

Scope of Organic Synthetic Reactions. Multivariate Methods for Exploring the Reaction Space. An Example with the Willgerodt-Kindler Reaction*

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New principles are presented by which the scope and limitations of synthetic reactions can be determined when substrates, reagents and solvents are allowed to vary simultaneously. The strategies are based on multivariate statistical methods: (a) Characterization of substrates, reagents and solvents by principal components (PC) analysis to determine the principal properties, (b) multivariate design based on the principal properties to select test systems, (c) optimization of the experimental conditions for the selected test systems, and (d) PLS modelling of optimum conditions as a function of the properties of the system to predict optimum conditions for new, as yet untested systems. The methods are briefly described.

The methodology is illustrated by experimental studies on the Willgerodt-Kindler reaction of *para*-substituted acetophenones.

Introduction

Current practice for determining the scope of reactions. To evaluate the utility of an organic reaction for synthetic purposes, it is essential that its scope and limitations are established. In a narrow sense, this usually means a knowledge of how the reaction will proceed when the structure of the substrate is changed; this generally implies variation with regard to steric and electronic effects which may play a role and/or to other functional groups in the substrate. In a broader sense, determining the scope of a reaction will also entail a knowledge of the influence of variations in the structure of attacking reagent as well as in the nature of the solvent. These variations can be illustrated by the *reaction space* shown in Fig. 1.

The “axes”, which span the reaction space, are defined in quantitative terms below, but for the time-being it is sufficient to regard them qualitatively as being merely *variations*. In these terms,

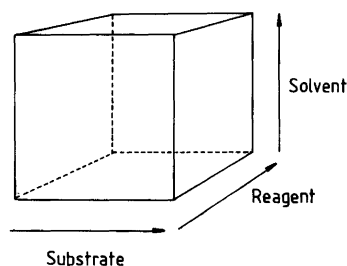


Fig. 1. The reaction space.

the general scope of a reaction is the domain of the reaction space which gives the desired reaction. The limitations will be those combinations of system variables (substrate, reagent and solvent) which fail to give the desired reaction.

It is often experienced that a sluggishly reacting substrate can be forced to react by using a more aggressive reagent. It is also known that substrates and reagents may be solvated differently if the solvent is changed, and that this may alter the reactivity pattern. From this it becomes apparent that the perturbations described by the

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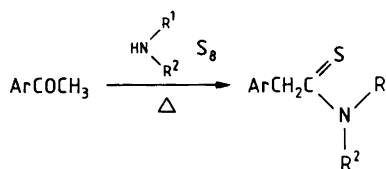
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“axes” in the reaction space are *not* independent, i.e. compensation effects resulting from interaction between system variables may play important roles. However, the common approach to the determination of the scope of a reaction is to use one-variable-at-a-time (OVAT) variation: The reaction is studied for a series of substrates while maintaining fixed reagent and solvent and (even worse, see below) reaction conditions. In this approach the study is then repeated with, e.g., a series of solvents. Such a strategy corresponds to one-dimensional excursions through the reaction space and, as with any OVAT procedure, no information on interaction effects whatsoever can be obtained. The OVAT approach is therefore a *poor* strategy for determining the scope of a synthetic reaction since we *know, a priori*, that compensation effects must be present. To account for these effects, it is necessary to treat the problem of the general scope of a reaction by methods that allow for a systematic, *simultaneous* variation of substrate *and* reagent *and* solvent. In this paper we present a new methodology for the systematic exploration of the reaction space.

Comment on the use of “standardized conditions”. It is common to use “standardized conditions” in series of experiments carried out to determine the scope of a reaction. However, it has been shown that the optimum experimental conditions are highly susceptible to variations in substrate,² in reagent³ and in solvent.⁴ Hence, conclusions drawn from a series of experiments under standardized conditions can be completely misleading. To make fair comparisons, it is therefore necessary to optimize the experimental conditions in *each case*. For optimization it is also necessary to use multivariate methods; this has been emphasized elsewhere.⁵

The Willgerodt-Kindler reaction

The oxidation/rearrangement of acetophenone to phenylacetamide in the presence of ammonium polysulfide is known as the Willgerodt reaction.⁶ Later, it was found by Kindler⁷ that aliphatic amines and elemental sulfur could replace ammonium polysulfide, leading to thioamides as the rearranged product (Scheme 1). Although the Willgerodt-Kindler reaction has been extensively studied over the years,⁸ a generally accepted reaction mechanism has not yet been established.



