Optimization in Organic Synthesis. Strategies When the Desired Reaction is Accompanied by Parasitic Side Reactions. An Example with Enamine Synthesis

Rolf Carlson, Lars Hansson and Torbjörn Lundstedt

Department of Organic Chemistry, University of Umeå, S-901 87 Umeå, Sweden

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The necessity of using multivariate experimental design in synthesis optimization is emphasized. Three computer-assisted multivariate methods for the simultaneous optimization of several responses are discussed, response surface methods, simplex optimization with exponential weighing of multiple responses and PLS modelling. Applications of the methods are illustrated by optimization of the $TiCl_4$-mediated synthesis of the morpholine enamine from pinacolone. This reaction is accompanied by self-condensation of the ketone. By each of the three strategies, the yield of the desired product (enamine) was increased and the yield of the by-product was suppressed. Advantages and disadvantages of the methods are briefly discussed.

A common problem in organic synthesis is a desired reaction which does not go cleanly; parasitic side reactions also occur and give rise to by-products. Recently, an optimized titanium tetrachloride procedure for enamine synthesis was reported from this laboratory.[1] Although the method is of general scope[2] the synthesis of the morpholine enamine, *1*, from 3,3-dimethyl-2-butanone (pinacolone) was complicated by considerable self-condensation of the ketone to give 2,2,3,6,6-pentamethyl-3-hepten-5-one, *2* (see Fig. 1). A brief discussion of one approach to this problem is given in Ref. 1. In this paper, we use this specific reaction as an illustration of the general problem of side reactions and discuss in more detail how the problem can be solved. The literature of organic chemistry shows that the problem of concurrent reactions is generally approached in two ways: by adjusting the reaction conditions to optimize the yield of the desired reaction; and/or by developing new, more selective or specific reagents. It is obviously a wasteful strategy to develop new reagents whenever this problem turns up. The preferred approach is, therefore, first to optimize the reaction conditions by adjusting various experimental variables such as temperature, concentration of reactants and reagents, composition of solvent, etc. to attain an acceptable performance from the system. If the obtained optimum is not good enough, then a search for new reagents is appropriate.

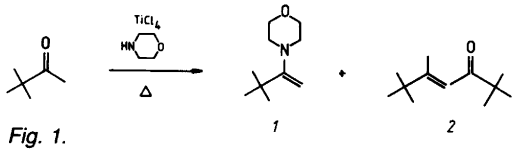

Fig. 1.

When reaction mechanisms are known, it is sometimes possible to predict by theoretical reasoning, ways to suppress the parasitic reaction and increase the yield of the desired reaction. However, in most cases, reaction mechanisms are not known in such detail that this is possible. This is always the case with new synthetic procedures. When mechanistic details are obscure, it is necessary to solve the problem by experiments. It is essential to use multivariate strategies which allow for a simultaneous variation of all intervening experimental variables.[3] In this paper, we discuss how the general problem can be approached by using such multivariate strategies as response surface methods,[4] sequential simplex optimiza-

tion[5] and PLS-MACUP.[6] We do not go deeply into the details of these methods; thorough accounts have been given in the references cited.

Methods and results

Response surface method. The result, y, of a synthetic procedure is dependent on *how* the experiment was done. Hence, we can assume a functional dependence between y and the experimental variables, $x_1, x_2, \ldots x_k$, eqn. (1). The nature of

$$y = f(x_1 \ldots x_k). \quad (1)$$

the function f is in most cases unknown, but it is likely that f is continuous and smooth, provided that the variations in x_i are not too large. Under these conditions; it is possible to approximate f by a Taylor expansion including a limited number of terms. This means that a low degree polynomial in the experimental variables will show the general features of f as in eqn. (2). In most

$$y = b_0 + b_1x_1 + \ldots + b_kx_k + b_{12}x_1x_2 + \ldots + b_{ij}x_ix_j + \ldots + b_{11}x_1^2 + \ldots + b_{kk}x_k^2 + e. \quad (2)$$

cases, it is sufficient to approximate f by a second degree response surface model. The residual term, e, contains contributions from higher degree terms in the Taylor expansion. The coefficients in the polynomial can be determined by multiple regression to fit a polynomial to known experimental results.

