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Development of a mathematical model by means of experimental design for alkylation of *m*-cresol with cyclopentene

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Abstract

Alkylation of *m*-cresol with cyclopentene in presence of benzenesulphonic acid 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 yields of alkylation. Reaction temperature, molar ratio of *m*-cresol to cyclopentene and amount of benzenesulphonic acid were considered as the major variables. A mathematical model was derived to calculate the predicted yield of alkylation of *m*-cresol with cyclopentene in presence of benzenesulphonic acid under certain reaction conditions. The adequacy of the suggested model was checked up. An optimum yield (about 94%) of the product was obtained under the reaction conditions of a temperature of 140 °C; a 5:1 molar ratio of *m*-cresol to cyclopentene and a 8% by weight benzenesulphonic acid of *m*-cresol.

Keywords: Alkylation; *m*-Cresol; Factorial design

1. Introduction

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 [1–7]. *m*-Cresol has been alkylated with different alcohols and esters by several research groups [8–16], while alkylation of *m*-cresol with alkenes especially cycloalkenes was not studied so much.

The concept of experimental design in synthetic chemistry is very much important to develop new methods or to improve existing methods. Many books and reviews have been written about experimental design in chemometrics [17–21]. Experimental design is used to synthesize a product in an efficient way. The objectives are to understand first the effect of factors and their interactions, and then to model the relationship between response y and factors $(x_1, x_2, \ldots, x_s)$ with a minimum number of experiments.

There are two types of variables in chemical experimental design: responses and factors. Responses are dependent variables while the factors are independent ones. In most of the cases responses and factors are denoted by y and x, respectively:

$$y = f(x_1, x_2, \ldots, x_s)$$

where s is the number of factors. Factors in experimental design may be qualitative or quantitative. For example, effects of different catalysts or type of solvents on the yield of a product are qualitative factors while temperature, time and pH are considered as quantitative factors. The quantitative factors can be taken in different levels.

Choosing suitable factors is very important and the number of factors should be minimized. There are several profile analysis procedures available for estimating the main effects of factors and their interaction effects and so on. There are already several excellent books describing the factorial designs in both statistics [22] and chemometrics [23].

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Factorial design generally needs too many runs if the number of levels and/or the number of factors are high. Total number of experiments for the full factorial design increases exponentially with an increase in the number of factors. For example, if there are 10 factors in a given experiment, for a two-level design, one needs $2^{10} = 1024$ experiments, and for three levels, $3^{10} = 59{,}049$ experiments. This is a severe problem in practice. Therefore, in many circumstances certain high order interactions are neglected and fractional factorial design is used to implement. The commonly used fractional factorial designs are in the form of 2^{s-p} and 3^{s-p}, where s denotes the number of factors and p is an integer less than s. Thus, 2^{s-p} and 3^{s-p} are the number of experimental runs.

In this study, three-factor two-level Yates Pattern experimental design is used for the analysis of alkylation of *m*-cresol with cyclopentene in presence of benzenesulphonic acid [24].

2. Experimental

m-Cresol and cyclopentene were purchased from Merck Chemicals Co. and were used without further purification unless stated. Benzenesulphonic acid was used as catalyst. It is milder in its action and causes less undesirable side reactions.

Required amounts of phenol and benzenesulphonic acid were taken in a three necked round bottomed flask fitted with a stirrer, a thermometer, a condenser and a dropping funnel and the mixture was warmed to the desired temperature. Cyclopentene was added dropwise to the stirred mixture during 2 h. The reaction mixture was then stirred for 1 h at the same temperature. 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 ether, washed with water several times and was dried with anhydrous magnesium sulphate. Unreacted reactants and solvent were removed by evaporation. The residual product was finally distilled and analyzed by IR, ^{1}H NMR spectroscopic analysis. A statistical analysis of yields of the experiments was performed to develop a mathematical model.

3. Results and discussions

A series of experiments were designed for alkylation of *m*-cresol with cyclopentene in presence of benzenesulphonic acid. The design table helps in setting the factors in the experimental runs and calculation of the effects (Yates). In the alkylation of *m*-cresol with cyclopentene temperature, molar ratio of *m*-cresol to cyclopentene and amount of catalyst were considered as the three variables which are 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 are 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 cycloalkylation product was considered as the critical response of the experimental design.

