ORIGINAL SCIENTIFIC PAPER

Croat. Chem. Acta **2024**, *97*(1), 1–14

DOI: 10.5562/cca4052

Intriguing Properties of Three-factor Cross-reaction Series. Isoparametricity and Non-interaction Phenomena

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RECEIVED: November 30, 2023 ✯ REVISED: March 25, 2024 ✯ ACCEPTED: March 26, 2024

Abstract: This article summarizes the results of a systematic study by the method of cross-correlation analysis of the mutual influence of three variable factors (structure, temperature, and polarity of the medium) on the rates and activation parameters of nucleophilic substitution reactions at the benzoyl and benzyl electrophilic centers, as well as nucleophilic oxirane ring-opening reactions. Co-variation of three factors allowed to reveal the manifestation of various combinations of the second-order interaction of their effects, as well as the third-order interaction in the cross-reaction series. The conducted studies have shown that in the case of second-order interactions, cross-reaction series exhibit isoparametric properties, while third-order interactions manifest themselves in a specific way. This concerns the critical values of the parameters of the variable factors, at which the corresponding terms of three-parameter polylinear regressions disappear. Significant third-order interactions ensure the realization of the non-interaction phenomenon: at certain critical values, the corresponding second-order interaction coefficients become equal to zero, and after passing these critical values, the signs of these coefficients become opposite.

Keywords: nucleophilic substitution, kinetics, activation parameters, compensation effect, cross-correlation analysis, isoparametricity, non-interaction phenomenon.

INTRODUCTION

THE joint non-additive influence of two or more factors on kinetic, activation, thermodynamic, and other characteristics of chemical processes is estimated by multiparameter relationships based on the principle of polylinearity in the change of free energies.[1–5] If three factors are varied simultaneously in a reaction series, this makes it possible to test the manifestation of various combinations of second-order interactions of their effects, as well as third-order interaction. The combined influence of two factors *i* and *j* at a fixed parameter of the third factor *h* on the correlated value F_{ijh} can be described by the following equation:

$$F_{ijh} = F_{00h} + q_i^{0h}x_i + q_j^{0h}x_j + q_{ij}^{h}x_ix_j. \qquad (1)$$

Here F_{00h} is the value of F_{ijh} at randomly selected standard values of the parameters of factors *i* and *j*, for example, $x_i = 0$ and $x_j = 0$; q_i^{0h} and q_j^{0h} are the sensitivity coefficients toward x_i and x_j under standard conditions ($x_j = 0$, and $x_i = 0$, respectively); q_{ij}^{h} is the second-order cross-interaction coefficient, which reflects the perturbing (non-additive) effects of factors *i* and *j* at a fixed factor *h* (in this and the following equations the subscripts and superscripts refer to the variable and fixed factors, respectively, the index 0 indicates the zero value of the parameter of the corresponding factor).

Eq. (1) exhibits the isoparametric properties.[1,6] The presence of a cross term ($q_{ij}^{h} \neq 0$) enables to calculate two isoparametric points: $x_{i(j)}^{h} = -q_j^{0h}(q_{ij}^{h})^{-1}$ and $x_{j(i)}^{h} = -q_i^{0h}(q_{ij}^{h})^{-1}$ (hereinafter, the subscript in parentheses refers to the second variable factor). At these points the magnitude of F_{ijh} is the same, i. e., $F_{ijh} = F_{00h} - q_i^{0h}q_j^{0h}(q_{ij}^{h})^{-1}$, and remains constant when either the factor j at $x_{i(j)}^{h}$ ($q_j^{ih} = 0$), or the factor i at $x_{j(i)}^{h}$ ($q_i^{jh} = 0$), is varied.

In practice, the isoparametricity manifests itself as a zero value of the sensitivity coefficient for the effects of one of the factors in one-parameter correlations at an isoparametric value of the parameter of another factor. After passing through the isoparametric point, the sign of the corresponding sensitivity coefficient is inverted (isoparametricity paradox).[1]

The nucleophilic substitution reactions at benzoyl and benzyl carbon atoms, along with nucleophilic oxirane ring opening reactions have shown to be promising for the experimental investigation of isoparametricity in all its aspects.[3–5,7,8]

Chemical systems with three variable factors, in addition to the isoparametric properties, have special unique properties. Their attributes are the critical values of the parameters of the variables, at which the sensitivity of the system to the effects of one of the factors or to the joint effects of two factors disappears. This article summarizes the results of systematic studies of the above reactions with cross-variation of such three factors, as structure, temperature, and polarity of the medium.

Mathematical Aspects of Formal Three-parameter Polylinear Relationships

The isoparametricity discussed above is an attribute of two-parameter polylinear relationships like Eq. (1). The mathematical features of polylinear equations with three or more parameters have been considered previously.[9] Here, the focus will be on analyzing some of the striking properties of three-parameter polylinear relationships using Eq. (2) as an example.

$$F_{ijh} = F_{000} + q_i^{00}x_i + q_{ih}^{0}x_ix_h + q_j^{00}x_j + q_h^{00}x_h + q_{ij}^{0}x_ix_j + q_{jh}^{0}x_jx_h + q_{ijh}x_ix_jx_h \tag{2}$$

In Eq. (2) F_{000} is the magnitude of F_{ijh} at standard values of the parameters of the variable factors *i, j* and *h* ($x_i = x_j = x_h = 0$); q_i^{00}, q_j^{00} and q_h^{00} are the coefficients of the sensitivity toward x_i, x_j and x_h under standard conditions ($x_j = x_h = 0$, $x_i = x_h = 0$ and $x_i = x_j = 0$, respectively); q_{ij}^{0}, q_{ih}^{0} and q_{jh}^{0} are the second-order interaction coefficients at standard values of $x_h = 0$, $x_j = 0$ and $x_i = 0$; q_{ijh} is the third-order cross-interaction coefficient. From a physical point of view, the cross terms are disturbances that various factors exert on each other.

Eq. (2) is characterized by the critical values of the parameters of the variable factors, at which some of its terms vanish. Consider, for example, Eq. (2) in the following form:

$$F_{ijh} = F_{000} + q_i^{00}x_i + (q_j^{00} + q_{ij}^{0}x_i)x_j + (q_h^{00} + q_{ih}^{0}x_i)x_h + (q_{jh}^{0} + q_{ijh}x_i)x_jx_h \tag{3}$$

Now we can easily determine three critical values of the parameter x_i for which the corresponding expressions in the brackets become zero: at $x_i = x_{i(j)}^{CV} = -q_j^{00}(q_{ij}^{0})^{-1}$, $x_i = x_{i(h)}^{CV} = -q_h^{00}(q_{ih}^{0})^{-1}$, and $x_i = x_{i(jh)}^{CV} = -q_{jh}^{0}(q_{ijh})^{-1}$ the following parts of Eq. (3) are disappeared: $(q_j^{00} + q_{ij}^{0}x_i)x_j = [q_j^{00} - q_{ij}^{0}q_j^{00}(q_{ij}^{0})^{-1}]x_j = 0$, $(q_h^{00} + q_{ih}^{0}x_i)x_h = [q_h^{00} - q_{ih}^{0}q_h^{00}(q_{ih}^{0})^{-1}]x_h = 0$, $(q_{jh}^{0} + q_{ijh}x_i)x_jx_h = [q_{jh}^{0} - q_{ijh}q_{jh}^{0}(q_{ijh})^{-1}]x_jx_h = 0$. Consequently, at these critical values, there is no influence of the factors indicated in the subscript brackets on F_{ijh}. In other words, in the series of indicated critical values, the sensitivity parameters in Eq. (3) will go to zero at x_j, x_h and x_jx_h, respectively ($q_j^{ih} = 0$ at $x_i = x_{i(j)}^{CV}$, $q_h^{ij} = 0$ at $x_i = x_{i(h)}^{CV}$, and $q_{jh}^{i} = 0$ at $x_i = x_{i(jh)}^{CV}$). Moreover, when passing through the critical values, the sign inversion of the corresponding sensitivity coefficients is predicted. For example, the fragment $(q_j^{00} + q_{ij}^{0}x_i)x_j$ in Eq. (3) can be represented as $q_j^{i0}x_j$, where $q_j^{i0} = (q_j^{00} + q_{ij}^{0}x_i)$ is the coefficient of sensitivity to the effect from variable factor *j* by fixed factors *i* and *h*. As $q_j^{i0} = 0$ at the critical value $x_{i(j)}^{CV} = -q_j^{00}(q_{ij}^{0})^{-1}$, the passage through this critical value, where on the one hand $x_i > -q_j^{00}(q_{ij}^{0})^{-1}$ and on the other $x_i < -q_j^{00}(q_{ij}^{0})^{-1}$, will be accompanied by inversion of the sign q_j^{i0}, *i.e.,* a reversal of the order of influence of the factor *j* on the correlated quantity F_{ijh}. In a similar way, one can predict the sign inversion for other sensitivity coefficients in Eq. (2) when passing through the corresponding critical values.