Response surface models showng y_1 (yield of enamine, *1*) and y_2 (yield of self-condensation product, *2*) as functions of the experimental variables x_1 (amount of morpholine), x_2 (amount of titanium tetrachloride) and x_3 (temperature) were obtained from the experimental design in Table 1. The experimental domain and the coding of the experimental variables are shown in Table 2. The models were calculated from the yields obtained after 4 h. The reactions were

$$y_1 = 58.54 + 5.36\,x_1 + 8.64\,x_2 + 5.25\,x_3 - 0.69\,x_1^2 - 1.17\,x_2^2 - 0.04\,x_3^2 + 1.80\,x_1x_2 + 0.88\,x_1x_3 + 0.85\,x_2x_3 + e \quad (3)$$

$$y_2 = 12.65 - 3.82\,x_1 + 3.81\,x_2 - 0.78\,x_3 + 1.68\,x_1^2 + 0.83\,x_2^2 + 0.88\,x_3^2 - 2.66\,x_1x_2 - 0.86\,x_1x_3 - 1.86\,x_2x_3 + e. \quad (4)$$

monitored by GLC and after 4 h, the increase in yield was insignificant.

Projections of the response surface models are shown in Fig. 2. Visual interpretation of the projections indicated that an improved result was to be expected under the following conditions: increase the reaction temperature, x_3; use a large

Table 1. Response surface design.

Entry[a]	x_1	x_2	x_3	y_1	y_2	D
1	−1	−1	−1	41.6	14.6	0.102
2	1	−1	−1	45.1	6.7	0.3449
3	−1	1	−1	51.7	26.2	2.1E-06
4	1	1	−1	64.7	17.7	0.0567
5	−1	−1	1	47.8	11.9	0.2188
6	1	−1	1	57.1	17.5	0.0551
7	−1	1	1	63.6	26.1	3.31E-06
8	1	1	1	77.8	11.0	0.4015
9	1.414	0	0	66.7	8.1	0.487
10	−1.414	0	0	49.5	22.2	0.00146
11	0	1.414	0	70.4	18.9	0.032
12	0	−1.414	0	43.9	8.0	0.3035
13	0	0	1.414	66.4	9.8	0.4142
14	0	0	−1.414	52.4	17.3	0.0547
15	0	0	0	56.5	13.8	0.1856
16	0	0	0	60.0	12.3	0.2668
17	0	0	0	58.6	12.6	0.2469
18	0	0	0	57.2	13.6	0.1967

[a]The experiments were performed in random order, not as they are reported in the table.

Table 2. Variables and levels for the response surface design.

Variables	Levels				
	−1.414	−1	0	1	1.414
x_1: Ratio morpholine/ketone (mol/mol)	3.00	3.59	5.00	6.41	7.00
x_2: Ratio $TiCl_4$/ketone (mol/mol)	0.50	0.57	0.75	0.93	1.00
x_3: Temperature (°C)	52	60	80	100	108

excess of morpholine, x_1; a moderate excess of titanium tetrachloride, x_2. These conclusions were confirmed experimentally (see below).

In the general case, a combination of isoresponse contour projections and canonical analysis of the response function[4] may suggest ways to improve the performance of the system.

Simplex optimization. For simplex optimization, it is necessary to have only one response which is to be optimized. Of course, it is possible to set the yield of the desired reaction as response and to optimize on this criterion, or, obversely, to minimize the yield of a parasitic reaction. Unfortunately, it may not be evident that these criteria can be met at the same time; often it may well be the case that an optimal performance is a compromise between them. Such a compromise can be achieved by weighing together all the individual responses into one. For applications to organic synthesis, a transformation into the overall desirability function, D, suggested by Harrington[7] seems appropriate. By this procedure, each individual response, y_i, is transformed into a dimensionless scale, d_i, by the exponential transformation of eqn. (5). The function d_i will have values between zero and one. A value close to zero means a very poor result and a value close to one means an extraordinarily good result. The parameters (c_0, c_1) in the function can be determined to describe *what* is a desired and poor result by assigning values to d_i for values of the response y_i.

