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Links between the Theoretical Rate Law and the Experimental Response Surface. An Example with a Solvolysis Reaction

Anna-Karin Axelsson[†,a] and Rolf Carlson[b]

[a]National Defence Research Establishment, Department of NBC Defence, S-901 82 Umeå, Sweden and [b]Institute of Mathematical and Physical Sciences, University of Tromsø, N-9000 Tromsø, Norway

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The relation between a statistically determined experimental response surface model and a physical chemical model based on the Arrhenius equation is analyzed. As a model reaction, first-order ethanolysis of chlorodiphenylmethane (benzhydryl chloride) was used. A Taylor expansion approximation of the integrated kinetic model is derived and the coefficients thus determined are compared with the corresponding least-squares estimates of the experimental response surface.

Reaction profiles are often used in organic chemistry to describe the variation in the energetics along a reaction coordinate. The shape of the potential energy surface, i.e., how deep the minima are, how high the activation energy barriers are, depends on the detailed experimental conditions used as well as on the nature of the constituents of the entire reaction system (e.g., nature of reagents, solvent, catalysts, etc.). Models which describe the outcome of chemical reactions can ultimately be related back to the shape of the potential energy surface. Examples are provided by, for instance, extrathermodynamical models (linear free energy relationships).

One way to establish quantitative models which relate variation of the *experimental conditions* to the observed outcome of a chemical reaction is to use response surface models.[1] Such models are described by a Taylor expansion of the underlying 'theoretical' model. In many cases, however, such theoretical models are difficult to derive if the complexity of the system is also to be taken into account. It can nevertheless be safely assumed that the potential energy surfaces are smooth and that any 'theoretical' model derived from them is continuous and smooth in a limited experimental domain and that they can be differentiated in this domain.

The important point is that, even if an analytical expression of the underlying 'theoretical' model is not known, a Taylor expansion approximation can be established by the estimation of its coefficients from a properly designed set of experiments. This is the scientific background to response surface methodology in chemistry.

Response surface models are determined by regression methods to fit the model to observed experimental results. Such models are unfortunately often assumed to be purely empirical and that relationships between the estimated regression coefficients and chemical theory are weak. An early example of links between an 'empirical' response surface and the basic mechanism of a chemical reaction is given in a paper by Box and Youle.[2] In this paper it is also shown how a canonical analysis of the response surface model gives the relationship between the surface variables and the basic physical laws controlling the system.

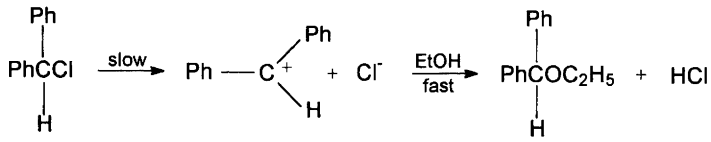
In this paper, we present another approach to show how a polynomial response surface model determined from experiment is related to a physical chemical model describing the kinetics of a chemical reaction. The reaction studied is the ethanolysis of chlorodiphenylmethane **1** for which a first-order kinetic law has been established.[3,4]

Results

Derivation of a response surface model from a kinetic model. Let $y = [\mathbf{P}]$ be the concentration of the solvolysis product, $[\mathbf{S}]_{\mathrm{INIT}}$ the initial concentration of chlorodiphenylmethane, k the specific rate of solvolysis, and let t be the reaction time (s). The integrated rate model for a reaction with first order kinetics, i.e., $-\mathrm{d}[\mathbf{S}]/\mathrm{d}t = \mathrm{d}[\mathbf{P}]/\mathrm{d}t = k[\mathbf{S}]$, will thus be eqn. (1).

$$y = [\mathbf{P}] = [\mathbf{S}]_{\mathrm{INIT}} - [\mathbf{S}]_{\mathrm{INIT}} \exp(-tk) \quad (1)$$

† To whom correspondence should be addressed.



1 2

Scheme 1.

The temperature dependence of the specific rate can be approximated by the Arrhenius equation (2).

$$k = A \exp(-E_a/RT) \tag{2}$$

A kinetic model which relates the observed yield y at the reaction time t as a function of the initial substrate concentration and reaction temperature [eqn. (3)] will thus follow from eqns. (1) and (2).

$$y = [\mathrm{S}]_{\mathrm{INIT}} - [\mathrm{S}]_{\mathrm{INIT}} \exp[-tA \exp(-E_a/RT)] \tag{3}$$

Assume that an analytical expression of the function, f, which relates the observed outcome of the reaction to the experimental variables is unknown. An approximation of f by a Taylor expansion can be derived as shown below. For convenience we will hereafter use response surface terminology and express the experimental variations by linearly scaled and zero-centered variables.[5]

The initial concentration of the substrate, $[\mathrm{S}]_{\mathrm{INIT}}$ is thus transformed into the design variable x_1 by the relation (4), where $[\mathrm{S}]_{\mathrm{AV}}$ is the average concentration of

$$x_1 = ([\mathrm{S}]_{\mathrm{INIT}} - [\mathrm{S}]_{\mathrm{AV}})/\Delta[\mathrm{S}] \tag{4}$$

substrate in the sets of experiments and $\Delta[\mathrm{S}]$ is the variation of substrate concentration corresponding to unit variations in x_1.