Six more critical values of the parameters x_j and x_h in Eq. (2) can be predicted: $x_{j(i)}^{CV} = -q_i^{00}(q_{ij}^{0})^{-1}$, $x_{j(h)}^{CV} = -q_h^{00}(q_{jh}^{0})^{-1}$, $x_{j(ih)}^{CV} = -q_{ih}^{0}(q_{ijh})^{-1}$, $x_{h(i)}^{CV} = -q_i^{00}(q_{hj}^{0})^{-1}$, $x_{h(j)}^{CV} = -q_j^{00}(q_{jh}^{0})^{-1}$, $x_{h(ij)}^{CV} = -q_{ij}^{0}(q_{ijh})^{-1}$. It should be noted that critical values of the type $x_{j(i)}^{CV}$ consistent to isoparametric point $x_{j(i)}^{h}$ in two-factor relation like Eq. (1) with standard value of the parameter of third fixed factor *h* ($x_h = 0$, $x_{j(i)}^{CV} = x_{j(i)}^{0}$).

The critical values $x_{i(jh)}^{CV}$, $x_{j(ih)}^{CV}$ and $x_{h(ij)}^{CV}$ are of particular interest because at them the second-order interactions of the effects of the factors *j* and *h, i* and *h, i* and *j,* vanish, *i.e.,* $q_{jh}^{i} = 0$, $q_{ih}^{j} = 0$, $q_{ij}^{h} = 0$. For example, at $x_i = x_{i(jh)}^{CV} = -q_{jh}^{0}(q_{ijh})^{-1}$ the fragment $(q_{jh}^{0} + q_{ijh}x_i)x_jx_h$ in Eq. (3) becomes equal to zero$\{(q_{jh}^{0} + q_{ijh}x_i)x_jx_h = [q_{jh}^{0} - q_{ijh}q_{jh}^{0}(q_{ijh})^{-1}]x_jx_h = 0\}$ as a result of which the mutual effects of the factors *j* and *h* on F_{ijh} are not manifested: $F_{ijh} = F_{000} - q_i^{00}q_{jh}^{0}(q_{ijh})^{-1} + [q_j^{00} - q_{ij}^{0}q_{jh}^{0}(q_{ijh})^{-1}]x_j + [q_h^{00} - q_{ih}^{0}q_{jh}^{0}(q_{ijh})^{-1}]x_h$. Such critical values have been called the additivity points or the non-interaction points,[3] since at them there are additivity conditions for the influence of corresponding pair of variable factors on the magnitude F_{ijh}.

In connection with these paradoxical predictions of the properties of the three-parameter polylinear relationship at the critical values of the parameters of the variable factors *i, j, h* and after passing through them, the question arises: are they only manifestations of the mathematical properties of such formal relationships or do they appear as a physical reality in chemical processes? The answer to this question was obtained in a systematic study of the nucleophilic substitution reactions under three-factorial conditions.

Joint Effects of Three Variable Factors in Cross-reaction Series

1. Effects of Structural Factors

The total interaction of the effects of three structural factors is clearly manifested in the cross-reaction series, that includes the reactions of benzyl benzenesulfonates with anilines in a volumetric mixture of DMSO and THF (*v* : *v*, 1 : 3) at 293 K with variation of substituents X in the nucleophile, substituents Y in the benzyl part of the substrate and substituents Z in the leaving group (Scheme 1).[3]

$$\text{Y-C}_6\text{H}_4\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{-Z} + 2\ \text{X-C}_6\text{H}_4\text{NH}_2 \longrightarrow$$

$$\text{Y-C}_6\text{H}_4\text{CH}_2\text{NHC}_6\text{H}_4\text{-X} + \text{X-C}_6\text{H}_4\text{NH}_3^+\ \text{Z-C}_6\text{H}_4\text{SO}_3^-$$

$X (\sigma_X) = \text{4-NH}_2 (-0.66), \text{4-OMe} (-0.27), \text{H} (0);$

$Y (\sigma_Y) = \text{H} (0), \text{3-Cl} (0.37), \text{4-NO}_2 (0.78);$

$Z (\sigma_Z) = \text{4-Me} (-0.17), \text{H} (0), \text{4-Cl} (0.23), \text{3-NO}_2 (0.71).$

Scheme 1. Reactions of Y, Z-substituted benzyl benzenesulfonates with X-substituted anilines.

Since three factors were cross-varied simultaneously in these reactions, this made it possible to identify different combinations of the second-order interactions of the effects of two factors at a fixed parameter of the third factor. Eqs. (4 – 6) describe the combined effects of substituents X and Y, X and Z, Y and Z at fixed substituents Z, Y, and X, respectively.

$$\log k_{XYZ} = \log k_{00Z} + \rho_X{}^{0Z}\sigma_X + \rho_Y{}^{0Z}\sigma_Y + \rho_{XY}{}^{Z}\sigma_X\sigma_Y, \tag{4}$$

$$\log k_{XYZ} = \log k_{0Y0} + \rho_X{}^{Y0}\sigma_X + \rho_Z{}^{Y0}\sigma_Z + \rho_{XZ}{}^{Y}\sigma_X\sigma_Z, \tag{5}$$

$$\log k_{XYZ} = \log k_{X00} + \rho_Y{}^{X0}\sigma_Y + \rho_Z{}^{X0}\sigma_Z + \rho_{YZ}{}^{X}\sigma_X\sigma_Z. \tag{6}$$

The index 0 in Eqs. (4 – 6) refers to the standard substituents X, Y, Z = H ($\sigma_{X(Y,Z)} = 0$). The values of the coefficients of these equations calculated for various two-factor cross-reaction series with the use of kinetic data[3] are given in Table 1. Hereinafter, the accuracy of determining the correlation parameters was estimated in terms of the standard deviation *S*, which was determined by a statistical method from *n* experimental data points. Statistical processing of the experimental data was done at a confidence level of 0.95 (*r* -Pearson's coefficient of correlation, *R* – cross-correlation coefficient).

The presented results show the manifestation of second-order interactions of all possible types ($\rho_{XY}{}^{Z}$, $\rho_{XZ}{}^{Y,}$ $\rho_{YZ}{}^{X}$) in the cross-reaction series 1–10. A significant interaction between the effects of substituents X and Y ($\rho_{XY}{}^{Z}$) provides experimental evidence for the existence of the isoparametricity phenomenon. In reaction series 1 – 3 the isoparametric points $\sigma_{X(Y)}{}^{Z} = -\rho_Y{}^{0Z}(\rho_{XY}{}^{Z})^{-1}$ are observable and the transition through them were carried out with reversals of the order of substrate reactivity with respect to the influence of Y substituents in the benzyl moiety. For example, in reaction series 1 represented in Figure 1, the sign of $\rho_Y{}^{XZ}$ changes after passing through the isoparametric point $\sigma_{X(Y)}{}^{Z} = -0.39$ (Z = 4-Me): $\rho_Y{}^{XZ}$ ($r \geq 0.980$) = 0.18 ± 0.03, –0.111 ± 0.004, –0.20 ± 0.01 if X (σ_X) = 4-NH$_2$ (–0.66), 4-OMe (–0.27), H (0).[3]

It should be emphasized that the isoparametric point $\sigma_{Z(Y)}{}^{X} = 0.38$ (X = 4-NH$_2$) was realized in reaction series 8, as

Table 1. The coefficients of Eqs. (4 – 6)[a] and the isoparametric points $x_{i(j)}{}^{h}$ for two-factor cross-reaction series including the reactions of Y, Z-substituted benzyl benzenesulfonates with X-substituted anilines in a volumetric mixture of DMSO with THF (*v* : *v*) 1 : 3 at 293 K.[3]

RS[b]	Fixed Z (σ_Z)	log k_{00Z}	$\rho_X{}^{0Z}$	$\rho_Y{}^{0Z}$	$\rho_{XY}{}^{Z}$	$\sigma_{X(Y)}{}^{Z}$	$\sigma_{Y(X)}{}^{Z}$
1	4-Me (–0.17)	–3.46 ± 0.02	–2.09 ± 0.05	–0.23 ± 0.04	–0.59 ± 0.09	–0.39[c]	–3.54
2	H (0)	–3.14 ± 0.02	–2.06 ± 0.04	–0.24 ± 0.03	–0.51 ± 0.08	–0.47[c]	–4.04
3	4-Cl (0.23)	–2.68 ± 0.02	–2.13 ± 0.05	–0.25 ± 0.04	–0.40 ± 0.09	–0.62[c]	–5.32
4	3-NO$_2$ (0.71)	–1.73 ± 0.01	–2.02 ± 0.02	–0.32 ± 0.02	–0.38 ± 0.05	–0.84	–5.32
RS	Fixed Y (σ_Y)	log k_{0Y0}	$\rho_X{}^{0Y}$	$\rho_Z{}^{0Y}$	$\rho_{XZ}{}^{Y}$	$\sigma_{X(Z)}{}^{Y}$	$\sigma_{Z(X)}{}^{Y}$
5	H (0)	–3.13 ± 0.02	–2.08 ± 0.04	1.97 ± 0.04	0.06 ± 0.10	–	–
6	3-Cl (0.37)	–3.22 ± 0.02	–2.27 ± 0.04	1.96 ± 0.04	0.16 ± 0.07	–12.2	14.2
7	4-NO$_2$ (0.78)	–3.32 ± 0.01	–2.49 ± 0.03	1.90 ± 0.03	0.25 ± 0.09	–7.60	9.96
RS	Fixed X (σ_X)	log k_{X00}	$\rho_Y{}^{0X}$	$\rho_Z{}^{0X}$	$\rho_{YZ}{}^{X}$	$\sigma_{Y(Z)}{}^{X}$	$\sigma_{Z(Y)}{}^{X}$
8	4-NH$_2$ (–0.66)	–1.77 ± 0.01	0.11 ± 0.02	1.95 ± 0.03	–0.29 ± 0.06	6.72	0.38[c]
9	4-OMe (–0.27)	–2.54 ± 0.01	–0.13 ± 0.02	1.92 ± 0.02	–0.10 ± 0.05	24.0	–1.30
10	H (0)	–3.15 ± 0.01	–0.23 ± 0.01	1.99 ± 0.01	–0.14 ± 0.03	14.2	–1.64

[a] Cross-correlation coefficient $R \geq 0.999$.

