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Lecture Transcripts

Canonical Analysis of Response Surfaces: A Valuable Tool for Process Development[1]

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Abstract:

The principles of response surface modelling are briefly described. The computations involved in the canonical analysis of response surface models are given in detail. Three examples of canonical analysis in the context of organic synthesis development are discussed. These examples treat enamine synthesis by a modified titanium tetrachloride procedure, kinetic modelling, and the synthesis of the trimethylsilyl enol ether from methyl vinyl ketone.

Introduction

An important task in synthetic chemistry, both in industrial process research and in academic research, is to establish optimum operation conditions for new methods. In this context, response surface methods are indispensable tools. The underlying principles of response surface modelling are simple, and the method is powerful and highly efficient for the experimental attainment of optimum operation conditions. Thorough accounts of response surface methodology have been presented[2] and in the sections that follow, only a brief introduction is given. Analysis of the eigenstructure of response surfaces is known as the *canonical analysis* of response surface model, and it is a technique that was introduced by George E. P. Box and co-workers in their pioneering works more than 50 years ago.[3] However, scanning the recent literature on process development reveals that this technique is either unknown to the experimenters in the field or overlooked. We think this is unfortunate since we have personally found that canonical analysis is a very useful tool in the development of new synthetic procedures. This presentation is an attempt from the our side to revive the interest of the technique in the community of process developers. In the text that follows, we have tried to present the underlying principles in sufficient detail so that the reader can follow the train of thoughts. In the description of the methodology, nothing new is presented; we owe much of this to George Box. We will use matrix algebra to express the calculations involved in canonical analysis. An excellent introductory text on linear algebra is given in the book by Strang.[4]

The utility of the method is illustrated by three examples. These have been taken from our own research but not as an attempt to frame our own results; there is another reason. In the examples shown, the underlying ideas and considerations are known in detail. In published works, the results are often presented in a very concise way, and certain details remain obscured. In the examples, full experimental data are given, so that the interested reader can check the computations.

Response Surfaces. The outcome, η, of an experiment is observed as an experimental response, y. Due to an omnipresent experimental error, e, the observed response is at best an unbiased estimator of η and

$$y = \eta + e$$

If y is an unbiassed estimator of η, $E(y) = \eta$, the error term is a random noise that can be analysed by simple statistical tools.

It is reasonable to assume that the outcome of an experiment depends on how it has been conducted and that there is some kind of functional dependence between the experimental conditions and the result, i.e.

$$\eta = f(\text{experimental conditions})$$

Let the experimental conditions be defined by the settings,

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(2) (a) Box, G. E. P.; Hunter, J. S.; Hunter, W. G. *Statistics for Experimenters*; Wiley: New York, 1978. (b) Box, G. E. P.; Draper, N. R. *Empirical Model-Building and Response Surfaces*; Wiley: New York, 1987. (c) Myers, R. M. *Response Surface Methodology*; Allyn and Bacon: Boston, 1971. (d) Carlson, R. *Design and Optimization in Organic Synthesis*; Elsevier: Amsterdam, 1992.

(3) (a) Box, G. E. P.; Wilson, K. B. *J. Roy. Statist. Soc.* **1951**, *B 11*, 1. (b) Box, G. E. P.; Youle, P. V. *Biometrics* **1955**, *11*, 287.

(4) Strang, G. *Linear Algebra and its Applications*, 3rd ed.; Harcourt Brace Jovanivich, Inc.: San Diego, 1988.

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x_i, of the experimental variables, $i = 1, 2, ..., k$. Hence, we can assume the following functional dependence between the observed response and the setting of the experimental variables as

$$y = f(x_1, x_2, ..., x_k) + e$$

It is, however, difficult to derive an analytical expression for the function f, except in very simple cases. An approximate description can be obtained by the following reasoning. The outcome of a chemical reaction depends on the energy of the chemical system. The transformation of starting material to reaction products can be described as a movement on a potential energy surface, from one minimum defined by the starting materials to another minimum defined by the products. The energy barrier to surmount is related to the rate of the reaction, and the energy differences between energy minima are related to equilibria. Rates and equilibria determine the results of interest in chemistry. How shallow the minima are and how high the energy barriers are are determined by the detailed experimental conditions. Perturbations of the experimental conditions will change the position of the minima and maxima of the potential energy surface. It is reasonable to assume that a gradual change of the experimental conditions will produce a gradual change of the shape of the potential energy surface. The potential energy surface can safely be assumed to be continuous and several times differentiable. Since the function f is ultimately determined by the potential energy surface, it is reasonable to assume that f is also continuous and several times differentiable. Provided that the experimental domain is not too vast, the general feature of f can be approximated by a truncated *Taylor* expansion.

Let $\boldsymbol{x} = \mathbf{0}$ and $x_1 = x_2 = ... = x_k = 0$ be the centre of the experimental domain spanned by the variations of the scaled and zero mean centered experimental variables. A *Taylor* expansion around $\boldsymbol{x} = \mathbf{0}$ will then be:

$$y = f(\mathbf{0}) + \sum \frac{\partial f(\mathbf{0})}{\partial \mathrm{x}_i} x_i + \frac{1}{2}\sum\sum \frac{\partial^2 f(\mathbf{0})}{\partial x_i \partial x_j x_i} x_j + \text{higher-order terms} + e$$

In most cases, a sufficiently good approximation is obtained if the *Taylor* expansion is truncated after the inclusion of the second degree terms; the contribution from the higher order terms is less than the random error term. The *Taylor* model is more conveniently written:

$$y = \beta_0 + \sum \beta_i x_i + \sum\sum \beta_{ij} x_i x_j + \sum \beta_{ii} x_i^2 + e$$

where the constant, β_0, is the value of the function at the centre point; the coefficients of the first degree terms, β_i, are the first-order partial derivatives; the coefficients of the cross-product terms, $\beta_{ij} = \beta_{ji}$, are the mixed second-order derivatives; the coefficient of the square terms, β_{ii}, are the pure second-order derivatives. Such models describe a surface in the space spanned by $\{y, x_1, x_2, ..., x_k\}$ and are therefore often called response surface models or, simply, response surfaces. The true values of the response surface parameters are not known, but their corresponding least-squares estimates can be obtained by fitting the *Taylor* polynomial using multiple linear regression methods to known experimental results obtained by a proper experimental design, $\boldsymbol{D}$. The row vectors, $\mathbf{x}_{(h)}$, of the design matrix $\boldsymbol{D}$ defines the setting of the experimental variables, $x_1, ..., x_k$ in the hth experiment, $h = 1$ to n. The columns, $\boldsymbol{x}_1, \boldsymbol{x}_2, ... \boldsymbol{x}_k$ of $\boldsymbol{D}$ define the setting of the experimental variables over the n experiments. A model matrix, $\boldsymbol{X}$, is obtained by expanding $\boldsymbol{D}$ with columns corresponding to each term in the model: a column of ones (corresponds to β_0) and columns for the cross-products, $\boldsymbol{x}_i\boldsymbol{x}_j$ and the squared variables, $\boldsymbol{x}_i^2$. Let $\boldsymbol{y} = [y_1\, y_2\, ...\, y_n]^T$ be the vector of observed responses in experiments 1 to n, let $\beta = [\beta_0\beta_1\, ...\, \beta_k\, ...\, \beta_{ij}\, ...\, \beta_{kk}]^T$ be the vector of the model parameters to be estimated, and let $\boldsymbol{e} = [e_1\, e_2\, ...\, e_n]^T$ be the vector of the unknown experimental errors in experiment 1 to n. The results can be summarized as the following matrix relation:

