption at $\lambda_{max.}$ = 296.0 nm in 0.01 M petroleum ether solution.

Table 5. Alkylation of o-cresol with cyclohexene in the presence of perchloric acid under various reaction conditions.

Trial	Temp., (^oC)	Molar ratio of *o*-cresol to cyclohexene	Amount of catalyst, % by wt. of *o*-cresol	Experimental yield (%)	Calculated yield (%)	Percent deviation
1	60	4:1	1	41.2	40.68	1.26
2	140	4:1	1	61.2	61.72	0.85
3	60	6:1	1	47.8	48.50	1.46
4	140	6:1	1	74.4	73.70	0.94
5	60	4:1	5	44.8	44.12	1.52
6	140	4:1	5	68.6	69.32	1.05
7	60	6:1	5	67.4	67.94	0.80
8	140	6:1	5	89.5	88.98	0.58
Time of addition: 2 h; time of stirring: 1 h						

In the IR spectrum, absorption band at 775 cm^{-1} accounted for 1,2,3-trisubstituted aromatic ring, while bands near 805 cm^{-1} and 855 cm^{-1} indicated the presence of 1,2,4-trisubstituted benzene ring. Band at 3400 cm^{-1} indicated the presence of –OH group. Aromatic C⋯C stretch and saturated C–H stretch were observed at 1570 cm^{-1} and 2850-2910 cm^{-1} respectively.

The ^1H NMR-spectrum of cyclohexyl *o*-cresol showed signal at δ = 6.26-7.1 ppm for aromatic ring protons. Signals for –OH group proton, methyl group protons, all the protons on the cyclohexyl group except one on the α-position relative to the aromatic ring and one proton on the α-position were observed at δ = 4.84 ppm, δ = 2.03-2.33 ppm, δ = 0.94-2.03 ppm and δ = 2.33-3.23 respectively.

Cyclohexyl *o*-cresol had b.p. = 297° C, d_4^{20} = 1.0418 and n_D^{20} = 1.5459.

IV. Conclusion

The yield of alkylation of *o*-cresol with cyclohexene in the presence of perchloric acid was optimized by means of experimental design. Results of this study indicated that all the three variables, e.g. temperature, molar ratio of *o*-cresol to cyclohexene and amount of perchloric acid, and interactions between molar ratio of *o*-cresol to cyclohexene and amount of perchloric acid (x_{23}), and temperature, molar ratio of *o*-cresol to cyclohexene and amount of perchloric acid (x_{123}) significantly affect the response (yield). The predicted yield calculated with the derived mathematical model showed a good agreement with the experimental yield and the discrepancies between the experimental and calculated values did not exceed 1.52%. Thus the mathematical model obtained provided a convenient set of experimental conditions for the production of cyclohexyl *o*-cresol and open up for efficient strategies for experimental studies.

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