[b] Reaction series.

[c] Experimentally observed isoparametric point.

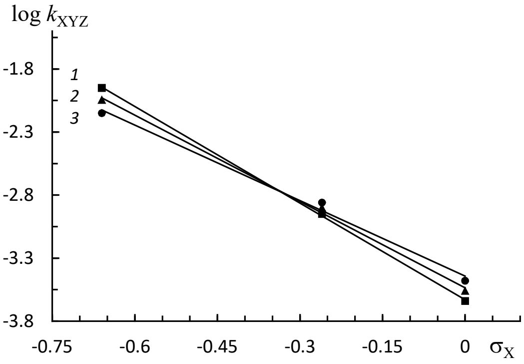


Figure 1. Transition through the isoparametric point $\sigma_{X(Y)}^Z$ = –0.39 (Z = 4-Me) in the reactions of Y, Z-substituted benzyl benzenesulfonates [Y = 4-NO$_2$ (*1*), 3-Cl (*2*), H (*3*)] with X-substituted anilines (reaction series 1 in Table 1).

shown in Figure 2. After passing this point, the order of substrate reactivity was reversed depending on the influence of Z substituents in the leaving group [ρ_Y^{XZ} ($r \geq 0.999$): 0.18 ± 0.03, 0.11 ± 0.01, 0, and –0.08 ± 0.01 for Z (σ_Z) = 4-Me (–0.17), H (0), 4-Cl (0.23), and 3-NO$_2$ (0.71)].[3]

According to the polylinearity principle the values of isoparametric points obtained by q_{ij}^h interaction of the effects of two cross-varied factors *i* and *j* turned out to be linearly dependent on the effects of a fixed factor *h*, Eq. (7).

$$x_{i(j)}^h = x_{i(j)}^0 + c_h x_h \tag{7}$$

Eqs. (8) and (9) demonstrate linear dependences of isoparametric points $\sigma_{X(Y)}^Z$ (reaction series 1–4) and $\sigma_{Z(Y)}^X$ (reaction series 8–10) on the effects of fixed substituents Z and X, respectively. Using these equations, we can quantitatively predict the conditions for the realization of these isoparametric points for a given value of the parameter of the fixed factors.

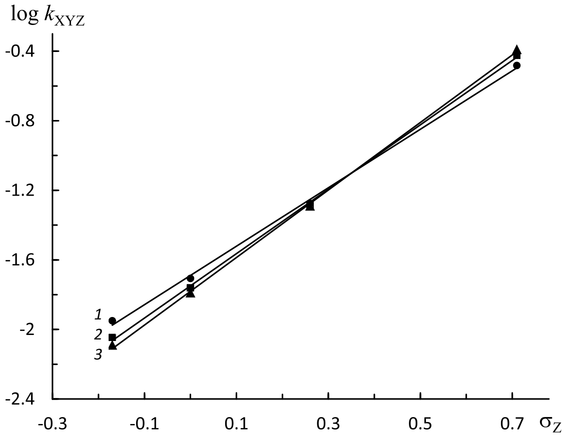


Figure 2. Transition through the isoparametric point $\sigma_{Z(Y)}^X$ = 0.38 (X = 4-NH$_2$) in the reactions of 4-NH$_2$-aniline with Y, Z-substituted benzyl benzenesulfonates [Y = 4-NO$_2$ (*1*), 3-Cl (*2*), H (*3*)] (reaction series 8 in Table 1).

$$\sigma_{X(Y)}^Z = (-0.48 \pm 0.01) + (-0.51 \pm 0.03)\sigma_Z \tag{8}$$

$S = 0.0059$, $r = 0.997$, $n = 4$.

$$\sigma_{Z(Y)}^X = (-1.8 \pm 0.3) + (-3.1 \pm 0.8)\sigma_X \tag{9}$$

$S = 0.966$, $r = 0.966$, $n = 3$.

Table 1 shows that the values of the second-order interaction coefficients ρ_{XY}^Z, ρ_{XZ}^Y, and ρ_{YZ}^X depend on the influence of the fixed substituents Z, Y, and X. This is indicative of complete non-additivity in the simultaneous effects of structural factors on the reactions under consideration, *i.e.,* there is a third-order interaction ρ_{XYZ}, which can be determined using the polylinear relationship, Eq. (10).

$$\log k_{XYZ} = \log k_{000} + \rho_X^{00}\sigma_X + \rho_Y^{00}\sigma_Y + \rho_Z^{00}\sigma_Z + \rho_{XY}^0\sigma_X\sigma_Y + \rho_{XZ}^0\sigma_X\sigma_Z + \rho_{YZ}^0\sigma_X\sigma_Z + \rho_{XYZ}\sigma_X\sigma_Y\sigma_Z. \tag{10}$$

When processing the results of a multifactorial kinetic experiment[3] using Eq. (10), the polylinear regression, Eq. (11), was obtained.

$$\log k_{XYZ} = (-3.13 \pm 0.01) + (-2.07 \pm 0.02)\sigma_X + (-0.25 \pm 0.02)\sigma_Y + (1.97 \pm 0.03)\sigma_Z + (-0.53 \pm 0.05)\sigma_X\sigma_Y + (0.05 \pm 0.06)\sigma_X\sigma_Z + (-0.14 \pm 0.05)\sigma_Y\sigma_Z + (0.25 \pm 0.06)\sigma_X\sigma_Y\sigma_Z. \tag{11}$$

$S = 0.022$, $R = 0.999$, $n = 36$.

Alternatively, according to the principle of polylinearity, the third-order interaction coefficient ρ_{XYZ} can be determined by the following relation:

$$\rho_{ij}^h = \rho_{ij}^0 + \rho_{ijh}\sigma_h. \tag{12}$$

For example, Eq. (13) shows a linear relationship between ρ_{XZ}^Y (reaction series 5–7) and σ_Y whose slope corresponds to the value ρ_{XYZ} = 0.25 ± 0.13 in Eq. (11).

$$\rho_{XZ}^Y = (-0.063 \pm 0.007) + (0.24 \pm 0.01)\sigma_Y \tag{13}$$

$S = 0.0000649$, $r = 0.998$, $n = 3$.

The regression under consideration is characterized by six critical values of type $x_{j(i)}^{CV}$: $\sigma_{X(Y)}^{CV} = -\rho_Y^{00}(\rho_{XY}^0)^{-1} = -0.47$, $\sigma_{X(Z)}^{CV} = -\rho_Z^{00}(\rho_{XZ}^0)^{-1} = -39.4$, $\sigma_{Y(X)}^{CV} = -\rho_X^{00}(\rho_{XY}^0)^{-1} = -3.90$, $\sigma_{Y(Z)}^{CV} = -\rho_Z^{00}(\rho_{YZ}^0)^{-1} = 14.1$, $\sigma_{Z(X)}^{CV} = -\rho_X^{00}(\rho_{XZ}^0)^{-1} = 41.4$, $\sigma_{Z(XY)}^{CV} = -\rho_{XY}^0(\rho_{XYZ})^{-1} = 2.12$. Some of them correspond to the isoparametric points $x_{i(j)}^h$ in Table 1 for reaction series 2, 5, and 10 with standard fixed substituents (Z, Y, X = H). For example, the isoparametric points $\sigma_{X(Y)}^Z$ = –0.47 and $\sigma_{Y(X)}^Z$ = –4.04 in reaction series 2 (Z = H) and the critical values $\sigma_{X(Y)}^{CV}$ = –0.47 and $\sigma_{Y(X)}^{CV}$ =–3.90 for the standard fixed substituent Z = H are in excellent agreement.