$$\boldsymbol{y} = \boldsymbol{X}\beta + \boldsymbol{e}$$

A least-squares estimate $\boldsymbol{b} = [b_1\, ...\, b_k\, ...\, b_{ij}\, ...\, b_{kk}]^T$ of β is obtained by computing

$$\boldsymbol{b} = (\boldsymbol{X}^T\boldsymbol{X})^{-1}\boldsymbol{X}^T\boldsymbol{y}$$

For examples of response surface designs, see ref 1.

Canonical Analysis. In most cases, it is difficult to understand the shape of a fitted response surface by mere inspection of the algebraic expression of the Taylor polynomial. When there are many independent variables in the model, it is also difficult to evaluate the shape of the surface by looking at isocontour projections of the variables two by two. A canonical analysis facilitates the interpretation. Such an analysis constitutes a mathematical transformation of the original experimental variables, x_i, into new variables, z_i, so that the response surface when expressed in the new variables contains only quadratic terms, i.e.

$$y = y_S + \lambda_1 z_1^2 + \lambda_2 z_2^2 + ... + \lambda_k z_k^2 + e$$

Since z_i^2 cannot be negative, it is seen that the shape of the response surface is determined by the sign and the magnitude of the coefficients λ_i. If all coefficients are negative, the response surface has a maximum, y_S, at $\boldsymbol{z} = \mathbf{0}$; $z_1 = z_2 = ... = z_k = 0$. If all coefficients are positive, the surface has a minimum at $\boldsymbol{z} = \mathbf{0}$. If there are both positive and negative coefficients, the surface passes through a maximum at $\boldsymbol{z} = \mathbf{0}$ in those z_i-directions for which the corresponding coefficients are negative and through a minimum in those directions with positive coefficients. The curvature is feeble in those z directions for which the coefficients are numerically small. This gives information on the peakedness of the response surface, for instance how sensitive the response is to variations of the experimental conditions in the vicinity of the maximum point. If one or more coefficients are zero (or close to zero within the limits of the experimental error) there are directions through the experimental space in which the response is constant. Such situations occur when there is some kind of functional dependence between the experi-

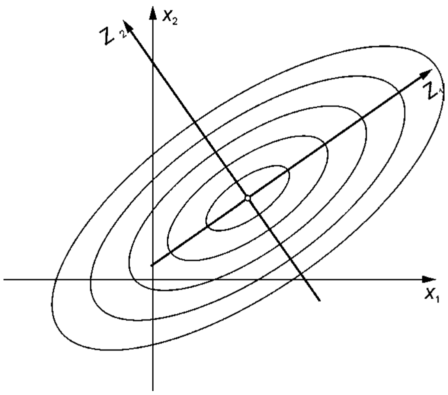

Figure 1. **Transformation of the experimental variables into canonical variables.**

mental variables. Sometimes such dependencies are unknown beforehand, and the observation of a zero coefficient in the canonical model may lead to new discoveries. A quadratic response surface has a stationary point at which the tangential plane has zero slope in all directions. The canonical coordinate system has its origin at the stationary point, and the z_i axes are oriented parallel to the principal axes of the quadratic surface (Figure 1). How to find the stationary point and how to rotate the coordinate system so that it becomes parallel to the principal axes of the surface is described in the next section.

Procedure for Canonical Analysis. (1) Determine the coordinates for the stationary point on the response surface. This is made by solving the equation system obtained by setting all first-order partial derivatives of the response surface model equal to zero, that is

$$\frac{\partial y}{\partial x_i} = 0 \quad \text{for } i = 1 \text{ to } k$$

The solution yields the vector of the coordinates of the stationary point

$$\boldsymbol{x}_S = [x_{1S}\ x_{2S}\ ....\ x_{kS}]^T$$

(2) Define a new coordinate system $\{w_1, w_2, ..., w_k\}$ by

$$\boldsymbol{w} = \boldsymbol{x} - \boldsymbol{x}_S$$

which gives

$$w_1 = x_1 - x_{1S}$$
$$w_2 = x_2 - x_{2S}$$
$$w_k = x_k - x_{kS}$$

This transformation moves the origin of the $\{w_1, w_2, ..., w_k\}$ system to the stationary point, see Figure 2.

When the response surface model is expressed in the transformed variables, $x_i = w_i + x_{iS}$, the linear terms vanish and the model will be

$$y = y_S + \sum\sum b_{ij} w_i w_j + \sum b_{ii} w_i^2 + e$$

In matrix notation this can be written

$$y = y_S + \boldsymbol{w}^T \boldsymbol{B} \boldsymbol{w}$$

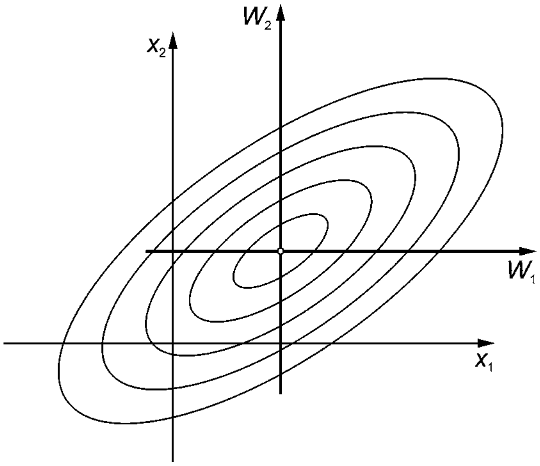

Figure 2. **Translation of the origin to the stationary point.**

where the coefficient matrix $\boldsymbol{B}$ is a symmetric matrix in which the diagonal elements are the quadratic coefficients, b_{ii}, and the off-diagonal elements are the cross product coefficients divided by two, $b_{ij}/2 = b_{ji}/2$. The elements of $\boldsymbol{B}$ are the second-order derivatives of the response function, and such a matrix is often called the Hessian matrix or the Hessian.