The scaled reaction temperature variance is given by x_2 by the relation (5), where T_{AV} is the average temperature

$$x_2 = (T - T_{\mathrm{AV}})/\Delta T \tag{5}$$

in the set of experiments and ΔT corresponds to unit variations in x_2.

By these transformations of the experimental variables eqn. (3) is transformed into eqn. (6).

$$y = ([\mathrm{S}]_{\mathrm{AV}} + \Delta[\mathrm{S}]x_1) - ([\mathrm{S}]_{\mathrm{AV}} + \Delta[\mathrm{S}]x_1) \times \exp\{-tA \exp[E_a/R(T_{\mathrm{AV}} + \Delta T x_2)]\} \tag{6}$$

Hence we see that the observed yield y is a function of the scaled variables x_1 and x_2 such that

$$y = f(x_1, x_2).$$

A Taylor expansion around the average experimental conditions $\boldsymbol{x} = (x_1, x_2) = (0, 0) = \mathbf{0}$ truncated after the second degree terms will be eqn. (7).

$$y = f(\mathbf{0}) = [\partial f(\mathbf{0})/\partial x_1]x_1 + [\partial f(\mathbf{0})/\partial x_2]x_2 + {}^1/_2[\partial^2 f(\mathbf{0})/\partial x_1 \partial x_2]x_1x_2 + {}^1/_2[\partial^2 f(\mathbf{0})/\partial x_1^2]x_1^2 + {}^1/_2[\partial^2 f(\mathbf{0})/\partial x_2^2]x_2^2 + R(\boldsymbol{x}) \tag{7}$$

The rest term, $R(\boldsymbol{x})$, contains the model error due to truncation. As y is an experimentally determined entity, it will be contaminated by a random experimental error e. At best, y will be an unbiased estimate of the true response η and $y = \eta + e$. If the model error $R(\boldsymbol{x})$ is significantly smaller than the random error e we will include these terms in an overall error term, ε.

A more convenient expression of eqn. (7) is eqn. (8),

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \varepsilon \tag{8}$$

which is the expression generally used in response surface modelling.

Differentiation of eqn. (6) with respect to x_i, yields expressions (9)–(14) for the partial derivatives which occur as coefficients in the response surface model eqn. (8)

$$\beta_0 = [\mathrm{S}]_{\mathrm{AV}} - [\mathrm{S}]_{\mathrm{AV}} \exp[-tA \exp(-E_a/RT_{\mathrm{AV}})] \tag{9}$$

$$\beta_1 = \Delta[\mathrm{S}] - \Delta[\mathrm{S}] \exp[-tA \exp(-E_a/RT_{\mathrm{AV}})] \tag{10}$$

$$\beta_2 = \{[\mathrm{S}]_{\mathrm{AV}}\, tAE_a\Delta T/R(T_{\mathrm{AV}})^2\} \exp(-E_a/RT_{\mathrm{AV}}) \times \exp[-tA \exp(-E_a/RT_{\mathrm{AV}})] \tag{11}$$

$$\beta_{12} = {}^1/_2(\{\Delta[\mathrm{S}]tAE_a\Delta T/R(T_{\mathrm{AV}})^2\} \exp(-E_a/RT_{\mathrm{AV}}) \times \exp[-tA \exp(-E_a/RT_{\mathrm{AV}})]) \tag{12}$$

$$\beta_{11} = 0 \tag{13}$$

$$\beta_{22} = {}^1/_2\{[\mathrm{S}]_{\mathrm{AV}}\, tAE_a(\Delta T)^2/R(T_{\mathrm{AV}})^3\} \exp(-E_a/RT_{\mathrm{AV}}) \times \exp[-tA \exp(-E_a/RT_{\mathrm{AV}})] * \{-2 + E_a/RT_{\mathrm{AV}} - tAE_a/RT_{\mathrm{AV}}[\exp(-E_a/RT_{\mathrm{AV}})]\} \tag{14}$$

Experimental response surface. The solvolysis experiments were carried out varying the initial concentration x_1, of chlorodiphenylmethane (0.0159 M–0.0441 M) and the reaction temperature x_2 (18.0°C–32.1°C) according to a central composite rotatable response surface design.[6]

The experimental design and yields observed after 2 h are given in Table 1. The present reaction has been extensively studied in the past[4a–e] and for this reason, es-

Table 1. Experimental design and observed responses y at time t = 7200 s.