At critical values $\sigma_{X(YZ)}^{CV} = -\rho_{YZ}^0(q_{XYZ})^{-1} = 0.56$, $\sigma_{Y(XZ)}^{CV} = -\rho_{XZ}^0(q_{XYZ})^{-1} = -0.2$, and $\sigma_{Z(XY)}^{CV} = -\rho_{YZ}^0(q_{XYZ})^{-1} = 2.12$, the second-order interaction coefficients ρ_{YZ}^{X}, ρ_{XZ}^{Y}, and ρ_{XY}^{Z} should be equal to zero. Only the critical value $\sigma_{Y(XZ)}^{CV} = -0.2$ is experimentally achievable. At this critical value the fragment $\rho_{XZ}^{0}\sigma_X\sigma_Z + \rho_{XYZ}\sigma_X\sigma_Y\sigma_Z = (\rho_{XZ}^{0} + \rho_{XYZ}\sigma_Y)\sigma_X\sigma_Z$ in Eq. (10) turns into zero in discussed regression, Eq. (11) ($\sigma_Y = \sigma_{Y(XZ)}^{CV} = -0.2$): $[0.05 + 0.25(-0.2)]\sigma_X\sigma_Z = 0$, as a result, the interaction of the effects of substituents X and Z does not appear ($\rho_{XZ}^{Y} = 0$). The near-zero value of $\sigma_{Y(XZ)}^{CV}$ explains the statistical insignificance of the coefficient $\rho_{XZ}^{0} = (0.05 \pm 0.06)$ in Eq. (11). In this case, the interaction of the effects of the substituents X and Z disappears ($\rho_{XZ}^{0} = 0$) at the fixed standard substituent Y = H with a sigma constant ($\sigma_Y = 0$), which differs little from the critical value $\sigma_{Y(XZ)}^{CV} = -0.2$. At other fixed Y, the values of ρ_{XZ}^{Y} differ statistically from zero: in reaction series 5–7 (Table 1) $\rho_{XZ}^{Y} = 0.06 \pm 0.10$, 0.16 ± 0.07, 0.25 ± 0.09 when Y (σ_Y) = H (0), 3-Cl (0.37), 4-NO_2 (0.78).

It should be noted that similar three-factor cross-reaction series were studied by Soo-Dong Yoh et al. They included the reactions of substituted (Z)-benzyl (X)-benzenesulfonates with substituted (Y)-pyridines in acetonitrile at 35 °C[10] and reactions of the same benzyl substrates with substituted (Y)-N,N-dimethylanilines in acetone at 35 °C.[11] In these reaction series the interactions of the effects of substituents X and Y, as well as Y and Z are noticeably manifested. So, the rates of reactions involving pyridines are described by the equation $\log k_{XYZ} - \lg k_{000} = 1.8\sigma_X - 2.0\sigma_Y - 0.86\sigma_Z + 0.15\sigma_X\sigma_Y - 0.58\sigma_Y\sigma_Z - 0.02\sigma_X\sigma_Z + 0.04\sigma_X\sigma_Y\sigma_Z$. Reactions involving N,N-dimethylanilines are characterized by $\rho_{XY} = 0.21$, $\rho_{YZ} = -0.50$, $\rho_{XZ} = -0.06$. However, the isoparametric properties of these reactions have not been considered. Calculations show that their isoparametric characteristics and critical values of structural parameters go far beyond the limits of experimental achievability. For example, in the first reaction series $\sigma_{X(Y)}^{Z=H} = \sigma_{X(Y)}^{CV} = 13$, $\sigma_{Y(X)}^{Z=H} = \sigma_{Y(X)}^{CV} = -12$, $\sigma_{Y(Z)}^{X=H} = \sigma_{Y(Z)}^{CV} = -1.5$, $\sigma_{Z(Y)}^{X=H} = \sigma_{Z(Y)}^{CV} = -3.5$.

2. Effects of Structure and Temperature

In reactions of Y-substituted benzyl benzenesulfonates (Z = H) with X-substituted anilines in a volumetric mixture of DMSO with THF (*v* : *v*, 1 : 3) at 293, 303, and 313 K (Scheme 1) the total interaction of the structure (substituents X and Y) and temperature effects is manifested.[3] The second-order interactions of the effects of the variable factors were estimated by Eqs. (14 – 16).

$$\log k_{XYT} = \log k_{00T} + \rho_X^{0T}\sigma_X + \rho_Y^{0T}\sigma_Y + \rho_{XY}^{T}\sigma_X\sigma_Y, \quad (14)$$

$$\log k_{XYT} = \log k_{0Y0} + \rho_X^{Y0}\sigma_X + q_T^{Y0}\tau_T + q_{XT}^{Y}\sigma_X\tau_T, \quad (15)$$

$$\log k_{XYT} = \log k_{X00} + \rho_Y^{X0}\sigma_Y + q_T^{X0}\tau_T + q_{YT}^{X}\sigma_Y\tau_T. \quad (16)$$

These equations consider the combined effects of substituents X and Y at a fixed temperature *T*, substituents X and *T* at a fixed substituent Y, and substituents Y and *T* at a fixed substituent X. In Eqs. (15) and (16) $\tau_T = (T^{-1} - 303^{-1})10^3$ is an operationally introduced temperature parameter [τ_T (*T*) = 0.113 (293 K), 0 (303 K), and –0.105 (313 K)]. The results of processing kinetic data[3] using Eqs. (14 – 16) are given in Table 2. They show the manifestation of all types of second-order interactions (ρ_{XY}^{T}, q_{XT}^{Y}, q_{YT}^{X}) in almost all cross-reaction series. Significant interaction of the effects of substituents X and Y (ρ_{XY}^{T}) at different temperatures provides experimental evidence for the existence of the isoparametric points $\sigma_{X(Y)}^{T} = -\rho_Y^{0T}(q_{XY}^{T})^{-1}$ in reaction series 1 [$\sigma_{X(Y)}^{T} = -0.47$ (*T* = 293 K)] and 2 [$\sigma_{X(Y)}^{T} = -0.68$ (*T* = 303 K)].

Table 2. The coefficients of Eqs. (14 – 16)(a) and the isoparametric points $x_{i(j)}^{h}$ for two-factor cross-reaction series including the reactions of Y-substituted benzyl benzenesulfonates Y-$C_6H_4CH_2OSO_2C_6H_5$ with X-substituted anilines X-$C_6H_4NH_2$ in a volumetric mixture of DMSO with THF (*v* : *v*) 1 : 3 at different temperatures.[3]

RS(b)	Fixed *T*	$\log k_{00T}$	ρ_X^{0T}	ρ_Y^{0T}	ρ_{XY}^{T}	$\sigma_{X(Y)}^{T}$	$\sigma_{Y(X)}^{T}$
1	293 K	–3.14 ± 0.02	–2.06 ± 0.04	–0.24 ± 0.03	–0.51 ± 0.08	–0.47(c)	–4.04
2	303 K	–2.84 ± 0.01	–2.01 ± 0.02	–0.17 ± 0.02	–0.25 ± 0.05	–0.68(c)	–8.04
3	313 K	–2.60 ± 0.01	–2.07 ± 0.01	–0.15 ± 0.01	–0.16 ± 0.01	–0.94	–12.9
RS	Fixed Y (σ_Y)	$\log k_{0Y0}$	ρ_X^{0Y}	q_T^{0Y}	q_{XT}^{Y}	$\sigma_{X(T)}^{Y}$	$\tau_{T(X)}^{Y}$
4	H (0)	–2.84 ± 0.01	–2.02 ± 0.01	–2.26 ± 0.03	0	–	–
5	3-Cl (0.37)	–2.93 ± 0.01	–2.15 ± 0.03	–2.62 ± 0.12	–0.31 ± 0.28	–6.94	–8.45
6	4-NO_2 (0.78)	–3.00 ± 0.01	–2.28 ± 0.02	–2.76 ± 0.12	–1.21 ± 0.29	–2.28	–1.88
RS	Fixed X (σ_X)	$\log k_{X00}$	ρ_Y^{0X}	q_T^{XO}	q_{YT}^{X}	$\sigma_{Y(T)}^{X}$	$\tau_{T(Y)}^{X}$
7	4-NH_2 (–0.66)	–1.51 ± 0.01	0.01 ± 0.02	–2.53 ± 0.11	0.71 ± 0.22	3.56	–0.01(c)
8	4-OMe (–0.27)	–2.30 ± 0.01	–0.10 ± 0.01	–2.35 ± 0.06	0	–	–
9	H (0)	–2.86 ± 0.01	–0.19 ± 0.02	–2.51 ± 0.11	–0.38 ± 0.12	–6.61	–0.50

(a) Cross-correlation coefficient *R* ≥ 0.995.

(b) Reaction series.

(c) Experimentally observed isoparametric point.

Due to the interaction of the effects of substituents Y and temperature the isoparametric point $\tau_{T(Y)}^{X} = -\rho_Y^{X0}(q_{YT}^{X})^{-1} = -0.01$ (T = 304 K) is realized in reaction series 7 (fixed X = 4-NH$_2$). This point practically coincides with the standard value of the temperature factor $\tau_T = 0$, corresponding to an experimental temperature of 303 K. At this temperature the reaction rate should not depend on the effects of the substituents Y, which is observed:[3] log k_{YT}^{X} (X = 4-NH$_2$, T = 303) = –1.53, –1.53, –1.52 when Y = H, 3-Cl, 4-NO$_2$ ($\rho_Y^{XT} = 0$).