Scheme 1.

This means that the scope of the reaction cannot be inferred from mechanistic considerations and that conclusions concerning the scope must be drawn from direct experimental observations.

In this reaction, the reaction space is spanned by the variations in (a) ketone substrate, (b) amine reagent and (c) solvent. We have recently shown that variation of any one of these strongly influences the optimum conditions for synthesis.²⁻⁴ These studies can, however, be viewed as “one-dimensional” excursions in the reaction space, which is a poor strategy for determining the general scope of the reaction. It is clear that the number of possible combinations of substrates, amines and solvents will be prohibitively high, ruling out an experimental optimization of the experimental conditions for each combination. The use of some strategy which reduces the number of combinations is therefore imperative, and for this purpose it is necessary to quantify the “axes” in the reaction space.

Quantification of the “axes” in the reaction space: Principal properties

Any chemical compound can be characterized by a large number of data. Examples are physical properties (m.p., dielectric constant, refractive index etc.), spectroscopic data (IR, UV, ¹H NMR etc.), structural data (bond lengths, bond angles, dipole moments etc.) and empirical structural parameters (σ , σ_1 , π , E_s etc.). The available data have increased dramatically through the use of instrumental methods in chemistry, and some of these data are likely to be related to the behaviour of the compound when it takes part in chemical reactions. By this we certainly do not mean that the chemical behaviour can be *explained*, in a philosophical sense, by e.g. the refractive index of the solvent or by proton shifts in an NMR spectrum. What is assumed is that macroscopic, observable properties are likely to be manifestations of intrinsic, molecular properties

responsible for the chemical behaviour. We can therefore use macroscopic properties as *probes* and not as *explanations* of intrinsic properties.

Compounds that are similar in some respect will have some properties that are similar, or the reverse may be more correct, *i.e.* compounds which have properties in common are regarded as being similar. When several property descriptors are collected for a series of compounds, large matrices (tables) are obtained. Such tables are difficult to analyse by mere inspection and the risk of spurious correlations of single property descriptors to any phenomenon increases dramatically with an increase in the number of descriptors. Another problem is that property descriptors are often correlated to each other.^{1,9} One possibility for coping with this situation is to analyze data tables by principal components (PC) decomposition. Details of PC analysis have been given elsewhere;⁹ here, we only give a brief outline of the method.

Principal components analysis. The principles involved can be illustrated geometrically as follows: Assume that an *object* (e.g. chemical compound) is characterized by m property descriptors. Let each property define a coordinate axis. The m different property descriptor axes will thus define an m -dimensional space. In this space the object will be described by a point with coordinates on the different axes equal to the measured properties. A series of different objects characterized by the same set of descriptors will define a swarm of points in the m -dimensional space. A principal

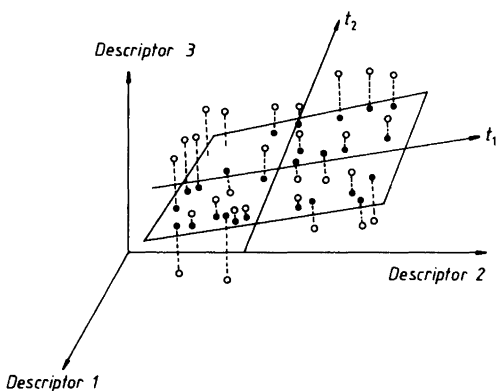


Fig. 2. PC projections: Data points in the m -dimensional descriptor space are projected down to an A -dimensional hyperplane.

components analysis constitutes a projection of this swarm of points down to a space of fewer dimensions. The projection is done so that the first component vector describes the direction through the swarm showing the largest variation. Each descriptor variable is previously scaled, generally to unit variance, so that different units of the descriptors will not "blow up" the variance and bias the projections. The second component vector describes the direction through the swarm showing the second largest variation, etc. The component vectors are mutually orthogonal. The projections are illustrated in Fig. 2.