Table 1
Experimental variables and their levels

Variables	Levels		
	Low (−)	Mid (0)	High (+)
x_1: temperature (°C)	100	120	140
x_2: molar ratio of *m*-cresol to cyclopentene	3:1	4:1	5:1
x_3: amount of catalyst/wt.% of *m*-cresol	5	6.5	8

Response: yield of cyclopentyl-*m*-cresol.

The results of the experiments of alkylation of *m*-cresol with cyclopentene in presence of benzenesulphonic acid are listed in Table 2. The experimental runs for trials 1–8 were run in duplicate; trial 9, the centre point trial was run four times, interspersed throughout the experimental run. 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 [16] and summarized in Table 2:

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

where y is the response value, $\bar{y}$ the mean response values and n is the 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.

$$\text{pooled variance} = S^2_{\text{pooled}} = \frac{(n_1 - 1)(S_1^2) + (n_2 - 1)(S_2^2) + \cdots + (n_K - 1)(S_K^2)}{(n_1 - 1) + (n_2 - 1) + \cdots + (n_K - 1)}$$
$$= \frac{0.72 + 1.28 + 1.62 + 2.42 + 0.98 + 2.88 + 2.42 + 3.92 + 3 \times 1.05}{1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 3} = 1.76 \quad (2)$$

Table 2
Results of the experiments

Trial	Yield			Variance
	y_1	y_2	$\bar{y}$	
1	32.5	33.7	33.1	0.72
2	49.8	51.4	50.6	1.28
3	44.2	46.0	45.1	1.62
4	55.4	57.6	56.5	2.42
5	41.9	43.3	42.6	0.98
6	67.3	69.7	68.5	2.88
7	57.9	60.1	59.0	2.42
8	93.3	96.1	94.7	3.92
9	54.3	56.0	55.4	1.05
	54.8	56.5		

Table 3
Factorial design: experimental matrix and results

Trial	Design			Computation				Response
	x_1	x_2	x_3	x_{12}	x_{13}	x_{23}	x_{123}	y
1	-	-	-	+	+	+	-	33.1
2	+	-	-	-	-	+	+	50.6
3	-	+	-	-	+	-	+	45.1
4	+	+	-	+	-	-	-	56.5
5	-	-	+	+	-	-	+	42.6
6	+	-	+	-	+	-	-	68.5
7	-	+	+	-	-	+	-	59.0
8	+	+	+	+	+	+	+	94.7
Sum +'s	270.3	255.3	264.8	226.9	241.4	237.4	233.0	
Sum -'s	179.8	194.8	185.3	223.2	208.7	212.7	217.1	
Sum	450.1	450.1	450.1	450.1	450.1	450.1	450.1	
Difference	90.5	60.5	79.5	3.7	32.7	24.7	15.9	
Effect	22.6*	15.1*	19.9*	0.93	8.18*	6.18*	3.98*	

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

$$\text{therefore, standard deviation}_{\text{pooled}} = \sqrt{S^2_{\text{pooled}}} = \sqrt{1.76} = 1.33$$

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

Table 3 illustrates the two-level three-factor designs with the factors in coded form. 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 3. 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 3, 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 algebric 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.

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:

$$[\text{MIN}] = ts\sqrt{\frac{2}{mk}} \tag{3}$$

$$[\text{MINC}] = ts\sqrt{\frac{1}{mk} + \frac{1}{c}} \tag{4}$$

where t is the appropriate value from "t table"; s the pooled standard deviation; m the number of plus signs in column; k the number of replicates in each trial and c is the number of centre points.

Degrees of freedom resulted from eight trials with two replicates and one trial with four replicates.

Therefore, degrees of freedom = $8(2-1)+1(4-1)=11$.

The t value of 2.20 was taken from the students' "t" table for the 95% confidence level and 11 degrees of freedom [16].