Entry	Variable[a] x_1	x_2	Response[b] $y \times 10^3$ experimental	Response $y \times 10^3$ ESSAI
1	−1	−1	3.28	3.21
2	1	−1	5.21	6.42
3	−1	1	9.26	9.04
4	1	1	17.20	18.09
5	−1.414	0	6.39	4.40
6	1.414	0	12.20	12.20
7	0	−1.414	3.56	3.98
8	0	1.414	15.69	15.68
9	0	0	7.78	8.32
10	0	0	7.70	
11	0	0	6.70	
12	0	0	8.17	

[a] x_1, concentration of chlorodiphenylmethane $[S]_{INIT}$: −1.414 = 0.0159 M; −1 = 0.02 M; 0 = 0.03 M, $[S]_{AV}$; 1 = 0.04 M; 1.414 = 0.0441 M. x_2, reaction temperature T: −1.414 = 291.15 K; −1 = 293.15 K; 0 = 298.15 K, T_{AV}; 1 = 303.15 K; 1.414 = 305.25 K. [b] Responses y (mM).

timates of the specific rate, k, as well as estimates of the Arrhenius activation energy, E_a, and the Arrhenius pre-exponential factor A were known from the literature. In our study we have used values of these parameters, given in the paper by Baddeley *et al.*[4a] for computing the specific rates at the temperature used in the response surface study; $E_a = 91.2766$ kJ mol^{-1} and $A = 4.47 \times 10^{11}$.

With a view to comparing the experimental yields observed we also computed yields predicted from the integrated rate model to check whether or not the first-order rate model was adequate. These results are also given in Table 1. The computer program ESSAI[7] was used for this.

Response surface parameters. From the experimental design and the yields given in Table 1, estimates of the response surface parameters were obtained by multiple linear least-squares regression.[1] 'Theoretical' values of the Taylor expression derived response surface parameters were computed by entering the known values of the Arrhenius parameters, the scaling variables from the experimental design, eqn. (4) and (5) and the reaction time into the expression in eqns. (9)–(14). The results are summarized in Table 2.

Table 2. Estimated Taylor parameters $b(i)$ at time t=7200 s.

Parameter	Estimated values $b(i) \times 10^3$ based on: Response surface model	Arrhenius model	ESSAI
b_0	7.59±0.81[a]	8.76	8.32
b_1	2.26±0.57	2.96	2.91
b_2	4.39±0.57	4.77	4.26
b_{12}	1.50±0.81	1.46	1.46
b_{11}	0.67±0.64	0	0.02
b_{22}	0.84±0.64	1.67	0.79

[a] Estimated 95% confidence limits are given.

Discussion

The good agreement between experimental and calculated yields in Table 1 shows that the assumption of first-order kinetics is justified and that the Arrhenius parameters, E_a and A, used to determine the simulation models give good predictions. From these results we conclude that the Arrhenius parameters could safely be used to parametrize the expressions of the Taylor coefficients [eqn. (9)–(14)]. A more accurate kinetic description of a chemical reaction's behavior could have been accomplished using a more sophisticated model,[8,9] for example the Eyring transition-state model that includes the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. However, the expression for the partial derivatives would be considerably more complicated and for our purpose, a simple model such as the Arrhenius equation was sufficient.

The experimental response surface parameters in Table 2 are close to those obtained from the derivations of the kinetic model. The response surface estimate of the constant term β_0, the linear coefficients β_1 and β_2 and the interaction term β_{12} are in good agreement with the theoretical values, whereas the coefficient of the second degree term, β_{22}, shows a slightly greater deviation. This was not unexpected when it is considered that the Arrhenius equation is a linear relation between the logarithm of the specific rate and the reciprocal temperature.

Eqns. (9)–(14) give an analytical expression of the response surface parameters. These relations are expressed in the experimental scaling parameters and the Arrhenius parameters and it is, therefore, in principle, possible to interpret them in 'chemical' terms. These equations for the partial derivatives can be rewritten in the form given below [eqns. (15)–(20)]. In these expressions we have introduced the rate constant at the experimental centerpoint k_{AV} (consistent with the rate at T_{AV}) and $[S]_{AV}$, $\Delta[S]$, T_{AV} and ΔT.