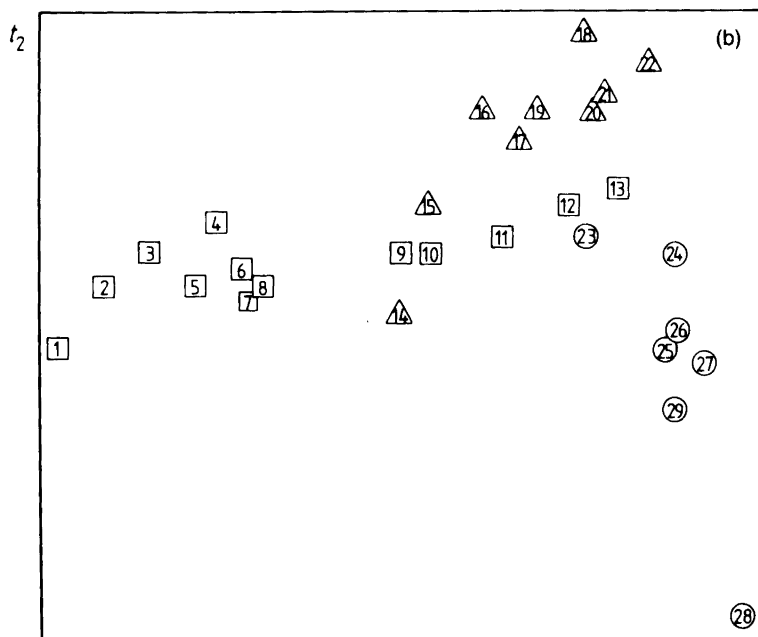
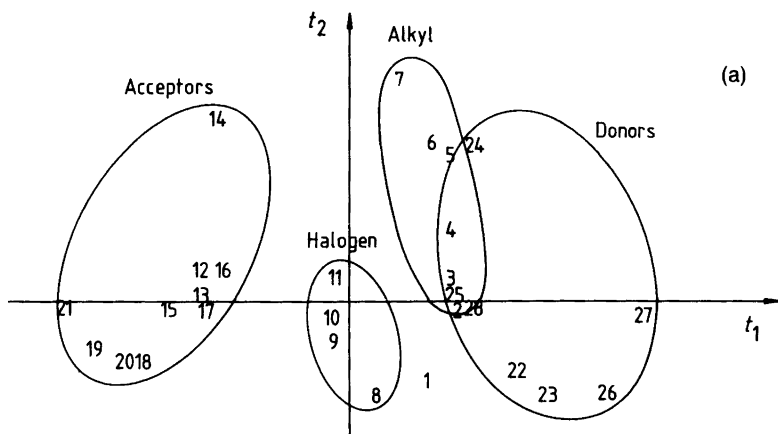
The mathematical expression for a PC model will take the form

$$x_{ik} = a_i + \sum_{j=1}^A b_{ij} t_{jk} + e_{ik} \quad (1)$$

where x_{ik} is the scaled value of the descriptor i for object k . The PC model is obtained by least-squares fitting of a straight line ($A = 1$) or an A -dimensional hyperplane to the data points in the descriptor space. The parameters a_i determine the centre of the data set (average of descriptor i). The parameters b_{ij} are the direction coefficients of the PC vectors (one for each descriptor and component). For each object, the parameters t_{jk} describe the position of the object point projected down to the model (coordinates of the projected point in the coordinate system defined by the PC vectors). Hence, t -values can be used to relate objects to each other. Objects that are close to each other in the descriptor space (similar objects) will be projected close to each other in the PC projection. The b_{ij} parameters (loadings) together with the residual variance, e_{ik} , can give information on how much each descriptor contributes to the model.