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

$$[\text{MIN}] = 2.20 \times 1.32 \times \sqrt{\frac{2}{4\times 2}} = 1.46,$$

$$[\text{MINC}] = 2.20 \times 1.32 \times \sqrt{\frac{1}{8\times 2} + \frac{1}{4}} = 1.63$$

By comparing the [MIN] and [MINC] values and effects calculated by experimental design (Table 3) 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 *m*-cresol to cyclopentene (x_2), amount of benzenesulphonic acid (x_3), interaction between temperature and amount of benzenesulphonic acid (x_{13}), molar ratio of *m*-cresol to cyclopentene and amount of benzenesulphonic acid (x_{23}), and temperature, molar ratio of *m*-cresol to cyclopentene and amount of benzenesulphonic 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 co-efficients are one half of the factor effects listed in the Table 3, 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:

$$y = 56.26 + 11.31x_1 + 7.56x_2 + 9.94x_3 + 4.09x_{13} + 3.09x_{23} + 1.99x_{123} \tag{5}$$

Table 4
Alkylation of *m*-cresol with cyclopentene in presence of benzenesulphonic acid under various reaction conditions

Trial	Temperature (°C)	Molar ratio of *m*-cresol to cyclopentene	Amount of benzene-sulphonic acid (% by wt. of *m*-cresol)	Yield (%)	Predicted yield (%)
1	100	3:1	5	33.1	32.61
2	140	3:1	5	50.6	51.01
3	100	5:1	5	45.1	45.51
4	140	5:1	5	56.5	55.99
5	100	3:1	8	42.6	42.12
6	140	3:1	8	68.5	68.92
7	100	5:1	8	59.0	59.46
8	140	5:1	8	94.7	94.18
9	120	4:1	6.5	56.2	56.23

Time of addition: 2 h; time of stirring: 1 h.

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

$$x_1 = \frac{T - ((100 + 140)/2)}{(140 - 100)/2} = \frac{T - 120}{20},$$

$$x_2 = \frac{m - ((5 + 3)/2)}{(5 - 3)/2} = m - 4,$$

$$x_3 = \frac{w - ((5 + 8)/2)}{(8 - 5)/2} = \frac{w - 6.5}{1.5}$$

The substitutions of x_1, x_2, x_3, x_{13}, x_{23}, and x_{123} values in Eq. (5) yield the final mathematical model:

$$y = 56.26 + 11.31\left(\frac{T - 120}{20}\right) + 7.56(m - 4) + 9.94\left(\frac{w - 6.5}{1.5}\right) + 4.09\left(\frac{T - 120}{20}\right)\left(\frac{w - 6.5}{1.5}\right) + 3.09(m - 4)\left(\frac{w - 6.5}{1.5}\right) + 1.99\left(\frac{T - 120}{20}\right)(m - 4) \times \left(\frac{w - 6.5}{1.5}\right),$$

$$y = -131.19 + 1.397T + 45.65m + 13.75w - 0.429Tm - 5.86mw - 0.128Tw + 0.066Tmw$$

where T is the temperature (°C); m the molar ratio of *m*-cresol to cyclopentene and w is the amount of benzenesulphonic acid (wt.%) of *m*-cresol.

Table 4 summarizes the experimental and predicted yields of alkylation of *m*-cresol with cyclopentene in presence of benzenesulphonic acid under various experimental conditions. The experimental yield and predicted yield showed a good agreement. Thus the application of statistical design provided a convenient set of experimental conditions for the synthesis of alkylated *m*-cresol.

4. Conclusion

The yield of alkylation of *m*-cresol with cyclopentene in presence of benzenesulphonic acid was optimized by means of experimental design. Results of this study indicate that all the three variables, e.g. temperature, molar ratio of *m*-cresol to cyclopentene and amount of benzenesulphonic acid, and interactions between temperature and amount of benzenesulphonic acid (x_{13}), molar ratio of *m*-cresol to cyclopentene and amount of benzenesulphonic acid (x_{23}), and temperature, molar ratio of *m*-cresol to cyclopentene and amount of benzenesulphonic 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. Thus statistically designed experiments are very powerful tools that open up for efficient strategies for experimental studies.

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