(3) Determine the eigenvalues and the corresponding eigenvectors of $\boldsymbol{B}$. The eigenvalues are obtained by solving the equation obtained by setting the secular determinant equal to zero

$$|\boldsymbol{B} - \lambda \boldsymbol{I}| = 0$$

The roots of the secular equation, λ_1, λ_2, ..., λ_k, are the coefficients of the canonical model. Since $\boldsymbol{B}$ is a real and symmetric matrix, all eigenvalues are real.

For each eigenvalue, λ_I, determine the corresponding eigenvector, $\boldsymbol{v}_i$, by solving the equation

$$\boldsymbol{B}\boldsymbol{v}_i = \lambda_I \boldsymbol{v}_i$$

which is equivalent to solving

$$(\boldsymbol{B} - \lambda_i \boldsymbol{I})\boldsymbol{v}_i = \boldsymbol{0}$$

Let $\boldsymbol{m}_i$ be the normalised eigenvector $\boldsymbol{v}_i$.

$$\boldsymbol{m}_i = (1/||\boldsymbol{v}_i||)\boldsymbol{v}_i$$

Let $\boldsymbol{M} = [\boldsymbol{m}_1\ \boldsymbol{m}_2\ ....\ \boldsymbol{m}_k]$ be the matrix in which the columns i are the normalised eigenvectors $\boldsymbol{m}_\mathrm{i}$. The matrix $\boldsymbol{M}$ is an orthonormal matrix which implies that its transpose is equal to its inverse.

$$\boldsymbol{M}^T = \boldsymbol{M}^{-1}$$

$\boldsymbol{M}$ is a matrix of rotation. Make the transformation of $\boldsymbol{w}$ to $\boldsymbol{z}$, where $\boldsymbol{z} = [z_1\ z_2\ ...\ z_k]^T$.

$$\boldsymbol{z} = \boldsymbol{M}^{-1}\boldsymbol{w}$$

which is equal to

$$\boldsymbol{w} = \boldsymbol{M}\boldsymbol{z}$$

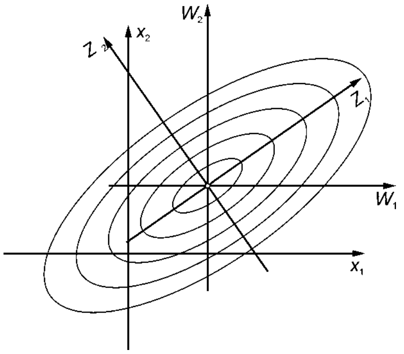

Figure 3. **Rotation of the coordinate system.**

This yields the following model expressed in $\boldsymbol{z}$

$$y = y_S + (\boldsymbol{Mz})^T\boldsymbol{B}(\boldsymbol{Mz})$$

which is equal to

$$y = y_S + \boldsymbol{z}^T\,(\boldsymbol{M}^T\boldsymbol{BM})\boldsymbol{z} + e$$

The matrix $\boldsymbol{M}^T\boldsymbol{BM}$ is a diagonal matrix $\boldsymbol{L}$ in which the diagonal elements are the eigenvalues λ_i. This yields

$$y = y_S + \boldsymbol{z}^T\boldsymbol{Lz} + e$$

which is the matrix notation of the canonical model (Figure 3).

$$y = y_S + \lambda_1 z_1^{\,2} + \lambda_2 z_2^{\,2} + ... + \lambda_k z_k^{\,2} + e$$

Another Form of the Canonical Model. When the stationary point, $\boldsymbol{x}_S$, is within the explored experimental domain, the canonical model described above is appropriate. This is, however, a situation that occurs rather seldom. In most cases, the stationary point outside the explored domain and sometimes it is far away. It may well be that the experimental conditions at the stationary point are totally unrealistic and that the model at the stationary point does not describe any real phenomenon. The situation is depicted in Figure 4.

When the stationary point is remote from the explored domain, the response surface is described by a rising or falling ridge in the experimental domain. The optimum conditions are then likely to be found along these ridges. Also in such cases a canonical analysis is helpful, but the model has to be modified. Instead of moving the origin of the canonical coordinate system to the stationary point, we just rotate the $\{x_1, x_2, ..., x_x\}$ system by the eigenvector matrix $\boldsymbol{M}$. For this, we make the transformation of $\boldsymbol{x} = [x_1\; x_2\; ...\; x_x]^T$ to $\boldsymbol{z}$ by

$$\boldsymbol{z} = \boldsymbol{M}^T\boldsymbol{x}$$

which is equal to

$$\boldsymbol{x} = \boldsymbol{Mz}$$

In matrix form, the original response surface is given by

$$y = b_0 + \boldsymbol{x}^T\boldsymbol{b} + \boldsymbol{x}^T\boldsymbol{Bx} + e$$

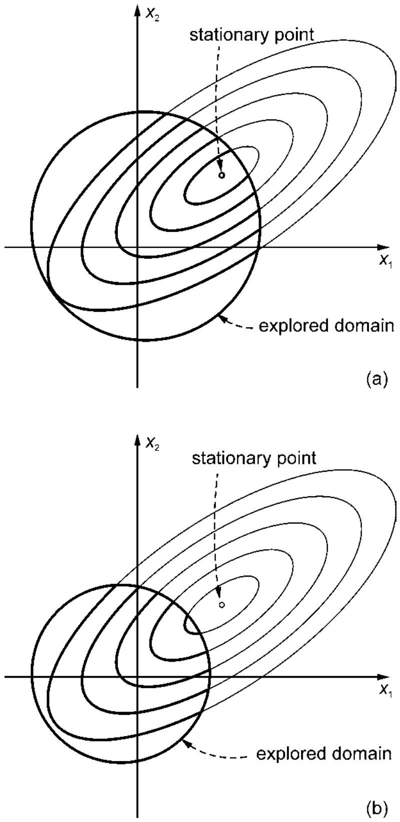

Figure 4. **Stationary point on response surfaces: (a) maximum or minimum within the explored domain; (b) maximum or minimum outside the explored domain.**

where $\boldsymbol{b} = [b_1\; b_2\; ....\; b_k]^T$ is the vector of the linear coefficients. Substituting $\boldsymbol{x}$ with $\boldsymbol{z}$ yields

$$y = b_0 + (\boldsymbol{Mz})^T\boldsymbol{b} + (\boldsymbol{Mz})^T\boldsymbol{B}(\boldsymbol{Mz}) + e$$

which can be simplified to

$$y = b_0 + \boldsymbol{z}^T(\boldsymbol{M}^T\boldsymbol{b}) + \boldsymbol{zLz} + e$$

This yields canonical models which contain linear terms in the canonical variables

$$y = b_0 + \sum \theta_i z_i + \sum \lambda_i z_i^{\,2} + e$$

and in which the vector of the coefficients of the linear terms, $\theta = [\theta_1\; \theta_2\; ....\; \theta_k]^T$ are obtained by

$$\theta = \boldsymbol{M}^T\boldsymbol{b}$$

At first sight, this may not seem to be a simplification of the response surface model. However, such models are very helpful in exploring ridge systems in which the curvatures are feeble along those z_i-axes corresponding to eigenvalues close to zero. In these directions, the variation of the response is largely described by the linear terms of the canonical variables.