$$d_i = \exp(-\exp(c_0 + c_1 y_i)). \qquad (5)$$

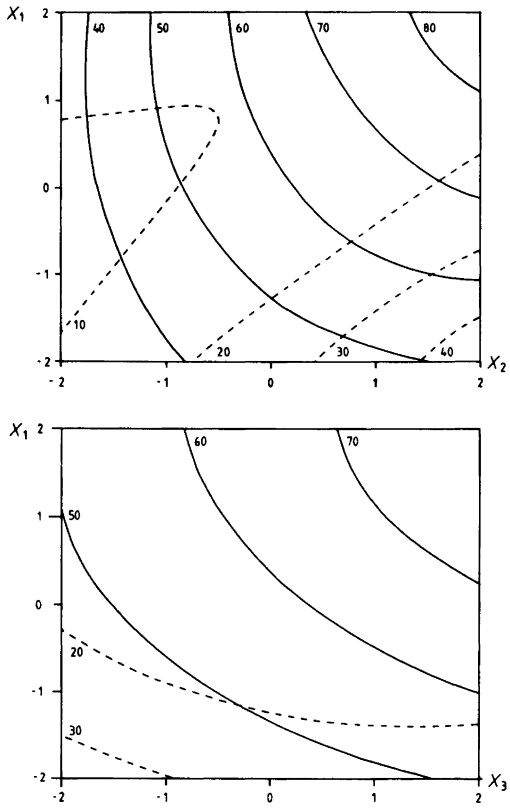

Fig. 2. Isocontour projections of the response surface models. Solid lines show the yield of enamine. Dashed lines show the yield of by-product.

An arbitrary scale for d can be set as $d > 0.8$ (excellent), 0.8–0.6 (good to acceptable), 0.6–0.4 (accaptable to fair), 0.4–0.3 (fair to poor), $0.3 > d$ (poor to very poor). The overall desirability function, D, is defined as the geometric mean of the individual desirability functions, eqn. (6).

$$D = (d_1 d_2 \ldots d_n)^{1/n}. \quad (6)$$

The function D fulfills the requirement for an overall judgement and even corresponds well with psychological expectations: it is sufficient for one of the responses to be poor to give a low overall desirability. The value of D is excellent only when the value of each individual d_i is excellent. The value of D is equal to d_i when all d_is are equal.

With the function D, it is possible to transform the outcome of any synthetic experiment into one response. All that is necessary is that the chemist state explicitly *what* is an acceptable and *what* is a poor result. Hence, D can serve as an optimization criterion in simplex optimization when a compromise between conflicting responses is necessary.

By the response surface models, given above in eqn. (3) and (4), we could predict the yield of *1*, y_1, and *2*, y_2 under any conditions specified by the variables x_1–x_3. With the function D, we could determine an overall desirability of the result. This made it possible to carry out a simplex optimization by simulation. The individual desirability functions were parameterized as follows: if the yield of enamine could reach 90 % it would be a good result, consequently, d_1 should be assigned a value of 0.8, $y_1 = 90$ %; a drop in yield to 50 % was regarded as a poor result, $d_1 = 0.3$, $y_1 = 50$ %; if the yield of by-product exceeds 10 % it is a poor result, $d_2 = 0.3$, $y_2 = 10$; a good result is obtained if the yield of *2* is less than 1 %, $d_2 = 0.8$, $y_2 = 1$ %. This gives eqn. (7), (8) and (9).

$$d_1 = \exp(-\exp(2.2956 - 0.4214\, y_1)) \quad (7)$$
$$d_2 = \exp(-\exp(-1.6872 + 0{\cdot}1873\, y_1)) \quad (8)$$
$$D = (d_1 d_2)^{0.5}. \quad (9)$$

The graphs of d_1 and d_2 are shown in Fig. 3.