$$\beta_0 = [S]_{AV} - [S]_{AV} \exp(-tk_{AV}) \quad (15)$$

$$\beta_1 = \Delta[S] - \Delta[S] \exp(-tk_{AV}) \quad (16)$$

$$\beta_2 = [S]_{AV} [\ln(A/k_{AV})] (\Delta T/T_{AV}) tk_{AV} \exp(-tk_{AV}) \quad (17)$$

$$\beta_{12} = {}^1/_2[\ln(A/K_{AV})] (\Delta T/T_{AV}) tk_{AV} \Delta[S] \exp(-tk_{AV}) \quad (18)$$

$$\beta_{11} = 0 \quad (19)$$

$$\beta_{22} = {}^1/_2[S]_{AV}(\Delta T/T_{AV})^2[\ln(A/k_{AV})] (tk_{AV}) \times \exp(-tk_{AV}) \times \{-2 + [\ln(A/k_{AV})] - [\ln(A/k_{AV})]tk_{AV}\} \quad (20)$$

From the Arrhenius equation it follows that eqn. (21) is valid.

$$E_a/RT = \ln(A/k_{AV}) \quad (21)$$

We interpret the entity $\ln(A/k_{AV})$ as a description of the number of successful collisions leading to transformation into product.

The constant term, β_0, is as expected the yield at time t under the experimental conditions defined by the central point of the design, $[S]_{AV}$ and T_{AV}.

The linear concentration term, β_1, describes the change in yield caused by the change in concentration.

The linear temperature term, β_2, describes how the average rate k_{AV} is modified by the function $\ln(A/k_{AV})$ at the average concentration and the relative change $\Delta T/T_{AV}$ of the temperature variance.

The interactive term, β_{12}, describes how the yield at time t is modified by the change in rate caused by variance in the experimental conditions, i.e., reaction temperature $\Delta T/T_{AV}$ and the concentration $\Delta[S]$.

The second degree concentration term, β_{11}, is zero. This is expected since the reaction is first order.

The second degree temperature term, β_{22}, is quite complex and contains several coefficients. An attempt to describe these is as follows. The yield is influenced by the modification on the rate k_{AV} by a square factor of the relative temperature change $(\Delta T/T_{AV})^2$. However, this is further modified by terms taking into account the exponential change of the concentration and the change of the rate due to the experimentally changing concentration.

The sometimes heard assertion that response surface modelling in chemistry is just purely empiricism with no relation theory is therefore shown to be unjustified.

Conclusions

This paper has demonstrated how a statistically determined model, a response surface, describing the variation in observed yield in a chemical reaction is related to a kinetic model for the same reaction. As response surface models are Taylor expansion approximates of the underlying 'theoretical' model, it is clear that response surface methodology has a sound scientific foundation. Our results show that the coefficients of the response surface model have well defined physical meanings and response surfaces should therefore be regarded as semiempirical models.

Experimental

Computations. The MODDE package (Umetri AB, P.O. Box 7960, S-907 19 Umeå, Sweden) was used for fitting the experimental response surfaces. ESSAI,[7] a program developed in-house was used for comparing the expected yield from the rate model.

Chemicals. Chlorodiphenylmethane (benzhydryl chloride), 98%, from Jansen was used as delivered; cyclohexylbenzene, internal standard on GLC, from Aldrich was fractionally distilled under reduced pressure. Ethanol, 99.5%, from Kemetyl was dried by the method of Lund and Bjerrum[10] and stored over 3 Å molecular sieves under an argon atmosphere.[11]

Equipment. The reaction temperature was adjusted using a temperature control device from Neslab Instruments Inc. (25 Nimble Hill Road, Newington, New Hampshire 03801, USA) with the following components: Agitainer Insulated Container (A), Digital Exatrol, Cryoflow Pump Assembly and Cryocool Immersion Cooler.

GLC analysis. A Carlo-Erba Fractovap 4130 gas chromatograph equipped with FID and a CP Sil-8 fused silica capillary column (0.22 mm i.d. × 25 m) was used, operating isothermally at 200 °C.

Experimental conditions for the solvolysis reaction. The calculated amount of chlorodiphenylmethane corresponding to x_1 (Table 1) and an accurately weighed amount of cyclohexylbenzene (internal standard), ca. 100 mg, was kept under argon in a three-necked 50 ml conical flask equipped with a moisture-protected reflux condenser, mechanical agitator and a glass stopper and was immersed in the thermostat. Super-dry ethanol, in a sealed test tube, was also kept in the thermostat to achieve temperature equilibrium at temperature x_2 (Table 1). The flask was charged in one amount with the calculated amount of the ethanol reagent. The reaction was allowed to proceed with stirring and a 0.75 ml sample was withdrawn after 2 h. The sample was quenched by being shaken in a two-phase system of water–hexane, 1 ml of each. The hexane layer was washed twice with 1 ml of water, dried with anhydrous $CaCl_2$ to remove any traces of water and ethanol and subsequently transferred to a 2 ml vial containing 3 Å molecular sieves. This solute was analyzed by GC. With these precautions the samples were stable over time and yielded reproducible analyses.

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