Examples. *Synthesis of an Enamine by a Modified $TiCl_4$ Method* (Scheme 1). Enamines are useful intermediates in organic synthesis. They are usually prepared by condensing the corresponding carbonyl compound (aldehyde or ketone) with a secondary amine under elimination of water. The

Scheme 1

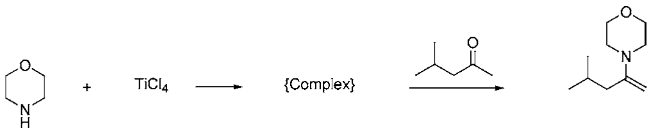

Table 1. **Experimental domain and scaling of variables**

variables	levels −1.414	 −1	 0	 1	 1.414
x_2: amount of TiCl$_4$/ketone (mol/mol)	0.50	0.57	0.75	0.93	1.00
x_2: amount of morpholine/ketone (mol/mol)	3.0	3.7	5.5	7.3	8.0

Table 2. **Experimental design and yields of enamine**

	variables		yield/(%)		variables		yield/(%)
exp. no	x_1	x_2	y	exp. no	x_1	x_2	y
1	−1	−1	73.4	8	0	1.414	81.3
2	1	−1	69.7	9	0	0	96.8
3	−1	1	88.7	10	0	0	96.4
4	1	1	98.7	11	0	0	87.5
5	−1.414	0	76.8	12	0	0	96.1
6	1.414	0	84.9	13	0	0	90.5
7	0	−1.414	56.6				

reaction is an equilibrium. A common method for displacing the equilibrium towards enamine formation is to eliminate the water formed by azeotropic distillation. However, this method fails with methyl ketones which undergo a self-condensation under such conditions.[5] These difficulties could be overcome by using titanium tetrachloride as water scavenger. In the original procedure,[6] titanium tetrachloride is added dropwise to a solution of the ketone, and the amine and the mixture are then stirred for several hours. We found that the reaction time could be considerably shortened by a modified procedure: Titanium tetrachloride is added at 0 °C to a solution of the amine in petroleum ether to form a solid TiCl$_4$−amine complex. The mixture is then heated to reflux with vigorous stirring, and the ketone is rapidly added. For nonhindered ketones, the reaction is completed within minutes.[7] It was, however, found that the amounts of TiCl$_4$/ketone and amine/ketone to be used for a rapid conversion were dependent on the structure of the ketone. For this reason, the amounts of titanium tetrachloride and amine to be used have to be determined for each ketone. For this, response surface methods were used. The example shown here is from the synthesis of the morpholine enamine from methyl isobutyl ketone.

The experimental domain and the scaling of the variables are shown in Table 1 and the experimental design and the yields of enamine obtained after 15 min are shown in Table 2.

The design is a central composite rotatable design augmented with five centre points to afford uniform precision in the predictions by the model.

The following response surface model was obtained

$$y = 93.46 + 2.22x_1 + 9.90x_2 + 3.42x_1x_2 - 4.37x_1^2 - 10.32x_2^2 + e$$

The stationary point

$$x_1 = 0.4721 \approx 0.47$$

$$x_2 = 0.5589 \approx 0.56$$

is located within the explored domain and corresponds to the following stoichiometry of the reagents: TiCl$_4$/ketone ≈ 0.83, and morholine/ketone ≈ 6.51. The calculated yield at the stationary point is $y_S = 96.75$.

The Hessian matrix has the following eigenvalues:

$$\lambda_1 = -3.92$$

$$\lambda_2 = -10.78$$

which clearly shows that the response at the stationary point is a maximum yield. Experiments carried out under the condition of the stationary point afforded 98 ± 2% yield, and this confirmed the conclusions.

By the transformation

$$z_1 = 0.9661x_1 + 0.2582x_2 - 0.6001$$

$$z_2 = -0.2582x_1 + 0.9661x_2 - 0.4171$$

the response surface model is converted into its canonical form

$$y = 96.75 - 3.92z_1^2 - 10.78z_2^2 + e$$

The orientation of the canonical axes is shown in Figure 5.

It is seen that the curvature of the surface is feeble in the z_1-direction and that the yield decreases fairly slowly when the experimental conditions are varied around the stationary point along this direction. Departure from the z_1-axis leads to a rapid decrease in yield.

The experimental conditions along the z_1-axis correspond to the following relations between the amounts of titanium tetrachloride and morpholine:

$$(\text{morpholine/ketone}) = 2.67(\text{TiCl}_4\text{/ketone}) + 4.27$$

It is interesting to note that when the modified titanium tetrachloride method was investigated by response surface modelling or by simplex techniques for a large series of ketones and different amines, the resulting response surfaces were very similar in shape although the positions of the stationary points varied considerably. The optimum settings of titanium tetrachloride and morpholine for the synthesis of enamines from a series of ketones are shown in Figure 6.

The canonical analysis of the response surface models for the ketones shown in Figure 6 shows negative eigenval-

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(5) (a) Hickmott, P. W.; Hopkins, B. J.; Yoxall, C. T. *J. Chem. Soc. B* **1971**, 205. (b) Hickmott, P. W.; Yoxall, C. T. *J. Chem. Soc. Perkin Trans. 2* **1972**, 890. (c) Madsen, P.; Laweson, S. O. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 753.

(6) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213.

(7) Carlson, R.; Nilsson, C.; Strömqvist, M. *Acta Chem. Scand.* **1983**, *B 37*, 7.