Eqs. (17) and (18) show perfect linear dependences of the isoparametric points $\sigma_{X(Y)}^{T}$ and $\sigma_{Y(X)}^{T}$ (reaction series 1–3) on the effects of a fixed temperature, which makes it possible to quantitatively predict their values at any temperature.

$$\sigma_{X(Y)}^{T} = (-0.70 \pm 0.01) + (-2.1 \pm 0.2)\tau_T \tag{17}$$

S =0.000753, r = 0.997, n = 3.

$$\sigma_{Y(X)}^{T} = (-8.43 \pm 0.28) + (-40.6 \pm 3.1)\tau_T \tag{18}$$

S =0.131, r = 0.997, n = 3.

It should be noted that the cross-interaction coefficients ρ_{XY}^{T}, q_{XT}^{Y}, and q_{YT}^{X} depend on the fixed substituents X, Y, and temperature. This is indicative of a total interaction of the effects of three variable factors, *i.e.,* their third-order interaction, which can be determined using the polylinear relationship, Eq. (19).

$$\log k_{XYT} = \log k_{000} + \rho_X^{00}\sigma_X + \rho_Y^{00}\sigma_Y + q_T^{00}\tau_T + \rho_{XY}^{0}\sigma_X\sigma_Y + q_{XT}^{0}\sigma_X\tau_T + q_{YT}^{0}\sigma_X\tau_T + q_{XYT}\sigma_X\sigma_Y\tau_T \tag{19}$$

The treatment of the experimental data[3] by Eq. (19) gave a polylinear regression, Eq. (20), adequately describing the reactivity of the considered cross-reaction series.

$$\log k_{XYT} = (-2.85 \pm 0.01) + (-2.02 \pm 0.02)\sigma_X + (-0.19 \pm 0.01)\sigma_Y + (-2.42 \pm 0.08)\tau_T + (-0.33 \pm 0.03)\sigma_X\sigma_Y + (0.11 \pm 0.18)\sigma_X\tau_T + (-0.44 \pm 0.16)\sigma_Y\tau_T + (-1.7 \pm 0.4)\sigma_X\sigma_Y\tau_T \tag{20}$$

S = 0.0156, R = 0.999, n = 27.

Of the six critical values of type $x_{i(j)}^{CV}$, only one, namely $\sigma_{X(Y)}^{CV} = -\rho_Y^{00}(\rho_{XY}^{0})^{-1} = -(-0.19)(-0.33)^{-1} = -0.58$, was experimentally realized. Its magnitude agrees with the value of the isoparametric point $\sigma_{X(Y)}^{T} = -0.68$ in the standard reaction series 2 (T =303 K, τ_T = 0) (Table 2). At this critical value the fragment $\rho_Y^{00}\sigma_Y + \rho_{XY}^{0}\sigma_X\sigma_Y = (\rho_Y^{00} + \rho_{XY}^{0}\sigma_X)\sigma_Y$ of Eq. (19) is equal to zero in regression, Eq. (20) ($\sigma_X = \sigma_{X(Y)}^{CV} = -0.58$): $[(-0.19 + (-0.33)(-0.58)]\sigma_Y = 0$, so that the effects of substituents Y do not appear ($\rho_Y^{X0} = 0$).

At the critical values $\tau_{T(XY)}^{CV} = -\rho_{XY}^{0}q_{XYT}^{-1} = -0.19$ (T = 321 K), $\sigma_{Y(XT)}^{CV} = -q_{XT}^{0}q_{XYT}^{-1} = 0.06$, and $\sigma_{X(YT)}^{CV} = -q_{YT}^{0}q_{XYT}^{-1} = -0.26$ the corresponding cross-interaction coefficients ρ_{XY}^{0}, q_{XT}^{0}, q_{YT}^{0} in Eq. (20) should disappear, *i.e.,* the second-order interaction of the structural effects as well as structure and temperature effects should not be manifested. This non-interaction phenomenon is indeed experimentally observed at the critical values $\sigma_{Y(XT)}^{CV} = 0.06$ and $\sigma_{X(YT)}^{CV} = -0.26$. Thus, the statistical insignificance of the coefficient $q_{XT}^{0} = 0.11 \pm 0.18$ in the regression, Eq. (20), can be explained by the fact that in reactions involving the standard substrate (Y = H), the sigma constant of substituent Y ($\sigma_Y = 0$) practically coincides with the critical value $\sigma_{Y(XT)}^{CV} = 0.06$ at which $q_{XT}^{0} = 0$. Along with this, outside of this critical value, the magnitude of q_{XT}^{Y} differs significantly from zero. The values of q_{XT}^{Y} in reaction series 4–6 (Table 2) change in magnitude when passing from one fixed substituent Y to another: q_{XT}^{Y} = 0, –0.31, –1.21 when Y (σ_Y) = H (0), 3-Cl (0.37), 4-NO$_2$ (0.71). A linear relationship exists between q_{XT}^{Y} and σ_Y: $q_{XT}^{Y} = (0.10 \pm 0.25) + (-1.7 \pm 0.5)\sigma_Y$ (r = 0.975). The angular slope (–1.7 ± 0.5) of this dependence is equal to the value of third-order interaction coefficient ρ_{XYT} = (–1.7 ± 0.4) in Eq. (20) in accordance with the principle of polylinearity.

Reaction series 7–9 (Table 2) as well as Figure 3 show an inversion of the sign of q_{YT}^{X} in the series of fixed substituents X upon passing through the non-interaction point $\sigma_{X(YT)}^{CV} = -0.26$ [q_{YT}^{X} = 0.71 ± 0.22, 0, –0.38 ± 0.12 when X (σ_X) = 4-NH$_2$ (–0.66), 4-OMe (–0.27), H (0)]. An excellent linear relationship is observed between the cross-interaction coefficients q_{YT}^{X} and the values σ_X of the fixed substituents X: $q_{YT}^{X} = (-0.39 \pm 0.03) + (-1.66 \pm 0.08)\sigma_{X(YT)}^{CV}$ (r = 0.999). The angular slope of this relationship corresponds to the third-order interaction coefficient q_{XYT} = (–1.7 ± 0.4) in regression, Eq. (20).

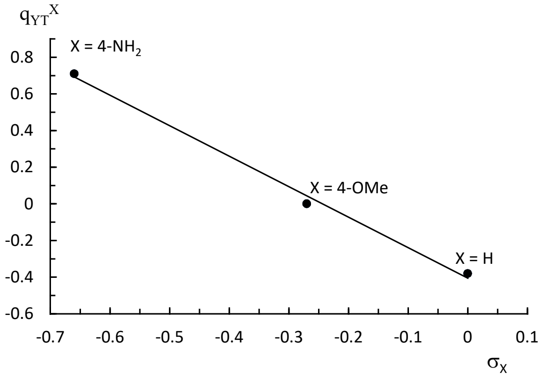


Figure 3. Inversion of the sign of the cross-interaction coefficient q_{YT}^{X} which estimates the non-additive effects of substituents Y and temperature T at different fixed substituents X in reaction series 7 – 9 (Table 2), when passing through the non-interaction point $\sigma_{X(YT)}^{CV} = -0.26$, where $q_{YT}^{X} = 0$.

Thus, for the first time in the history of chemistry, the mathematically predicted change in the sign of the second-order cross-interaction coefficient after the transition of the critical value of the parameter of fixed variables was confirmed experimentally.

The combined effects of structure and temperature were studied in the reactions of X-substituted anilines with Y-substituted benzoyl bromides in benzene at 283, 298, 313, and 328 K (Scheme 2).[12]

$$\text{Y-C}_6\text{H}_m\text{COBr} + 2\ \text{X-C}_6\text{H}_m\text{NH}_2 \xrightarrow{T} \text{Y-C}_6\text{H}_m\text{CONHC}_6\text{H}_m\text{-X} + \text{X-C}_6\text{H}_m\text{NH}_3{}^+\text{Br}^-$$

Y (σ_Y) = H (0), 3-Cl (0.37), 3-NO_2 (0.71) (m = 4); 3,5-Me_2 (-0.14) (m = 3).
X (σ_X) = 3-COOMe (0.26), 3-Cl (0.37), 3-NO_2 (0.71) (m = 4); 3,5-$(COOMe)_2$ (0.52), 3-NO_2-5-COOMe (0.97) (m = 3).
T = 283, 298, 313, 328 K.

Scheme 2. Reactions of Y-substituted benzoyl bromides with X-substituted anilines at different temperatures.