An important result of PC modelling is that the *systematic variation* can be described by *fewer* variables than in the original data set. Determination of the significant number of product terms (components) in eqn. 1 is made by cross-validation. Details on this are given elsewhere.¹⁰

Since the PC vectors are mutually orthogonal, the t -values will be independent measures of the systematic variation. The term *principal properties* has been suggested¹¹ for t -values of significant PC components of descriptor matrices. Analyses to determine principal properties have been



- Primary
- △ Secondary
- Sec. cyclic

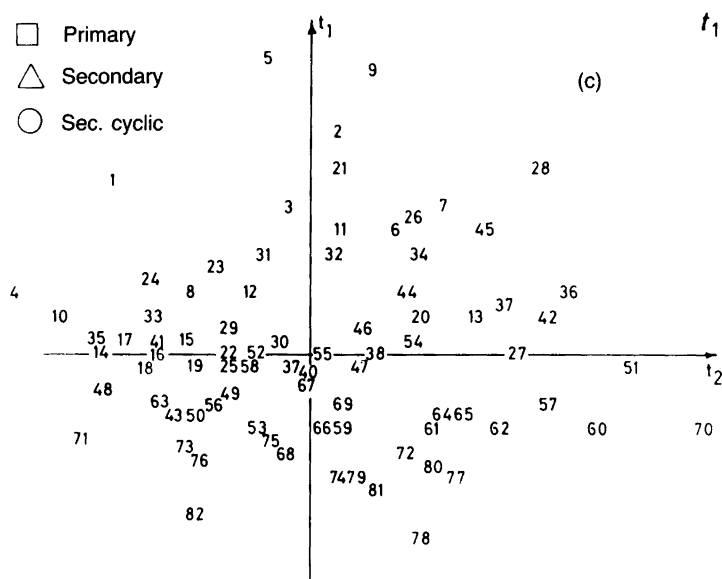


Fig. 3. Principal properties: (a) The variation in substituents (see Ref. 16 for identification of individual data points); (b) the variation in amines (see Ref. 3); (c) the variation in solvent (see Ref. 12).

presented previously for organic solvents,¹² Lewis acids,¹³ amines in the Willgerodt-Kindler reaction¹⁴ and for amino acids.^{11,15}

The "axes" in the reaction space describe "variations" in substrate, reagent and solvent. Provided that these can be characterized by property descriptors which we believe to be relevant, we can use the principal properties to quantitatively describe the systematic variation, i.e. the "axes" in the reaction space can be defined by the corresponding principal properties. These "axes" will be multi-dimensional, with more than one principal property.

Principal properties in the Willgerodt-Kindler reaction

The principles involved in exploring the reaction space are shown by an example employing the Willgerodt-Kindler reaction of *para*-substituted acetophenones.

Substrate variation can be described by the properties of the *para* substituent. A report¹⁶ on PC analysis of common empirical parameters for substituents on aromatic rings (σ_m^o , σ_p^o , σ_R^o , $\sigma^{+/-}$, E_s , π , MR) shows that substituents are clustered into four groups (donors, acceptors, alkyls and halogens). The same clustering is also found upon PC analysis of ¹³C NMR shifts measured for substituted benzenes.¹⁷ We therefore consider it safe to assume that PC projections of empirical substituent parameters really portray chemically

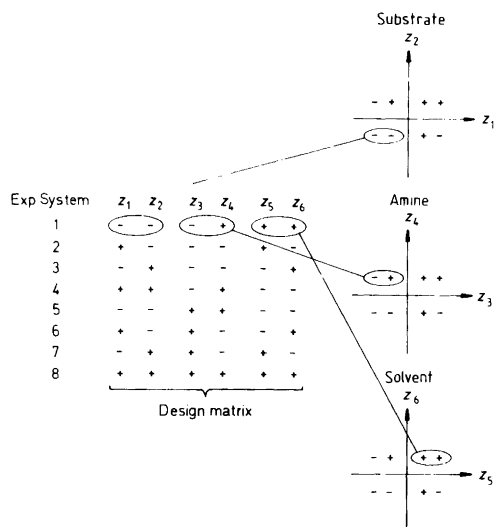


Fig. 4. Selection of test systems by a fractional factorial design in principal properties.

significant features of substituted aromatics. Hence, we can use the projection in Ref. 16 as measures of principal properties (see Fig. 3a).

We have previously found that *para*-acceptor-substituted acetophenones fail to give the Willgerodt-Kindler reaction product.⁴ For this reason, acceptor substituents were not included in the present study.

Amine reagent variation is described by a PC analysis given in Ref. 3. The PC projection is

Table 1. Optimum conditions for selected test systems.