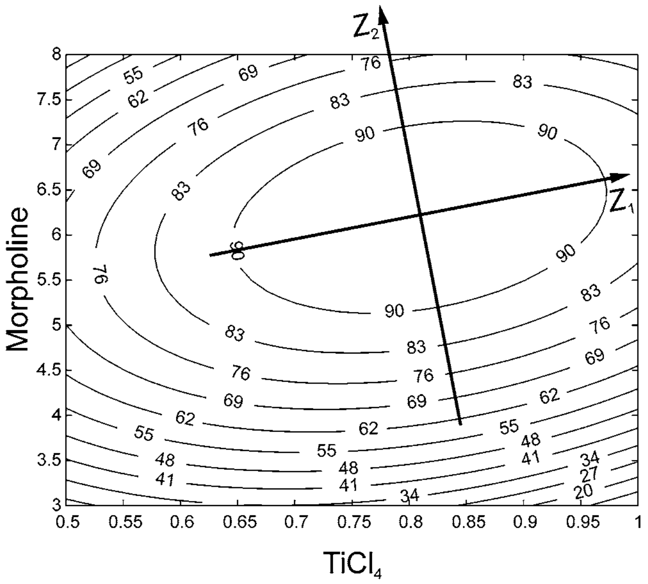

Figure 5. **Response surface for the enamine synthesis. The orientation of the canonical system is shown.**

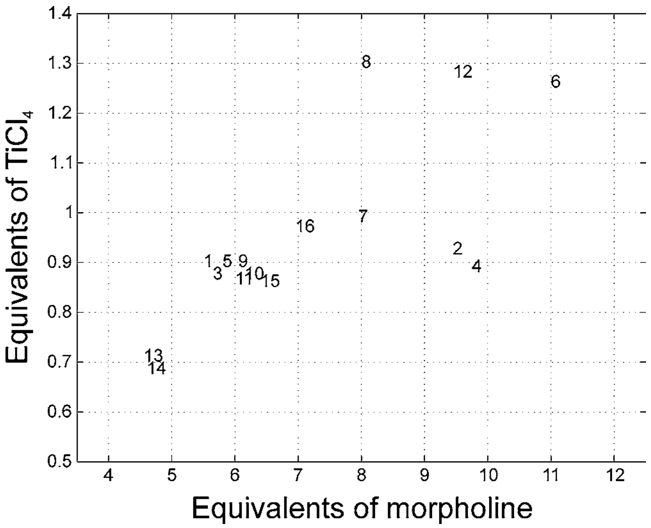

Figure 6. **Optimum settings for the synthesis of morpholine enamines from different carbonyl compounds: (1) methyl isopropyl ketone, (2) pinacolone, (3) methyl isobutyl ketone, (5) diethyl ketone, (6) diisopropyl ketone, (7) ethyl isobutyl ketone, (8) diisobutyl ketone, (9) isobutyraldehyde, (10) isovaleraldehyde, (11) cyclohexanone, (12) camphor, (13) acetophenone, (14) 4-methoxyacetophenone, (15) 4-nitroacetophenone, (16) isobutyrophenone.**

ues, one being numerically smaller than the other, and corresponds to a direction of the canonical axis along which the variation in yield is small. An interesting result is that this direction, with the exception of sterically hindered ketones, corresponds to a stoichiometric relation

$$\text{(morpholine/ketone)} = (3.0 \pm 0.5)(\text{TiCl}_4\text{/ketone}) + (4.0 \pm 0.5)$$

which is in good agreement to what was found in the example with methyl isobutyl ketone shown above.

The overall stoichiometry of the reaction is

$$\text{ketone} + 3\ \text{amine} + 0.5\ \text{TiCl}_4 \rightarrow \text{enamine} + 0.5\ \text{TiO}_2 + 2\ \text{amine-HCl}$$

However, using the stoichiometric amounts of the reagents affords a slow conversion to enamine, and for a rapid conversion an excess of the reagents is necessary. Although a detailed reaction mechanism is not known for this reaction, the results obtained by the response surface modelling suggest the following interpretation. Addition of titanium tetrachloride to an amine yields a series of $TiCl_4$−amine complexes in equilibrium with each other. At least one of these complexes rapidly coordinates to the carbonyl oxygen. A nucleophilic attack of the amine on the carbonyl carbon, followed by a base-induced elimination of the elements of water through a titanium-coordinated oxygen, produces the enamine. The titanium-coordinated oxygen produces solid TiO_2 which precipitates from the reaction mixture. For obtaining a rapid reaction, the concentration of the reactive $TiCl_4$−amine complex must be present in sufficiently high concentration.[5] The canonical analysis of the morpholine enamines suggests that a stoichiometric relation (morpholine/ketone:$TiCl_4$/ketone) ≈ 3:1 holds for this complex.

Reaction Kinetics by Sequential Response Surface Modelling. A method for extracting kinetic information by sequential response surface modelling has previously been described in detail in a paper from our group.[8] Here follows only a short description of the underlying principles.

Assume for convenience that the measured response is the estimated molar concentration of the reaction product:

$$y = [\text{product}]$$

Assume also that a response surface design has been laid out and that samples have been withdrawn from the reaction mixture at regular time intervals and that the yield has been determined at each sampling time. This will give a response matrix in which the column $y(t)$ are the yields determined at time t. For each sampling time, a response surface model can be determined. The estimated coefficients of these models will change over time, and it is reasonable to assume that they can be expressed as functions of time,

$$\mathrm{y}(t) = b_0(t) + \sum b_i(t)x_i + \sum\sum b_{ij}(t)x_i x_j + \sum b_{ii}(t)x_i^2 + e$$

At the outset of the reaction, no yield is obtained, and all coefficients are zero. During the first progressive phase of the reaction, the yield will increase monotonically with time. At later stages, the yield may decrease due to decomposition or parasite reactions. Assume that samples from the reaction mixture have been withdrawn during the progressive initial phase. Plots of the estimated response surface model coefficients versus time will then describe monotonically slightly curved increasing or decreasing functions. We assume that a second-degree polynomial in time will give an adequate description and that for each coefficient an approximation of the form below will apply. At the time $t = 0$, no product is formed, and all response surface parameters are zero. Therefore, the constant term is omitted from the time polynomial

$$b_{(i)}(t) = a_{(i)1}t + a_{(i)2}t^2 + e_i$$

Estimates of the coefficients in these time polynomials are obtained by multiple linear regression.

Scheme 2

$$\mathbf{A} + \mathbf{B} \rightleftharpoons \mathbf{P}$$

The rate of the reaction

$$\frac{\mathrm{d}[\text{product}]}{\mathrm{d}t} = \frac{\mathrm{d}y}{\mathrm{d}t}$$

can then be expressed by the following model

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \frac{\mathrm{d}[b_0(t)]}{\mathrm{d}t} + \sum\sum \frac{\mathrm{d}[b_1(t)]}{\mathrm{d}t} x_i + \sum\sum \frac{\mathrm{d}[b_{ij}(t)]}{\mathrm{d}t} x_i x_j + \sum \frac{\mathrm{d}[b_{ii}(t)]}{\mathrm{d}t} x_i^2 + e$$

The time derivatives of the coefficients are obtained from the time polynomials. A model that describes how the rate of the reaction at the time t depends on the initial experimental conditions, i.e., the settings of the x variables will thus be:

$$\frac{\mathrm{d}y}{\mathrm{d}t} = (a_{(0)1} + 2a_{(0)2}t) + \sum(a_{(i)1} + 2a_{(i)2}t)x_i + \sum\sum(a_{(ij)1} + 2a_{(ij)2}t)x_i x_j + \sum(a_{(ii)1} + 2a_{(ii)2}t)x_i^2 + e$$

The initial rate is obtained by setting $t = 0$, and a response surface that describes how the initial rate is related to the experimental conditions will thus be:

$$\frac{\mathrm{d}y}{\mathrm{d}t} = a_{(0)1} + \sum a_{(i)1}x_i + \sum\sum a_{(ij)1}x_i x_j + \sum a_{(ii)1}x_i^2 + e$$

This rate surface can be used to estimate several important kinetic parameters. Provided that the concentrations of the reactants have been varied in the design, estimates of the reaction order of the reactants can be obtained. Knowledge of the reaction order of the reactants makes it possible to obtain an estimate of the phenomenological rate constant, $k^{\mathrm{Obs.}}$. If the reaction temperature has been varied in the design, an Arrhenius plot of ln k^{Obs} versus $1/T$ yields an estimate of the Arrhenius activation energy, E_a. It is also possible to carry out a canonical analysis of the rate surface. This is shown in the example below.