The results of six simplex simulations are summarized in Table 3. The modified simplex strategy by Nelder and Mead[5b] was used. The simulations were restricted by the following constraints: (1) A suggested experiment outside a possible experimental domain was assigned $D = 0$, i.e., $x_1 < -1.41$, or $x_2 < -1.41$ (less than stoichiometric amounts), or $x_3 > 2.0$ (above the boiling point of solvent). (2) A predicted yield of $y_1 > 105$ % (precision in y_1 (predicted) = ±5 %, $p = 0.95$) was also assigned $D = 0$. This meant that the response surface model was no longer valid in extrapolating results far outside the explored domain (Table 1). Without this restriction rather ridiculous results were obtained, e.g., $y_1 = 172.6$ for $x_1 = 8.8$, $x_2 = 5.5$, $x_3 = 2.0$.

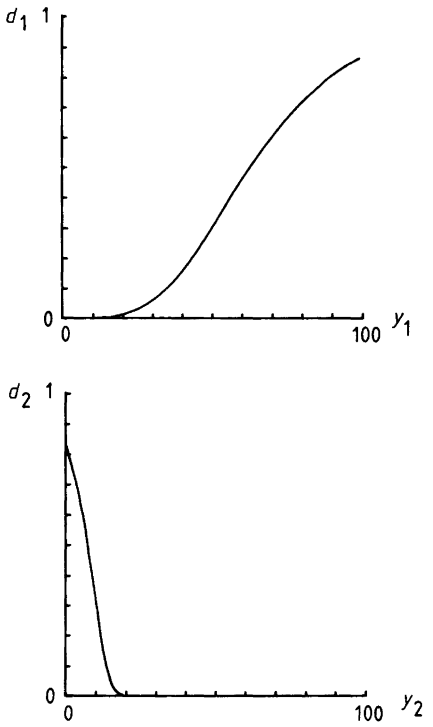

Fig. 3. Desirability functions.

It is seen from Table 3 that approximately the same optimum conditions are found regardless of the orientation of the starting simplex. An average is $x_1 = 2.00$, $x_2 = 1.67$, $x_3 = 1.78$ which affords y_1 (pred.) = 104.0 and y_2 (pred.) = 10.3, $D = 0.500$. Experiments performed under these conditions yielded $y_2 = 86.5$ % and $y_2 = 7.8$ which was better than predicted for y_2 but not as high as predicted for y_1. This clearly demonstrates that it is necessary to be cautious in extrapolations from response surface models.

PLS method, MACUP. In the response surface strategy outlined above, it is assumed that the re-

Table 3. Simplex optimization.

Starting simplex					Optimum conditions					
Entry	x_1	x_2	x_3	Iterations	x_1	x_2	x_3	y_1	y_2	D
1	−0.5	−0.5	0.5	31	1.98	1.88	1.64	104.6	10.4	0.492
	0.5	−0.5	−0.5							
	−0.5	0.5	−0.5							
	0.5	0.5	0.5							
2	0.8	0	0.8	31	1.85	1.88	1.99	105.0	10.2	0.507
	1.2	0	1.2							
	0.8	0.6	1.2							
	1.2	0.6	0.8							
3	0.5	0	1.0	32	1.93	1.77	1.71	103.7	10.3	0.495
	0	0	0.5							
	0.5	0.5	0.5							
	0	0.5	1.0							
4	0	0	0	31	2.19	1.53	1.77	104.9	10.4	0.492
	0.9	0.2	0.2							
	0.2	0.9	0.2							
	0.2	0.2	0.9							
5	kk45−0.5	−0.5	−0.5	21	2.01	1.76	1.75	104.9	10.3	0.501
	0.5	−0.5	0.5							
	−0.5	0.5	0.5							
	0.5	0.5	−0.5							
6	0	0.6	−0.3	25	2.05	1.67	1.79	104.8	10.3	0.501
	0.5	−0.3	−0.3							
	−0.5	−0.3	−0.3							
	0	0	0.6							

actions leading to the various products are independent processes, that they respond independently to perturbations in the experimental conditions. This may perhaps be true in systems like the present one where the products are formed in *parallel* reactions. These assumptions do not apply, where, in other systems, however, parasitic products arise from *consecutive* reactions. The problems faced by the chemist look the same whether or not parallel or consecutive reactions cause the trouble, therefore we suggest yet another strategy, namely MACUP, which does not rely on prior assumptions of the causes about the trouble.[8]