Selected test systems ^a			Optimum conditions ^b			Yield ^c %
<i>para</i> -Substituent	Amine	Solvent	u_1	u_2	u_3	
Cl	Et ₂ NH	TEG ^d	8.4	5.3	123	89
H	<i>i</i> -PrNH ₂	Quinoline	10.3	4.8	133	89
OMe	<i>i</i> -PrNH ₂	EtOH	3.8	6.6	80	91
OPh	Et ₂ NH	Benzene	9.6	5.8	80	85
Cl	Pe ₂ NH ^e	Benzene	13.6	8.5	80	68
H	Morpholine	EtOH	3.7	13.4	80	86
OMe	Morpholine	Quinoline	9.3	8.9	130	100
OPh	Pe ₂ NH	TEG	13.0	8.3	118	73

^aBased on the design shown in Fig. 4. ^bDetermined by response surface modelling: u_1 is the ratio of sulfur/ketone (mol/mol), u_2 the ratio of amine/ketone (mol/mol) and u_3 the reaction temperature (°C). ^cDetermined by GLC (internal standard technique). ^dTriethylene glycol. ^eDipentylamine.

based on 29 primary and secondary amines characterized by seven descriptors (see Fig. 3b).

Solvent variation has been characterized by PC analysis of 82 solvents characterized by eight descriptors¹² (see Fig. 3c).

Design of experiments to explore the reaction space

In this reaction space there are a total of six principal properties to consider: two for each "axis" in the reaction space, i.e. the space is six-dimensional. To determine the scope of the reaction, it is essential that the test objects are selected so that they will cover the entire space as efficiently as possible. This means that test objects should be selected so as to lie close to the "corners" of the space (represented by a cube in Fig. 1). In the present case, the "cube" is six-dimensional and will thus have $2^6 = 64$ "corners". To determine the scope of the reaction, it is essential to make comparisons under optimized conditions.²⁻⁴ It is, however, rather cumbersome to optimize 64 different reaction systems, and to achieve a more manageable number of test systems we will use the principles of fractional factorial experimental design¹⁸ to select a sub-set of the 64 possible "corners" in such a way that this sub-set will span as much of the reaction space as possible. In three dimensions (see Fig. 1), this will correspond to a selection of four objects in the corners linked by the diagonals of the sides (these points will span a tetrahedron, which is the figure of largest volume that can be spanned by four points in three dimensions).

The 64 "corners" of the reaction space corre-

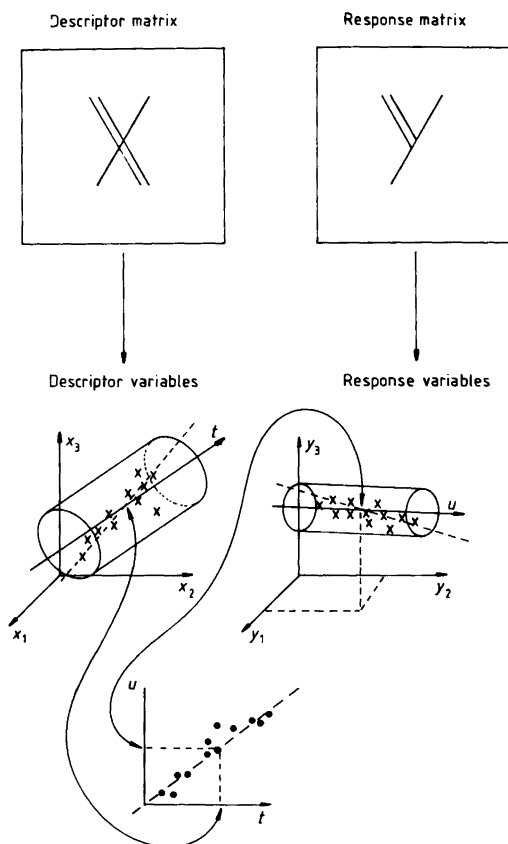


Fig. 5. PLS modelling: Quantitative relations between a descriptor matrix, X , and a response matrix, Y , are obtained by PLS decomposition of X and Y . The PLC components t and u are slightly tilted from PC vectors (dashed) to achieve a maximum correlation between the descriptor components, t_i , and the response components, u_i .