Example. The example is taken from ref 6 and was obtained by simulation against an integrated rate model for a second-order reaction, first order in each reactant, and in which the forward reaction is, in practise, irreversible (Scheme 2). The "true" rate constants were: $k_1 = 2.768 \times 10^{-4}$ L mol^{-1} s^{-1} and for the backward reaction, $k_{-1} = 1.980 \times 10^{-10}$ L mol^{-1} s^{-1}.

The experimental conditions were varied according to a central composite rotatable design with one experiment at the centre point. The scaling of the variables are shown in Table 3, and the experimental design is given in Table 4.

The responses, $y = [\mathbf{P}]$ in the experiments in Table 4 at different reaction times were estimated from the integrated "theoretical" rate model. These results are summarised in Table 5.

Table 3. **Variables and scaling in the rate example**

	levels				
variablesG	−1.414	−1	0	1	1.414
x_1: [**A**]/M	0.79	1.0	1.5	2.0	2.21
x_2: [**B**]/M	0.79	1.0	1.5	2.0	2.21

Table 4. **Experimental design in the rate example**

exp. no	x_1	x_2	exp. no	x_1	x_2
1	−1	−1	6	1.414	0
2	1	−1	7	0	−1.414
3	−1	1	8	0	1.414
4	1	1	9	0	0
5	−1.414	0			

Table 5. **Yields obtained at different reaction times**

	response: $y \cdot 10^2$				
	t/s				
exp no	120	240	360	480	600
1	3.216	6.084	8.833	11.623	14.246
2	6.330	11.808	16.912	21.945	26.551
3	6.330	11.801	16.912	21.945	26.551
4	12.465	22.948	32.476	41.658	49.886
5	3.807	7.172	10.370	13.484	16.583
6	10.363	19.150	27.193	34.992	42.019
7	3.807	7.172	10.378	13.484	16.583
8	10.363	19.150	17.193	34.992	42.019
9	7.122	13.288	19.039	24.718	29.924

Table 6. **Response surface parameters at different reactions times**

	estimated values of the parameters $b_{(\mathrm{I})}(t) \times 10^3$				
	t (s)				
parameter	120	240	360	480	600
b_0	71.712	132.878	190.178	247.178	299.243
$b_1 = b_2$	23.152	42.254	59.291	75.388	89.518
b_{12}	7.553	13.543	18.717	23.478	27.573
$b_{11} = b_{22}$	−0.183	−0.632	−1.282	−2.136	−3.101

Fitting response surface models to the responses obtained at different reaction times, t, afforded the parameters summarised in Table 6.

The estimates of the coefficients of the time polynomial are shown in Table 7.

The response surface of the initial rate (initial rate surface) will thus be:

$$\left(\frac{\mathrm{d}y}{\mathrm{d}t}\right)_{t=0} = (5.814 \times 10^{-4}) + (1.904 \times 10^{-4})x_1 + (1.904 \times 10^{-4})x_2 + (6.195 \times 10^{-5})x_1x_2 - (1.098 \times 10^{-6})x_1^2 - (1.098 \times 10^{-6})x_2^2$$

The features of the rate surface are shown in Figure 7.

We can use this rate surface to estimate the reaction order of the reactants and the rate constant, k^{Obs}.

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(8) Carlson, R.; Axelsson, A.-K.; Nordahl, C.; Barth, T. *J. Chemometrics* **1993**, *7*, 341.

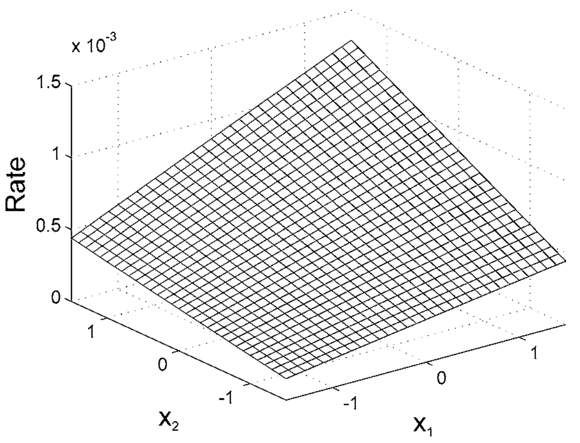

Figure 7. **Rate surface.**

Table 7. **Polynomial coefficient for the time dependence of the response surface parameters**

parameter	estimated value of the coefficient $a_{(i)1}$	estimated value of the coefficient $a_{(i)2}$
b_0	5.814×10^{-4}	-1.429×10^{-7}
$b_1 = b_2$	1.904×10^{-4}	-7.085×10^{-8}
b_{12}	6.195×10^{-5}	-2.752×10^{-8}
$b_{11} = b_{22}$	-1.098×10^{-6}	-6.910×10^{-9}

Reaction Order. Assume that the rate law is

$$\text{rate} = k[\mathbf{A}]^a[\mathbf{B}]^b$$

If the concentration **A** is varied at two levels, $[\mathbf{A}]_1$ and $[\mathbf{A}]_2$, respectively, while maintaining the concentration of **B** at a fixed level, the following expressions are obtained:

$$\text{rate}([\mathbf{A}]_1) = k[\mathbf{A}]_1{}^a[\mathbf{B}]^b$$

and

$$\text{rate}([\mathbf{A}]_2) = k[\mathbf{A}]_2{}^a[\mathbf{B}]^b$$

By taking the ratios of these expression, we obtain

$$\frac{\text{rate}([\mathbf{A}]_1)}{\text{rate}([\mathbf{A}]_2)} = \left\{\frac{[\mathbf{A}]_1}{[\mathbf{A}]_2}\right\}^a$$

and by taking the logarithm of both sides we obtain

$$a = \frac{\log\left\{\dfrac{\text{rate}([\mathbf{A}]_1)}{\text{rate}([\mathbf{A}]_2)}\right\}}{\log\left\{\dfrac{[\mathbf{A}]_1}{[\mathbf{A}]_2}\right\}}$$