The result of a synthesis experiment can be characterized by the yields of *all* products formed, $y_1 \ldots y_r$. Experiments carried out under different reaction conditions can be characterized by their constellations of the various experimental variables, $x_1 \ldots x_k$. Thus, each experiment is characterized by a variable vector $\boldsymbol{x} = (x_1 \ldots x_k)$ and a response vector $\boldsymbol{y} = (y_1 \ldots y_r)$. A series of experiments can be described by an experiment matrix, $\boldsymbol{X}$ (where the rows are the $\boldsymbol{x}$ vectors), and a response matrix, $\boldsymbol{Y}$, where the rows are the $\boldsymbol{y}$ vectors. With the PLS method, it is possible to establish functional relationships between $\boldsymbol{X}$ and $\boldsymbol{Y}$ and *vice versa*. This is the essence of MACUP (*M*odelling *A*nd *C*lassification *U*sing the *P*LS method).[6,9] The method is based on PLS decomposition of the matrices $\boldsymbol{X}$ and $\boldsymbol{Y}$ (eqn. (10, 11)) and a correlation between these models. The resulting models are slightly tilted (biased) from principal components (PC) models to obtain a maximum correlation between the components of the X block and the Y block. The PLS al-

gorithm is very fast and completes the modelling and correlation in one step. The procedure can be summarized. A correlation between $\boldsymbol{X}$ and $\boldsymbol{Y}$ is expressed by eqn. (12). The matrices $\boldsymbol{A}$ and $\boldsymbol{G}$

$$\boldsymbol{X} = \boldsymbol{A} + \boldsymbol{TB} + \boldsymbol{E} \quad (10)$$
$$\boldsymbol{Y} = \boldsymbol{G} + \boldsymbol{UC} + \boldsymbol{F} \quad (11)$$
$$\boldsymbol{U} = \boldsymbol{TD} + \boldsymbol{H}. \quad (12)$$

contain the averages of the corresponding variables. The columns in $\boldsymbol{T}$ and $\boldsymbol{U}$ are singular vectors of the corresponding PC-like model of $\boldsymbol{X}$ and $\boldsymbol{Y}$. This means that each experiment can be characterized by the corresponding columns in the matrices. The matrices $\boldsymbol{B}$ and $\boldsymbol{C}$ describe the contribution of each of the original variables (x_1 ... x_k) and (y_1 ... y_r) to the components $\boldsymbol{t}_i$ and $\boldsymbol{u}_i$. The matrix $\boldsymbol{D}$ is a diagonal matrix showing the linear correlation between $\boldsymbol{u}$ and $\boldsymbol{t}$. $\boldsymbol{E}$, $\boldsymbol{F}$ and $\boldsymbol{H}$ are matrices of the residuals. The procedure is subjected to cross validation[10] to extract a correct number of significant components in the models and can be illustrated geometrically as in Fig. 4. The experiments in Table 1 were analyzed by the PLS method. Two significant components (cross validation) were extracted. The first component accounted for 46.6 % of the total variance in the response matrix $\boldsymbol{Y}$ (98.7 % of the variance in y_1 and 9.0 % of the variance in y_2). With two components, 90.4 % of the total variance was described by the model. In applying the methods, the original variables, x_i, y_j, were transformed by scaling to unit variance (autoscaling) over the whole data set, i.e., each variable was divided by its standard deviation. In the calculations were also included the squares of the experimental variables, x_i^2, and the cross-products, $x_i x_j$ as variables. This meant that the matrix $\boldsymbol{X}$ also contained columns for these derived variables. The squares and cross-products were also autoscaled. the jth experiment was thus described by row j in $\boldsymbol{X}$ and contained the following elements, z_i (original variable): $z_1(x_1)$, $z_2(x_2)$, $z_3(x_3)$, $z_4(x_1^2)$, $z_5(x_2^2)$, $z_6(x_3^2)$, $z_7(x_1x_2)$, $z_8(x_1x_3)$, $z_9(x_2x_3)$. The response variables were also scaled: $w_1(y_1)$ and $w_2(y_2)$. The PLS calculations gave the relations in eqn. (13) and (14) between u_1 and u_2 and the scaled response variables. It is seen that the first component mainly describes the variation in yield of enamine, y_1, and the second mainly the variation in yield of by-product, y_2. The coefficients in the relations are the elements of the matrix C above. For the experimental variables, the relations in eqn. (15) and (16) were found for the components t_1 and t_2.