Table 2. PLS predictions of optimum conditions for new systems and experimental yields obtained under these conditions.

Test systems			Predicted optimum conditions ^a				Exptl. yield ^b /%
Substi-tuent	Amine	Solvent	u_1	u_2	u_3	Yield/%	
<i>p</i> -H	Et ₂ NH	EtOH	4.2	9.4	80	89	79
<i>p</i> -OMe	Et ₂ NH	Quinoline	8.4	5.0	130	98	83
<i>p</i> -Cl	Morpholine	TEG	10.4	9.0	118	84	86
<i>p</i> -OPh	Morpholine	Benzene	9.0	9.2	80	84	75

^aSee Table 1 for identification of u_1 – u_3 . ^bIsolated by flash chromatography.

spond to a complete two-level factorial design¹⁹ in the principal property variables. In such designs, each variable is investigated at two levels, viz. high (+) and low (-). A complete factorial design consists of all combinations of variables and levels. With six principal properties it is necessary to have at least seven test systems to span the reaction space (a simplex in six dimensions). A more easily applied approach is that in which a 2^{6-3} fractional factorial design¹⁸ is used to select a sub-set of eight test systems. The design matrix for a 1/8 fraction of the complete 2^6 factorial design in six principal property variables, z_1 - z_6 , is shown in Fig. 4. The variables describe the following variations: z_1, z_2 (substrate), z_3, z_4 (amine), z_5, z_6 (solvent). In the first test system (the first row in the design matrix) z_1 - z_6 have the levels (-, -, -, +, +, +). This will give the following combination: The substrate is (-, -), which means that it should be selected with both principal properties at low levels. This corresponds to selection of a substrate projected in the lower left quadrant in the PC projection (see Fig. 3). This substrate shall be combined with an amine (-, +), i.e. located in the upper left quadrant in the PC projection. The (-, -)-substrate and the (-, +)-amine shall be allowed to react in a (+, +)-solvent, i.e. a solvent projected in the upper right quadrant in the PC projection. These principles are illustrated in Fig. 4. In the second and subsequent test systems, other combinations of principal properties are selected according to the design matrix. Table 1 shows a series of test systems arrived at by application of these principles.

Results

Screening of the scope of the reaction. For each system in Table 1, the yields of thioamide were optimized with regard to the following experimental variables: u_1 , the amount of sulfur; u_2 , the amount of amine and u_3 , the reaction temperature. The optimum conditions were determined by response surface methods.²⁰ Doehlert uniform shell designs²¹ were used to establish the response surface models. The optimum conditions and yields obtained are shown in Table 1.

PLS modelling⁹ and predictions for new systems. PLS (Projections to Latent Structures) is a computational method for relating multivariate de-

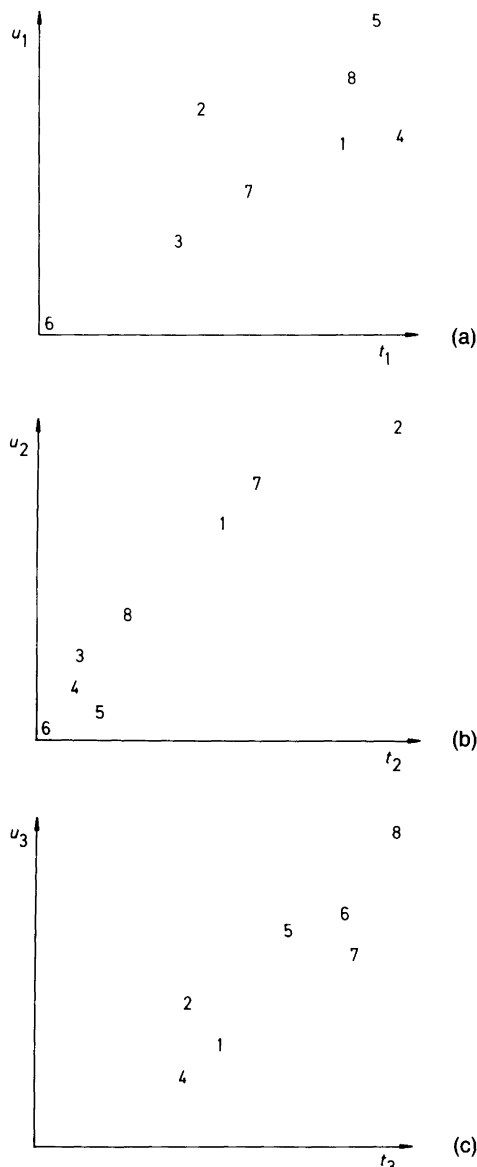


Fig. 6. PLS correlations between the properties of the reaction system (t -components) and the optimum conditions (u -components). The first three PLS components are shown.