The third-order interaction of the effects of the variable factors was estimated by the polylinear regression, Eq. (21), the coefficients of which were calculated using data from a multifactorial kinetic experiment.[12] The temperature T = 298 K was selected as the standard for calculating the temperature parameter $\tau_T = (T^{-1} - 298^{-1})10^3$ [τ_T (T) = 0.177 (283 K), 0 (298 K), –0.161 (313 K), and –0.307 (328 K)].

$$\begin{aligned}\log k_{XYT} &= (0.59 \pm 0.09) + (-2.95 \pm 0.03)\sigma_X + \\ &(1.01 \pm 0.05)\sigma_Y + (-0.94 \pm 0.09)\tau_T + \\ &(-0.71 \pm 0.08)\sigma_X\sigma_Y + (-0.79 \pm 0.19)\sigma_X\tau_T + \\ &(0.35 \pm 0.28)\sigma_Y\tau_T + (-0.34 \pm 0.46)\sigma_X\sigma_Y\tau_T \qquad (21)\end{aligned}$$

S = 0.052, R = 0.998, n = 72.

The statistical characteristics of this regression indicate the absence of third-order interactions (q_{XYT} = –0.34 ± 0.46) in the cross-reaction series. The reason for this is the lack of interaction between the effects of substituents Y and temperature ($q_{YT}{}^0$ = 0.35 ± 0.28). After excluding statistically unreliable cross-terms, Eq. (21) is simplified to Eq. (22).

$$\begin{aligned}\log k_{XYT} &= (0.60 \pm 0.05) + (-2.93 \pm 0.02)\sigma_X + \\ &(0.99 \pm 0.03)\sigma_Y + (-0.96 \pm 0.07)\tau_T + \\ &(-0.73 \pm 0.05)\sigma_X\sigma_Y + (-0.80 \pm 0.09)\sigma_X\tau_T \qquad (22)\end{aligned}$$

S = 0.056, R = 0.998, n = 72.

Only one critical value $\sigma_{X(Y)}{}^{CV}$ (τ_T =0, T = 298 K) = –(0.99)(–0.73)$^{-1}$ = 1.36 in Eq. (22) is experimentally achievable. At this critical value of the parameter σ_X = 1.36, the fragment (0.99 ± 0.03)σ_Y + (–0.73 ± 0.05)$\sigma_X\sigma_Y$ = [(0.99 ± 0.03) + (–0.73 ± 0.05)1.36]σ_Y is equal to zero, therefore the effects of substituents Y must not appear ($\rho_Y{}^{XT}$ = 0). The critical value $\sigma_{X(Y)}{}^{CV}$ = 1.36 corresponds to the isoparametric point $\sigma_{X(Y)}{}^{T}$ = 1.39 in the reactions of 3,5-dinitroaniline [X = 3,5-$(NO_2)_2$, σ_X =1.40] with benzoyl bromides in benzene at the standard temperature T =298 K.[12] As can be seen in Figure 4, the rate of these reactions does not depend on the Y substituents ($\rho_Y{}^{XT}$ = 0).

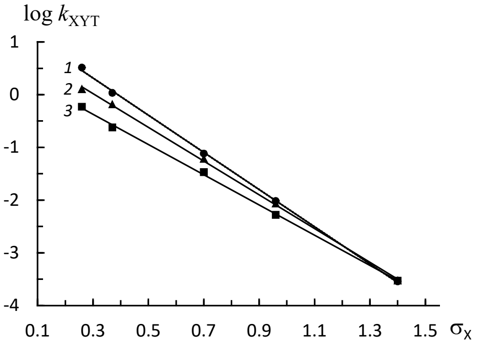
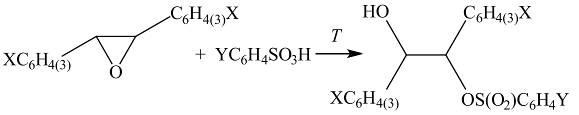


Figure 4. Intersection of the correlation lines in the coordinates of the Hammett equation at σ_X =1.40 [X = 3,5-$(NO_2)_2$] near the isoparametric point $\sigma_{X(Y)}{}^{T}$ = 1.39 (T = 298 K) in the reactions of X-substituted anilines with Y-substituted benzoyl bromides [Y = 3-NO_2 (*1*), 3-Cl (*2*), 3.5-$(CH_3)_2$ (*3*)] in benzene.[12]

In reactions of symmetrically X-substituted trans-2,3-diaryloxiranes with Y-substituted arenesulfonic acids in a mixture of dioxane with 1,2-dichloroethane (v : v, 7 : 3) (Scheme 3), the joint effects of the structure of the oxirane substrate and acidic reagent, as well as temperature were studied.[13–16]



X (ω_X) = H (0), 4-Br (2.02), 4-NO_2 (3.47), 3-Br-5-NO_2 (4.38);
Y (σ_Y) = 4-OMe (-0.27), 4-Me (-0.17), H (0), 4-Cl (0.23), 3-NO_2 (0.71).
T = 265, 281, 298 K;

Scheme 3. Reactions of symmetrically X-substituted *trans*-2,3-diaryloxiranes with Y-substituted arenesulfonic acids at different temperatures.

The following polylinear relationships were used to estimate the influence of two variable factors at a fixed parameter of the third factor:

$$\log k_{XYT} = \log k_{00T} + q_X{}^{0T}\omega_X + \rho_Y{}^{0T}\sigma_Y + q_{XY}{}^{T}\omega_X\sigma_Y, \qquad (23)$$

$$\begin{aligned}\log k_{XYT} &= \log k_{X0T=\infty} + \rho_Y{}^{XT=\infty}\sigma_Y + \\ &q_T{}^{X0}(10^3\,T^{-1}) + q_{YT}{}^{X}\sigma_Y(10^3\,T^{-1}), \qquad (24)\end{aligned}$$

$$\begin{aligned}\log k_{XYT} &= \log k_{0YT=\infty} + q_X{}^{YT=\infty}\omega_X + \\ &q_T{}^{0Y}(10^3\,T^{-1}) + q_{XT}{}^{Y}\omega_X\,(10^3\,T^{-1}). \qquad (25)\end{aligned}$$

In Eqs. (23), and (25) $\omega_X = \log k_{00T} - \log k_{X0T}$ (T = 265 K) is a quantitative characteristic of total effects of substituents X (the ω_X values for the substituents X = H, 4-Br, 4-NO_2, 3-Br-5-NO_2 are equal to 0, 2.02, 3.47, and 4.38, respectively).[14] The values of the coefficients of Eqs. (23 – 25) calculated for various two-factor cross-reaction series with the use of kinetic data[15] are given in Table 3. Statistical significance of the cross-interaction coefficients q_{XY}^T, q_{YT}^X, and q_{XT}^Y in reaction series 1–10 shows that all variants of the second-order interactions of the effects of the substituents X, Y and temperature T should be considered when assessing the reactivity of the considered reaction system. At the same time, the invariance of these coefficients when the parameters of fixed factors are changed indicates the absence of third-order interaction ($q_{XYT} = 0$).

Of all the calculated isoparametric points, only two proved to be experimentally achievable. The isoparametric point $\omega_{X(Y)}^T = -\rho_Y^{0T}(q_{XY}^T)^{-1} = 4.73$ was almost reached in the reaction series 1 with variable substituents X and Y at a fixed temperature of 265 K, since the value $\omega_X = 4.38$ for the substituent X = 3-Br-5-NO_2 in oxirane is close to the value of this point. At this point the effects of the substituents Y should not appear, which is confirmed by a decrease to almost zero of ρ_Y^{XT} (T = 265 K) = 1.57 ± 0.02, 1.00 ± 0.04, 0.50 ± 0.03, 0.10 ± 0.05 with an increase in the electron-withdrawing properties of the substituents X (ω_X) = H (0), 4-Br (2.02), 4-NO_2 (3.47), 3-Br-5-NO_2 (4.38).[15]

In the cross-reaction series 6 with variable substituents Y and temperature T at the fixed substituent X = 3-Br-5-NO_2 in oxirane substrate the isoparametric point $T_{(Y)}^X = 262$ K $[10^3(T_{(Y)}^X)^{-1} = -\rho_Y^{XT=\infty}(q_{YT}^X)^{-1} = 3.82]$ is close to a temperature of 265 K in an experiment. In accordance with the regularities of isoparametric dependencies at this point substituents Y in the acidic reagent should not influence on the rate of the reactions ($\rho_Y^{XT} = 0$). This is evidenced by a decrease in the sensitivity coefficient ρ_Y^{XT} (X = 3-Br-5-NO_2) to the effects of Y substituents to almost zero when the temperature decreases to 265 K: ρ_Y^{XT} (T K) = 1.01 ± 0.09 (298 K), 0.50 ± 0.04 (281 K), 0.10 ± 0.05 (265 K).[15,16]

To estimate the total effects of substituents X, Y, and temperature T on the rate of these reactions considering all types of second-order interactions of the effects of the cross-varied factors, the following polylinear equation was used:

$$\log k_{XYT} = \log k_{000} + q_X^{00}\omega_X + \rho_Y^{00}\sigma_Y + q_T^{00}\tau_T + q_{XY}^0\omega_X\sigma_Y + q_{XT}^0\sigma_X\tau_T + q_{YT}^0\sigma_Y\tau_T. \qquad (26)$$

Here $\tau_T(T) = (T^{-1} - 281^{-1})10^3$ = 0.215 (265 K), 0 (281 K), and –0.203 (298 K). Processing the results of a multifactorial kinetic experiment[15] using Eq. (26) yielded a multilinear regression, Eq. (27), that adequately describes the reactivity of the cross-reaction series.[13]

$$\log k_{XYT} = (-0.83 \pm 0.02) + (-0.886 \pm 0.007)\omega_X + (2.0 \pm 0.1)\sigma_Y + (-1.8 \pm 0.1)\tau_T + (-0.32 \pm 0.03)\omega_X\sigma_Y + (-0.55 \pm 0.04)\omega_X\tau_T + (-2.1 \pm 0.2)\sigma_Y\tau_T \qquad (27)$$

$S = 0.077$, $R = 0.998$, $n = 43$.