$$u_1 = 0.9471w_1 + 0.3208w_2 \quad (13)$$
$$u_2 = 0.3338w_1 + 0.9428w_2 \quad (14)$$

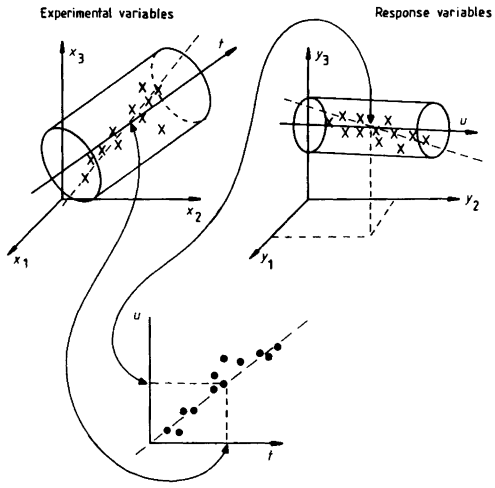

Fig. 4. PLS method. The PLS components, t and u are marked by solid vectors. They are slightly tilted from PC eigenvectors (dashed) to achieve a maximum correlation between the yield components, u_i, and the experimental variable components, t_i.

$$t_1 = 0.2469z_1 + 0.8820z_2 + 0.3858z_3 - 0.0210z_4 - 0.0440z_5 + 0.0321z_6 + 0.0130z_7 - 0.0918z_8 - 0.0179z_9 \quad (15)$$

$$t_2 = 0.7351z_1 - 0.3144z_2 + 0.2738z_3 - 0.2232z_4 - 0.1305z_5 - 0.1091z_6 + 0.3710z_7 - 0.0845z_8 - 0.2495z_9. \quad (16)$$

The coefficients (loadings) in the z_i terms show how much each variable contributes to the component t. These loadings are the elements of the matrix $\boldsymbol{B}$ above. Evaluation by cross validation showed that for t_1 only z_2 was significant and that neither the linear variables z_1, z_3 nor the quadratic and cross-product terms, z_4–z_9, contributed to the systematic variation in response y_1. This meant that the yield of enamine was mainly controlled by the amount of titanium tetrachloride. For the second component, only the linear variables, z_1–z_3 were significant. To reduce the amount of by-product it was therefore necessary to pay attention to the whole experimental set-up, i.e., the amounts of the reagents and the reaction temperature. The correlation between the

components for the response variables in the Y block and the components for the experimental variables in the X block is shown in Fig. 5.

The PLS models can be used for predictions in both directions: *what* is the expected result, $\boldsymbol{y} = (y_1, y_2)$, with a given constellation of the experimental variables, $\boldsymbol{x} = (x_1, x_2, x_3)$; and the reverse, *which* experimental conditions, $\boldsymbol{x}$, *shall* be used to obtain a given result, $\boldsymbol{y}$.

Prediction of $\boldsymbol{y}$ from $\boldsymbol{x}$ can be exemplified by the optimum conditions determined by the simplex optimization, $x_1 = 2.00$, $x_2 = 1.67$, $x_3 = 1.78$, which afforded $y_1 = 104.0$, $y_2 = 10.3$ by the response surface models and $y_1 = 98.5$, $y_2 = 10.5$ by the PLS model. The result obtained by experiment was $y_1 = 86.5$, $y_2 = 7.8$.

For predictions of $\boldsymbol{x}$ from $\boldsymbol{y}$, the PLS model was updated by including the simplex experiment in the matrices $\boldsymbol{x}$ and $\boldsymbol{y}$. A desired result, $y_1 = 100$, $y_2 = 0$, corresponded to experimental conditions $x_1 = 3.70$, $x_2 = 1.64$, $x_3 = 2.61$. However, these conditions could not be obtained since $x_3 = 2.61$ corresponded to a reaction temperature of 132 °C which is above the boiling point of the solvent (petroleum ether, b.p. 100–120 °C). Predictions for experiments under reflux conditions ($x_3 = 2.00$) gave $y_1 = 95.8$, $y_2 = 0.5$. Experiments carried out under these conditions yielded $(y_1, y_2) = (92.6, 3.0)$ and $(94.3, 2.0)$) in a duplicate run. This was an improvement compared to the results obtained in the simplex optimization. An isolated yield of 85 % of distilled product was obtained on preparative scale.