The settings of x_1 correspond to the following concentrations of **A**: $x_1 = -1$, $[\mathbf{A}] = 1.00$ M, and $x_1 = 1$, $[\mathbf{A}] = 2.00$ M, and inserting these values into the rate model and setting $x_2 = 0$ (the average concentration of **B**) yields: rate $= 3.899 \times 10^{-4}$ mol L^{-1} s^{-1} for $[\mathbf{A}] = 1.00$ M, and rate $= 7.707 \times 10^{-4}$ mol L^{-1} s^{-1} for $[\mathbf{A}] = 2.00$ M. Hence, the reaction order, *a*, for **A** can be computed as

$$a = \frac{[\log 3.899 \times 10^{-4} - \log 7.707 \times 10^{-4}]}{[\log 1.00 - \log 2.00]} \approx 0.99$$

The reaction order *b* for reactant **B** is computed analogously. From this, the reaction orders of **A** and **B**, respectively were estimated to be 0.99, an obviously reasonable result.

Rate Constant. If we assume that reaction is first order in both reactants, we can use the rate model to determine the reaction rate at varying concentrations of the reactants and from the rate law we can obtain an estimate of the rate constant, k^{Obs}. Setting $x_1 = x_2 = -1$ corresponds to $[\mathbf{A}] = [\mathbf{B}] = 1.00$ M, and the computed rate equals the rate constant. The estimated rate constant is $k^{\text{Obs}} = (2.60 \pm 0.15) \times 10^{-4}$ L mol^{-1} s^{-1} which is fairly close the "true" rate constant, $k_1 = 2.768 \times 10^{-4}$ L mol^{-1} s^{-1}.

Canonical Analysis of the Rate Surface. The stationary point is found for $x_1 = x_2 = -3.19$, which is clearly outside the explored domain. The estimated rate at the stationary point is $-(2.56 \pm 2.15) \times 10^{-5}$ mol L^{-1} s^{-1}, and it is not a reliable value since it is obtained by extrapolation outside the explored domain. The standard error of prediction is very close to the estimated value, and the response at the stationary point in not significantly different from zero. It is interesting to note that the stationary point corresponds to approximate zero concentrations of the reactants **A** and **B**.

The eigenvalues are $\lambda_1 = 3.21 \times 10^{-5}$ and $\lambda_2 = -2.99 \times 10^{-5}$, and by the transformation

$$z_1 = 0.707x_1 + 0.707x_2 + 4.5075$$

$$z_2 = -0.707x_1 + 0.707x_2$$

the initial rate surface is transformed into the canonical model:

$$\left(\frac{\mathrm{d}y}{\mathrm{d}t}\right)_{t=0} = -2.56 \times 10^{-5} + (3.21 \times 10^{-5})z_1{}^2 - (2.99 \times 10^{-5})z_2{}^2$$

The model can be interpreted as follows: For a given total concentration of **A** + **B** (specified by z_1) the maximum rate is obtained when the concentrations of **A** and **B** are equal ($z_2 = 0$).

If we round the eigenvalues to $\lambda_1 = 3 \times 10^{-5}$ and $\lambda_2 = -3 \times 10^{-5}$ and set the constant to zero and do some algebra, the canonical model yields the following expression

$$\left(\frac{\mathrm{d}y}{\mathrm{d}t}\right)_{t=0} = (2.54 \times 10^{-4})[\mathbf{A}][\mathbf{B}]$$

an obviously reasonable result.

Synthesis of 2-(Trimethylsilyloxy)-1,3-butadiene (Scheme 3). This example is taken from ref 2d and is based on the works presented in ref 9. An expedient synthesis of 2-(trimethylsilyloxy)-1,3-butadiene from methyl vinyl ketone (MVK) was desired. The method should be possible to scale-up and not involve expensive reagents. It should also give acceptable yields. A number of methods for the synthesis of silyl enol ethers are described in the literature,[10] but when several of these methods were applied to methyl vinyl ketone,

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(9) (a) Hansson, L.; Carlson, R. *Acta Chem. Scand.* **1989**, *43*, 188. (b) Hansson, L. Ph.D. Dissertation, Umeå University, Umeå, Sweden, 1990.

Scheme 3

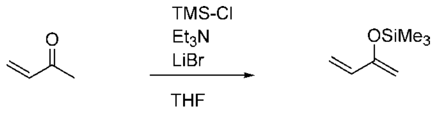

Table 8. **Experimental domain and scaling in the silyloxydiene synthesis**

variables (mol/mol)	levels				
	−1.75	−1	0	1	1.75
x_1: TEA/ketone	1.56	1.75	2.00	2.25	2.44
x_2: TMSCl/ketone	0.97	1.20	1.50	1.80	2.03
x_3: LiBr/ketone	0.70	1.00	1.40	1.80	2.10

they were found to be inefficient in our hands and caused polymerisations. The efficient methods involve expensive reagents and were ruled out for this reason. One method, described by Danishefsky and Kitahara,[11] uses zinc chloride as a Lewis acid catalyst. We therefore thought that other Lewis acids might be useful in our case. However, since hard, strongly oxophilic Lewis acids are known to cleave silyl ethers, the search was limited to soft Lewis acids. We also included the alkali halides, NaI and LiBr, among the possible catalysts. It is generally believed that iodide ions, from potassium iodide, catalyse silylation reactions. We were interested in the roles played by the cation, and for this reason we selected sodium iodide instead. A screening experiment with the Lewis acids in different solvents (a full factorial design) showed that lithium bromide in tetrahydrofuran was a promising combination candidate for future development. It was also found that the order of mixing the reactants was important. The following procedure was adopted.

Dried lithium bromide was dissolved in ice-cooled dry tetrahydrofuran whereafter the solution was warmed to room temperature. Chlorotrimethylsilane was then added, followed by MVK and triethylamine. The reaction was monitored by gas chromatography using toluene as an internal standard.

It was not known how much of the reagents should be used; to determine this, a response surface study was undertaken in which the amounts of lithium bromide, chlorotrimethylsilane (TMSCl), and triethylamine (TEA) were varied. The reactions were run at 25 °C (thermostated oil bath).

The experimental domain and scaling are shown in Table 8. The design and yields obtained are summarised in Table 9.

The response surface thus obtained was:

$$y = 83.45 - 3.76x_1 + 0.96x_2 + 0.60x_3 + 1.71x_1x_2 - 0.41x_1x_3 - 0.46x_2x_3 - 0.63{x_1}^2 - 2.20{x_2}^2 - 0.88{x_3}^2 + e$$

The contour projections are shown in Figure 8.