Table 3. The coefficients of Eqs. (23 – 25)[a] and isoparametric points $x_{i(j)}^h$ for two-factor cross-reaction series including reactions of symmetrically X-substituted *trans*-2,3-diaryloxiranes with Y-substituted arenesulfonic acids in a volumetric mixture of dioxane with 1,2-dichloroethane (v : v) 7 : 3 at different temperatures.[15]

RS[b]	Fixed T	$\log k_{00T}$	q_X^{0T}	ρ_Y^{0T}	q_{XY}^T	$\omega_{X(Y)}^T$	$\sigma_{Y(X)}^T$
1	265 K	–1.24 ± 0.01	–1.00 ± 0.01	1.61 ± 0.04	–0.34 ± 0.01	4.73[c]	–2.94
2	281 K	–0.79 ± 0.04	–0.90 ± 0.01	2.01 ± 0.02	–0.33 ± 0.06	6.09	–2.73
3	298 K	–0.46 ± 0.05	–0.76 ± 0.01	2.50 ± 0.03	–0.34 ± 0.08	7.35	–2.23
RS	Fixed X (ω_X)	$\log k_{X0T=\infty}$	$\rho_Y^{XT=\infty}$	q_T^{X0}	q_{YT}^X	$\sigma_{Y(T)}^X$	$T_{(Y)}^X$/K
4	H (0)	6.2 ± 0.3	10.1 ± 0.9	–1.96 ± 0.07	–2.2 ± 0.4	–0.89	220
5	4-NO_2 (3.47)	8.5 ± 0.3	8.3 ± 0.9	–3.52 ± 0.09	–2.0 ± 0.2	–1.76	241
6	3-Br-5-NO_2 (4.38)	11.7 ± 0.1	8.4 ± 0.7	–4.61 ± 0.04	–2.2 ± 0.2	–2.09	262[c]
RS	Fixed Y (σ_Y)	$\log k_{0YT=\infty}$	$q_X^{YT=\infty}$	q_T^{0Y}	q_{XT}^Y	$\omega_{X(T)}^Y$	$T_{(X)}^Y$/K
7	4-OCH_3 (-0.27)	3.1 ± 0.3	1.1 ± 0.4	–1.4 ± 0.3	–0.51 ± 0.09	–2.74	464
8	4-CH_3 (-0.17)	4.0 ± 0.5	1.2 ±0.3	–1.5 ± 0.3	–0.60 ± 0.09	–2.50	500
9	H (0)	5.0 ± 0.4	1.3 ± 0.4	–1.8 ± 0.3	–0.61 ± 0.08	–2.95	469
10	4-Cl (0.23)	8.3. ± 0.7	1.0 ± 0.2	–2.4 ±0.2	–0.55 ± 0.07	–4.36	550

[a] Cross-correlation coefficient $R \geq 0.995$.

[b] Reaction series.

[c] Experimentally observed isoparametric point.

None of the critical values of type $x_{i(j)}^{CV}$ has been experimentally implemented in this cross-reaction series.

In terms of activation parameters, the second-order interactions of the effects of structure and temperature in this three-factor cross-reaction series can be described by Eqs. (28 – 30).

$$\Delta G_{XYT}^{\neq} = \Delta G_{00T}^{\neq} + Q_X^{0T}\omega_X + Q_Y^{0T}\sigma_Y + Q_{XY}^{T}\omega_X\sigma_Y, \qquad (28)$$

$$\Delta G_{XYT}^{\neq} = \Delta G_{X00}^{\neq} + Q_Y^{X0}\sigma_Y + Q_T^{X0}T + Q_{YT}^{X}\sigma_Y T, \qquad (29)$$

$$\Delta G_{XYT}^{\neq} = \Delta G_{0Y0} + Q_X^{Y0}\omega_X + Q_T^{0Y}T + Q_{XT}^{Y}\omega_X T. \qquad (30)$$

The coefficients of Eqs. (28 – 30) calculated for two-factor reaction series with the use of the $\Delta G_{XYT}^{\neq}$ values taken from work[15] are presented in Table 4. The values of the cross-interaction coefficients Q_{XY}^{T}, Q_{YT}^{X}, and Q_{XT}^{Y} indicate the influence of all types of the second-order interactions of the effects of the cross-varied factors on the free activation energy $\Delta G_{XYT}^{\neq}$. At the same time, the invariance of these coefficients when the parameters of fixed factors are changed indicates the absence of third-order interaction (Q_{XYT} = 0). Only three of twenty isoparametric points turned out to be experimentally achievable. First, it should be noted the isoparametric point for the temperature $T_{(Y)}^{X(G)}$ = 261 K (X = 3-Br-5-NO$_2$) in reaction series 6G, which is consistent with the above calculated value of the isoparametric point $T_{(Y)}^{X}$ = 262 K in reaction series 6 (Table 3). At this point, the free activation energy $\Delta G_{XYT}^{\neq IP}$ should not depend on the effects of the substituents Y. The reason for the disappearance of the effects Y on $\Delta G_{XYT}^{\neq}$ at this isoparametric point is the enthalpy-entropy compensation effect: $\delta_Y\Delta H_Y^{X\neq}$ = $T_{(Y)}^{X(G)}\delta_Y\Delta S_Y^{X\neq}$, as a result of which $\delta_Y\Delta G_{XYT}^{\neq IP}$ = $\delta_Y\Delta H_Y^{X\neq}$ – $T_{(Y)}^{X(G)}\delta_Y\Delta S_Y^{X\neq}$ = 0 and $\Delta G_{XYT}^{\neq IP}$ = constant (log k_{XYT} = constant, ρ_Y^{XT} = 0). Because of the small difference between $T_{(Y)}^{X(G)}$ = 261 K and temperature 265 K in the experiment, we have a rare opportunity to prove the physical reality of the enthalpy-entropy compensation phenomenon. Due to the enthalpy-entropy compensation in the reaction series 6G at 265 K, the substituents Y have no effect on the values of the free activation energy: $\Delta G_{XYT}^{\neq}$ (Y) = 93.3 (4-OMe), 92.9 (4-Me), 93.0 (H), 93.1 (4-Cl) kJ mol^{-1}.[15]

Note that the isoparametric point $T_{(Y)}^{X(G)}$, calculated from the activation parameters [Eqs. (29), (30)], is called the compensation temperature T_{comp}, while the term isokinetic temperature T_{iso} refers to the isoparametric point $T_{(Y)}^{X}$, calculated from the kinetic data [Eqs. (24), (25)]. These points, calculated in different ways, practically coincide in magnitude.

The isoparametric points $\sigma_{Y(T)}^{X(G)}$ = 0.52 (X = 4-NO$_2$) and $\sigma_{Y(T)}^{X(G)}$ = 0.20 (X = 3-Br-5-NO$_2$), were realized in the reaction series 5G and 6G.[13,15] They fall in the experimental range of variation of σ_Y from –0.27 (Y = 4-OMe) to 0.71 (Y = 3-NO$_2$). A remarkable feature of these points is that the free activation energy $\Delta G_{XYT}^{\neq IP}$ at them does not depend on temperature, that is possible if in the expression $\Delta G_{XYT}^{\neq IP} = \Delta H_Y^{X\neq} - T\Delta S_Y^{X\neq}$ the activation entropy $\Delta S_Y^{X\neq}$ = 0 and the free activation energy is determined only by the enthalpy term ($\Delta G_{XYT}^{\neq IP} = \Delta H_Y^{X\neq}$). These reactions demonstrate not only a rare case of realization of two isoparametric points for the structural parameter $\sigma_{Y(T)}^{X(G)}$, but also unique transitions through these points when the

Table 4. The coefficients of Eqs. (28 – 30)[a] and isoparametric points $x_{i(j)}^{h}$ for two-factor cross-reaction series including reactions of symmetrically X-substituted *trans*-2,3-diaryloxiranes with Y-substituted arenesulfonic acids in a volumetric mixture of dioxane with 1,2-dichloroethane (*v* : *v*) 7 : 3 at different temperatures.[15]