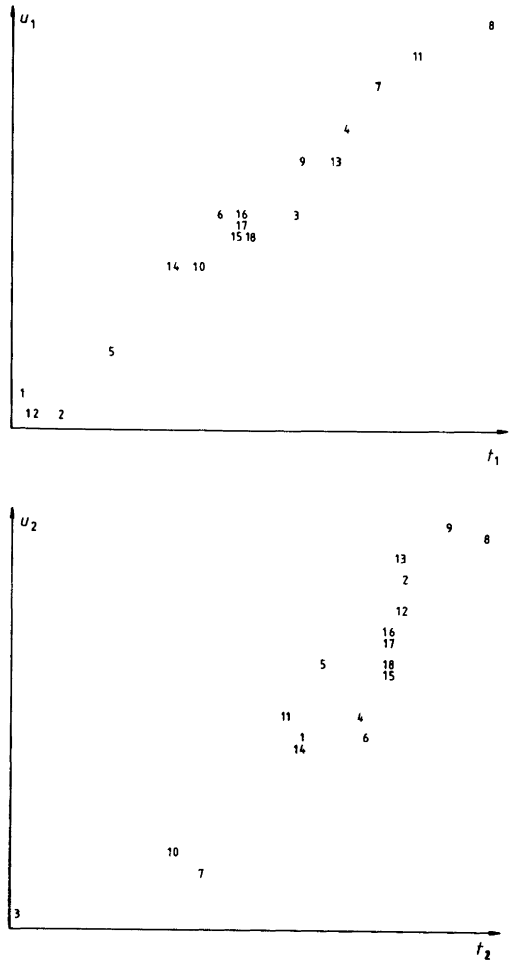

Fig. 5. PLS correlation between yield components, u_i, and experimental variable components, t_i.

Discussion

We note that the traditional approach to optimization in chemistry (adjust one variable at a time) is a poor strategy, since it fails to attain the optimum conditions when there are interactions among the experimental variables.[3] Unfortunately, such interactions are almost always involved, even in simple systems. It is, therefore, necessary to design experiments in such a way that interactions among variables can be detected and taken into account when the reaction conditions are adjusted toward optimum performance by using multivariate experimental design.[4b] A proper design becomes even more important when several responses have to be considered. It is not likely that the variables will exert a similar influence on the different responses. In this context, we suggest three different general methods for optimization of a desired synthetic reaction with a concomitant suppression of parasitic side reactions. Each method has merits (+) and disadvantages (−).

Response surface method. (+): Gives easily interpreted models; results can be analyzed graphically (isocontour projections); calculations can be carried out using any computer program for multiple regression. (−): The number of experiments increases rapidly when the number of variables increases; a complete set of experiments has to be accomplished before the result can be evalu-

ated; the method can give misleading results when responses are interdependent (e.g., yields in consecutive reactions); extrapolations are unreliable.

Simplex method. (+): Easy to apply; does not necessarily need a computer, calculations can be handled on a pocket calculator; since the desirability function, D, can be applied to any system with measurable responses, the simplex method is general; interactive strategy-experimentation can be interrupted at any moment when a satisfactory result has been obtained; no dangerous extrapolations. (−): The method becomes unmanageable with many variables; may progress only slowly towards the optimum.

PLS method (+): Describes all response variables in one model; can be used for predictions in both directions; models can be established with a ratio (number of experiments/number of variables) <1 which is not possible in response surface methods; models can be updated and refined by including new experimental results as they become available, which permits a stepwise approach; results can be analyzed graphically. (−): The method needs a special computer program; extrapolations are unreliable.

All these methods led to an improvement of the result when they were applied to a model reaction (enamine synthesis). The best result was obtained by the PLS strategy. Predictions were also closer to actual experimental results by this method compared to predictions by response surface models.