scriptor data sets to multivariate response data sets. Thorough accounts of the method are given in the reference indicated; the following is only a brief outline of the principles.

In the present case, the descriptor set contains property descriptors for the systems and the re-

sponse data set contains the optimum conditions as specified by the experimental variables u_1 – u_3 and the optimum yield. For a series of systems this will give a descriptor data matrix, X , and a response data matrix, Y . A quantitative relation between these is established by a PC-like decomposition of the matrices X and Y , and a correlation between the models is thus obtained. These models are slightly tilted (biased) from ordinary PC models to achieve a maximum correlation between the components of the X -block and the components of the Y -block. A geometric illustration of the principles is shown in Fig. 5.

The results given in Table 1 were used as a calibration set to establish a PLS model which relates the properties of substrate, amine and solvent to the optimum conditions. Using the PLS model, optimum conditions for new, as yet untested systems were predicted. The test set for these predictions was selected among the remaining combinations of principal properties not used in the design in Table 1. The predictions of the PLS model and the yields obtained which validate the predictions are shown in Table 2. PLS correlations obtained from Table 1 are shown in Fig. 6. For PLS modelling, we have used the original complete data set of descriptors rather than the principal properties. The reason for this is that PLS models are stabilized by an increasing number of variables in the X -block.⁹

Discussion

Modern chemistry suffers from the "data explosion". Any chemical compound can be characterized by a number of descriptors; any single experiment can produce a multitude of quantitative observations. PC projections to principal properties provide a means of taking *all* available background information into account prior to designing experiments. In view of this, the results in Tables 1 and 2 show that the scope of the Willgerodt-Kindler reaction is very wide with regard to variations in substrate, amine and solvent, since the test systems were selected with a maximum spread in all properties considered.

The methodology outlined in this paper is general and can be extended to the investigation of any complex system. To the best of our knowledge, the present study is the first application of this general strategy to organic synthesis. A similar approach to drug design, based on substituent

parameters, has been suggested by Austel,²¹ and a refinement of this approach using principal properties as design variables has recently been described by Hellberg *et al.*¹¹

Experimental designs based on the use of tabulated substituent parameters to select test objects have also been used in kinetic studies on the solvolysis of Mannich bases,²³ on the Menschutkin reaction,²⁴ and for the study of stereoselectivity in the reduction of imino ketones.²⁵ However, these studies suffer from the weakness that the results have been analyzed and interpreted by multiple regression (MR) methods. In MR it is assumed *a priori* that the substituent parameters used as independent variables are: (a) 100% relevant to the phenomenon under study and (b) accurately known. This is equivalent to saying that properties measured in one system can *explain* the chemical behaviour of other systems.

Scope and limitations. In the example given in this paper, all selected test systems were found to give high to excellent yields of the desired product. This is an exception. In general, it is likely that some combinations of principal properties will fail. The next step in the investigation is then to select other candidates in the vicinity of the failing candidate to ensure that the failing combination really does constitute a limitation in the scope of the reaction.

Analysis within the PLS model can be used to obtain information about which of the properties that have an influence. This may give clues to interpretation of the results in mechanistic terms.

Conclusion and summary of the proposed methodology

This paper presents a new methodology for determining the scope of a synthetic reaction. The methodology allows all important factors to be considered before designing experiments. Using this approach the information content of individual experiments is increased, and by using proper designs for ensembles of experiments the methodology will lead to increased efficiency in experimentation. Another advantage is that the results thus obtained will be consistent, which is hardly the case at present.