Canonical Analysis. The stationary point

$$x_1 = -8.6733$$

$$x_2 = -3.4906$$

$$x_3 = 3.2737$$

is clearly outside the explored domain, and any prediction at this point is unreliable. The predicted yield at the stationary point was, however, promising, $y_S = 99.22$. The eigenvalues are:

$$\lambda_1 = -0.1528$$

$$\lambda_2 = -0.9842$$

$$\lambda_3 = -2.5937$$

The eigenvalues are all negative and show that the stationary point is a maximum.

By the transformation

$$z_1 = 0.8451x_1 + 0.3931x_2 - 0.3624x_3 + 9.8685$$

$$z_2 = 0.3622x_1 + 0.0780x_2 - 0.9289x_3 + 0.3684$$

$$z_3 = -0.3934x_1 + 0.9162x_2 + 0.0765x_3 - 0.1424$$

the response surface is converted to the canonical model:

$$y = 99.22 - 0.15{z_1}^2 - 0.98{z_2}^2 - 2.59{z_3}^2 + e$$

From the variable transformation, it is seen that the z_1-axis passes far from the origin in the $\{x_1, x_2, x_3\}$ system.

By the transformation

$$Z_1 = z_1 - 9.8685$$

the origin of the canonical system is moved into the experimental domain; inserting

$$z_1 = Z_1 + 9.8685$$

into the canonical model yields a new model with a linear term in Z_1:

$$y = 99.23 - 0.15(Z_1 + 9.8685)^2 - 0.98{z_2}^2 - 2.59{z_3}^2 + e$$

Simplification and rounding to handy figures give

$$y = 84.62 - 2.96Z_1 - 0.15{Z_1}^2 - 0.98{z_2}^2 - 2.59{z_3}^2 + e$$

To improve the yield, the experimental conditions should be adjusted so that z_2 and z_3 are maintained at zero. The curvature is feeble along the Z_1-axis, and the main variation is described by the linear term in the experimental domain. The response surface is described by a rising ridge. An improved yield is expected by adjusting the experimental conditions in the negative direction of the Z_1-axis. Setting $z_2 = z_3 = 0$ and adjusting the conditions along the negative Z_1-axis yields the experimental condition and the predicted yields shown in Table 10.

An improved yield is obtained if the stoichiometriy of the reagents

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(10) (a) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736. (b) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (c) Jung, M. E.; McCombs, C. A. *Tetrahedron Lett.* **1976**, *34*, 2395. (d) Jung, M. E.; McCombs, C. A. *Org. Synth.* **1976**, *58*, 163. (e) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron Lett.* **1987**, *41*, 2089. (f) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.

(11) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *98*, 7807.

Table 9. **Experimental design and yield in the silyloxydiene synthesis**

	experimental variables			yield/%		experimental variables			yield/%
exp no	x_1	x_2	x_3	y	exp no	x_1	x_2	x_3	y
1	−1	−1	−1	82.9	10	−1.75	0	0	87.1
2	1	−1	−1	72.1	11	0	−1.75	0	75.0
3	−1	1	−1	82.5	12	0	0	−1.75	80.8
4	1	1	−1	77.9	13	1.75	0	0	76.8
5	−1	−1	1	87.0	14	0	1.75	0	78.8
6	1	−1	1	73.9	15	0	0	1.75	81.0
7	−1	1	1	84.1	16	0	0	0	83.6
8	1	1	1	78.5	17	0	0	0	84.2
9	0	0	0	83.4	18	0	0	0	82.8

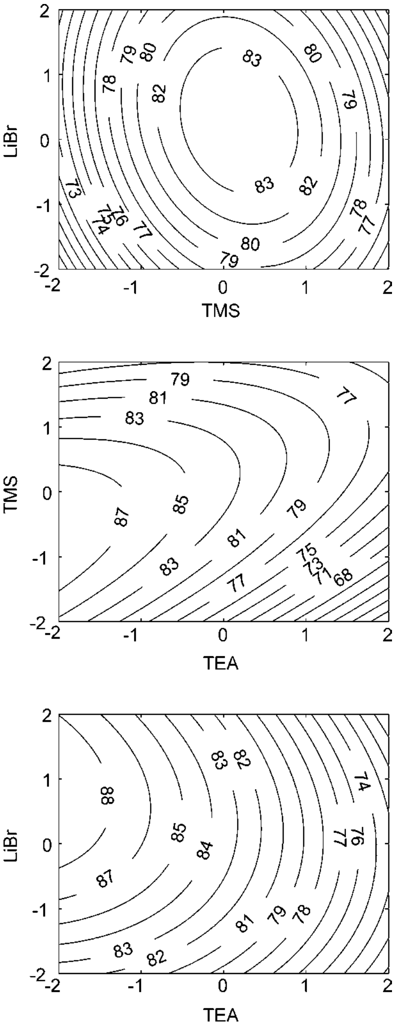

Figure 8. **Contour projections of the response surface in the 2-(trimethylsilyloxy)-1,3-butadiene synthesis.**

(TEA/MVK):(TMSCl/MVK):(LiBr/MVK) approaches the relation 1:1:2. This result was obtained by the canonical analysis.

A second response surface study was then undertaken to determine how much of the reagents in the above relation should be used and at which temperature the reaction should be run for obtaining a maximum yield. An excess of reagents (20%) and a reaction temperature of 40 °C afforded a quantitative conversion to the silyl enol ether. It was then found that the reaction is more rapid when an excess of triethylamine was used. The method was then used for the synthesis of several trimethylsilyloxydienes from α, β-unsaturated ketones; see ref 7 for examples.

Table 10. **Experimental conditions and predicted yields along the rising ridge**

	experimental condition			predicted yield (%)
Z_1	TEA/MVK	TMSCl/MVK	LiBr/MVK	y
0	1.95	1.53	1.27	84.6
−0.5	1.85	1.47	1.34	86.0
−1.0	1.74	1.41	1.42	87.4
−1.5	1.63	1.35	1.49	88.7
−2.0	1.53	1.29	1.56	89.0
−2.5	1.43	1.24	1.63	89.1
−3.0	1.32	1.18	1.71	92.2
−3.5	1.21	1.12	1.78	93.1
−4.0	1.11	1.06	1.85	94.1
−4.5	1.00	1.00	1.92	94.9

Conclusions

The coefficients of response surface model are partial derivatives of an underlying, but unknown, “theoretical” model. As such, the response surface coefficients have physical meanings although they can be difficult to interpret. Canonical analysis of response surfaces determines the eigenstructure of the second-order derivatives. It is obvious that this may furnish information related to the underlying “theoretical” model. In the examples shown, canonical analysis revealed the necessary stoichiometric requirement for the optimum yield in the syntheses of enamines and silyloxydienes. This information would have been difficult to obtain by other means. In another example, canonical analysis was applied to a rate model. This yielded a correct rate law of the reaction.

Acknowledgment

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