Conclusion

The advent of small, powerful and cheap microcomputers makes computerized tools applicable to many branches of chemistry. One such area is synthesis optimization where multivariate methods are indispensable. In this paper, we have discussed three general computer-assisted strategies which can be applied to solve the common problem of how to optimize the yield of a desired reaction with a simultaneous suppression of undesired side reactions. The application of the methods was demonstrated on a model reaction (enamine synthesis). It is our hope that these methods will prove useful in many other applications. In a forthcoming publication, we will discuss how the PLS strategy can be used for screening significant variables when a complex mixture of reaction products is formed.

Calculations and experimental

The calculations for response surface and PLS modelling were carried out using Zampo (8-bit), Toshiba T1100 (16-bit) or Toshiba T1500 (16-bit) microcomputers. For simplex optimization a programmable pocket calculator, Casio FX-702P, was used. Response surface models were obtained by the REGFAC program package and PLS models by the SIMCA package (SIMCA-3B version). These programs are available from Sepanova AB, Östrandsvägen 14, S-112 43 Enskede, Sweden. The SIMCA program is also available from Principal Data Components, 2505 Shepherd Blvd., Columbia, MO 65201, USA. A program for simplex optimization is also available from Sepanova AB.

GLC analyses were performed on PYE Unicam M64 and PYE Unicam GCD gas chromatographs equipped with FID. A 2.1 m × 4 mm i.d. glass column packed with 6 % QF-1 on Chromosorb® W-AW 100–120 mesh was used. Yields were determined by internal standard technique and integrated peak areas were used for quantification. A Spectra Physics Minigrator® or Milton Roy C-10 integrator was used.

3,3-Dimethyl-2-butanone (*purum*) from Merck was distilled. Morpholine (*purum*) from Kebo Lab was dried over KOH. Titanium tetrachloride (*purum*) from Reidel–de Haen was used as delivered. Petroleum ether (*p.a.*) b.p. 100–120 °C from Kebo Lab was dried over sodium wire.

For the experiments in Table 1, a 500 ml three-necked flask was equipped with a reflux condenser, dropping funnel and a Hershberg stirrer. The flask was charged with the given amount of morpholine, x_1, and the amount of petroleum ether to adjust the volume to 200 ml. The flask was cooled in an ice bath and the given amount of titanium tetrachloride, x_2, was added dropwise with vigorous stirring. Titanium tetrachloride was dissolved in an amount of petroleum ether to adjust the volume to 50 ml. When the addition was complete, the ice bath was replaced by a thermostated oil bath at the temperature x_3 and the greenish-brown suspension of precipitated $TiCl_4$-amine complex was allowed to reach temperature equilibrium. The reaction was restarted by the

rapid addition of a solution of 10.00 g (10.0 mmol) of 3,3-dimethyl-2-butanone and an accurately weighed amount (~10 g) of phenylcyclohexane (internal standard) in 30 ml of petroleum ether. Samples were withdrawn at regular intervals and filtered through a plug of cotton, diluted with hexane and analyzed by GLC.

A preparative scale run was carried out in a three-necked liter flask mounted with a Hershberg stirrer, reflux condenser and a dropping funnel. The flask was immersed in an ice bath and charged with 180 ml (2.05 mol) of morpholine dissolved in 220 ml of petroleum ether (b.p. 100–120 °C). A solution of 22.5 ml titanium tetrachloride (0.206 mol) in 80 ml of petroleum ether was added over 10 min with vigorous stirring. The resulting mixture was heated to reflux and 20.0 g (0.20 mol) of 3,3-dimethyl-2-butanone dissolved in 80 ml of petroleum ether rapidly introduced. The reaction mixture was maintained at reflux for 1 h. Towards the end of this period, the mixture became very thick and 100 ml of petroleum ether were added to facilitate agitation. After cooling, the reaction mixture was filtered through a sintered glass filter. The solvent and excess of morpholine were removed under reduced pressure. The crude product was fractionated over a 25 cm Vigreux column. After a small forerun (4.12 g, containing ~80 % of enamine) the pure (>97 %) enamine (28.9 g, 85 %) was collected at 70–71 °C/8 mmHg.

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