The methodology can be summarized in a flow-sheet:

- (1) Define the problem.
- (2) Analyse the problem and identify factors that must be considered.
- (3) Compile relevant quantitative data that describe these factors.
- (4) Analyse the descriptors and determine the principal properties.
- (5) Span the system space by selecting test candidates defined by a proper design, e.g. fractional factorial design.
- (6) Run the experiments with the selected systems. If necessary, determine the optimum experimental conditions for each test system.
- (7) Analyse the result by PLS modelling and predict results for *new* systems.
- (8) Validate the predictions by experiments.
- (9) Draw conclusions: If a satisfactory result has been obtained then go to (10); if not, reformulate the problem and go to (1).
- (10) End; prepare a report.

Calculations and experimental

Calculations. Calculations were carried out on a Toshiba M15 (16-bit) micro-computer. The SIMCA program package (SIMCA 3B version) was used to obtain PC and PLS models. Response surface models used in optimization of the yields were calculated using the REGFAC program. These programs are available from SEPA-NOVA AB, Östrandsvägen 14, S-122 43 Enskede, Sweden. The SIMCA package is also available from Principal Data Components, Shepherd Blvd., Columbia, Missouri 65201, USA.

Chemicals. *p*-Substituted acetophenones were of commercial reagent grade and were used as delivered, with the exception of *p*-phenoxyacetophenone which was prepared by standard Friedel-Crafts acylation²⁶ of diphenyl ether with acetic anhydride. Amines were of commercial *puriss.* or *p.a.* grade and were dried over solid KOH. Solvents were of *p.a.* grade and were used as delivered, with the exception of quinoline which was distilled. Ketones, amines and solvents were pur-

chased from EGA or FLUKA. Sublimed sulfur from KEBO LAB was used as delivered.

Experimental procedures for GLC analyses and for the Willgerodt-Kindler reaction were as described previously in Ref. 2c.

Physical properties of new thioamides. ¹H NMR spectra were recorded on a Bruker AC-80 instrument (80 MHz) using deuteriochloroform as solvent.

p-Methoxyphenylacetic acid N,N-diethylthioamide: m.p. 64–65 °C; ¹H NMR: δ 0.87–1.36 (m, 6H), 3.33–3.61 (m, 2H), 3.76 (s, 3H), 3.85–4.03 (m, 2H), 4.22 (s, 2H), 6.89–7.01 (m, 2H), 7.86–8.01 (m, 2H).

p-Phenoxyphenylacetic acid thiomorpholide: m.p. 96–98 °C; ¹H NMR: δ 3.44–3.89 (m, 6H), 4.27 (s, 2H), 4.31–4.42 (m, 2H), 6.78–7.91 (m, 9H).

p-Chlorophenylacetic acid N,N-diethylthioamide: b.p. 192–196 °C; ¹H NMR: δ 0.95–1.39 (m, 6H), 3.38–3.61 (m, 2H), 3.81–4.07 (m, 2H), 4.23 (s, 2H), 7.23–7.31 (m, 4H).

p-Methoxyphenylacetic acid N-isopropylthioamide: m.p. 87–88 °C; ¹H NMR: δ 1.08–1.31 (m, 6H), 2.67 (s, 1H), 3.81 (s, 1H), 4.19 (s, 2H), 4.35–5.01 (m, 1H), 6.90–7.13 (m, 2H), 7.38–7.61 (m, 2H).

p-Phenoxyphenylacetic acid N,N-diethylthioamide: m.p. 57–59 °C; ¹H NMR: δ 1.01–1.20 (m, 6H), 2.62–2.88 (m, 2H), 3.14–3.61 (m, 2H), 3.82 (s, 2H), 6.85–7.80 (m, 9H).

p-Chlorophenylacetic acid N,N-dipentylthioamide: m.p. 65–67 °C; ¹H NMR: δ 0.85–0.97 (m, 6H), 1.03–1.54 (m, 12H), 2.81–3.45 (m, 4H), 3.54 (s, 2H), 7.26–7.31 (m, 4H).

p-Phenoxyphenylacetic acid N,N-dipentylthioamide: m.p. 100–102 °C; ¹H NMR: δ 0.85–1.03 (m, 6H), 1.18–1.59 (m, 12H), 3.56 (s, 2H), 3.69–4.01 (m, 2H), 6.81–7.78 (m, 9H).

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