RS[b]	Fixed *T*	$\Delta G_{00T}^{\neq}$	Q_X^{0T}	Q_Y^{0T}	Q_{XY}^{T}	$\omega_{X(Y)}^{T(G)}$	$\sigma_{Y(X)}^{T(G)}$
1G	265 K	70.2 ± 0.3	5.3 ± 0.1	–7.0 ± 0.9	1.3 ± 0.4	5.4	–4.1
2G	281 K	72.5 ± 0.3	4.9 ± 0.1	–10 ± 0.2	1.4 ± 0.5	7.1	–3.5
3G	298 K	74.8 ± 0.5	4.6 ± 0.1	–14 ± 0.2	1.7 ± 0.7	8.2	–2.7
RS	Fixed X (ω_X)	$\Delta G_{X00}^{\neq}$	Q_Y^{X0}	Q_T^{X0}	Q_{YT}^{X}	$\sigma_{Y(T)}^{X(G)}$	$T_{(Y)}^{X(G)}$/K
4G	H (0)	34 ± 3	45 ± 9	0.134 ± 0.009	–0.19 ± 0.05	0.70	237
5G	4-NO$_2$ (3.47)	67 ± 1	39 ± 3	0.083 ± 0.004	–0.16 ± 0.01	0.52[c]	244
6G	3-Br-5-NO$_2$ (4.38)	83 ± 1	47 ± 5	0.036 ± 0.003	–0.18 ± 0.02	0.20[c]	261[c]
RS	Fixed Y (σ_Y)	$\Delta G_{0Y0}^{\neq}$	Q_X^{Y0}	Q_T^{0Y}	Q_{XT}^{Y}	$\omega_{X(T)}^{Y(G)}$	$T_{(X)}^{Y(G)}$/K
7G	4-OCH$_3$ (–0.26)	23 ± 8	11 ± 4	0.19 ± 0.05	–0.021 ± 0.007	9.0	524
8G	4-CH$_3$ (–0.17)	26 ± 3	11 ± 3	0.17 ± 0.03	–0.021 ± 0.005	8.1	524
9G	H (0)	31 ± 8	11 ± 2	0.14 ± 0.03	–0.023 ± 0.009	6.1	478
10G	4-Cl (0.26)	45 ± 4	10 ± 1	0.09 ± 0.01	–0.018 ± 0.004	5.0	555

[a] Cross-correlation coefficient $R \geq 0.995$.

[b] Reaction series.

[c] Experimentally observed isoparametric point.

substituents Y were varied. After passing through these points, the reversal of the sign of the activation entropy $\Delta S_Y^{X\neq}$ occurs. For example, in reaction series 5G (fixed X = 4-NO$_2$), where $\sigma_{Y(T)}^{X(G)} = 0.52$, $\Delta S_Y^{X\neq}$/(J mol^{-1} K^{-1}) (Y, σ_Y) = –140 (4-OMe, -0.27), –121 (4-Me, –0.17), –86 (H, 0), –42 (4-Cl, 0.23), 44 (3-NO$_2$, 0.71).[15]. Such a change in entropy causes an inversion of the temperature effect on the free activation energy $\Delta G_{XYT}^{\neq}$. In reaction series 5G, the coefficient b_T^{XY} of sensitivity of the free activation energy to the influence of temperature in equation $\Delta G_{XYT}^{\neq} = \Delta G_{XY0}^{\neq} + b_T^{XY}T$ changes sign in the series of substituents Y given above after passing through the isoparametric point $\sigma_{Y(T)}^{X(G)}$ (X = 4-NO$_2$) = 0.52: b_T^{XY} ($r \geq 0.985$) = 0.136 ± 0.006, 0.106 ± 0.007, 0.076 ± 0.007, 0.046 ± 0.008, –0.0303 ± 0.0005.[15]

The combined effects of substituents X, Y, and temperature on the free activation energy $\Delta G_{XYT}^{\neq}$ were evaluated by Eq. (31).

$$\Delta G_{XYT}^{\neq} = \Delta G_{000}^{\neq} + Q_X^{00}\omega_X + Q_Y^{00}\sigma_Y + Q_T^{00}T_G +$$

$$Q_{XY}^{0}\omega_X\sigma_Y + Q_{XT}^{0}\omega_X T_G + Q_{YT}^{0}\sigma_Y T_G \tag{31}$$

Here $T_G(T) = T - 281 = -16$ (265 K), 0 (281 K), 17 (298 K). When calculating the coefficients of Eq. (31), the following regression was obtained:[13]

$$\Delta G_{XYT}^{\neq} = (72.4 \pm 0.2) + (4.93 \pm 0.07)\omega_X +$$

$$(-10 \pm 0.1)\sigma_Y + (0.12 \pm 0.02)T_G +$$

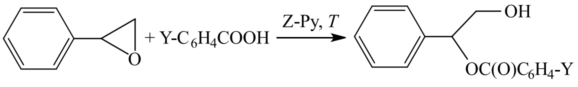
$$(1.3 \pm 0.3)\omega_X\sigma_Y + (-0.016 \pm 0.005)\omega_X T_G +$$

$$(-0.15 \pm 0.03)\sigma_Y T_G \tag{32}$$

$S = 0.773$, $R = 0.994$, $n = 39$.

All coefficients of second-order interactions of this regression agree within the accuracy limits of their determination with those calculated in partial correlations at standard conditions [see the values $Q_{XY}^T = 1.4 \pm 0.5$ (T = 281 K), $Q_{YT}^X = -0.19 \pm 0.05$ (X = H), and $Q_{XT}^Y = -0.023 \pm 0.009$ (Y = H) in reaction series 2G, 4G, and 9G (Table 4)]. None of the critical values of type $x_{i(j)}^{CV}$ was realized in this cross-reaction series.

The joint effects of the structure and temperature were studied in catalyzed by Z-substituted pyridines reactions of phenyloxirane with Y-substituted benzoic acids in acetonitrile at different temperatures (Scheme 4).[17–19]



Y (σ_Y) = H (0), 3-Br (0.39), 3-NO$_2$ (0.71);
Z (σ_Z) = 4-OMe (-0.27), 4-Et (-0.15), H (0), 3-COOEt (0.37), 3-CN (0.56);
T = 279, 295, 308, 323, 343 K.

Scheme 4. Reactions of phenyloxirane with Y-substituted benzoic acids catalyzed by Z-substituted pyridines at different temperatures.

According to the polylinearity principle, the cumulative effects of the substituents Y, Z, and temperature T on the rate of the catalytic reactions are described by Eq. (33).

$$\log k_{YZT} = \log k_{00T=\infty} + \rho_Y^{0T=\infty}\sigma_Y + \rho_Z^{0T=\infty}\sigma_Z +$$

$$q_T^{00}(10^3\,T^{-1}) + \rho_{YZ}^{T=\infty}\sigma_Y\sigma_Z + q_{YT}^{0}\sigma_Y(10^3\,T^{-1}) +$$

$$q_{ZT}^{0}\sigma_Z(10^3\,T^{-1}) + q_{YZT}\sigma_Y\sigma_Z(10^3\,T^{-1}). \tag{33}$$

Here, the indices 0 and ∞ refer respectively to the standard substituents Y = Z = H ($\sigma_{Y(Z)} = 0$) and standard temperature (T = ∞ K, $10^3\,T^{-1} = 0$). By processing the results of the multifactor kinetic experiment[18] using Eq. (33), a polylinear regression, Eq. (34), was calculated.[19]

$$\log k_{YZT} = (5.1 \pm 0.2) + (1.2 \pm 0.3)\sigma_Y +$$

$$(-15.6 \pm 0.7)\sigma_Z + (-2.83 \pm 0.05)(10^3\,T^{-1}) +$$

$$(0.4 \pm 1.4)\sigma_Y\sigma_Z + (-0.08 \pm 0.09)\sigma_Y(10^3\,T^{-1}) +$$

$$(4.6 \pm 0.2)\sigma_Z(10^3\,T^{-1}) +$$

$$(-0.1 \pm 0.4)\sigma_Y\sigma_Z(10^3\,T^{-1}). \tag{34}$$

$S = 0.0367$, $R = 0.998$, $n = 58$.

In this regression, some coefficients, namely $\rho_{YZ}^{T=\infty}$, q_{YT}^{0}, and q_{YZT} are statistically insignificant. This indicates the absence of the second-order interactions of the effects of substituents Y and Z as well as substituents Y and temperature T. Therefore, there is no interaction between the effects of all three variables in the cross-reaction series ($q_{YZT} = (-0.1 \pm 0.4)$. After the exclusion of the cross-terms with these coefficients, Eq. (34) is simplified to Eq. (35).[19]

$$\log k_{YZT} = (5.18 \pm 0.08) + (0.91 \pm 0.02)\sigma_Y +$$

$$(-15.4 \pm 0.3)\sigma_Z + (-2.85 \pm 0.02)(10^3\,T^{-1}) +$$

$$(4.5 \pm 0.1)\sigma_Z(10^3\,T^{-1}) \tag{35}$$

$S = 0.0362$, $R = 0.998$, $n = 58$.

Owing to the statistical significance of the cross-interaction coefficient $q_{ZT} = 4.5 \pm 0.1$, Eq. (35) is characterized by isoparametric points for the inverse temperature $(T_{(Z)}^{Y})^{-1}10^3 = -\rho_Z^{0T=\infty}(q_{ZT}^{0})^{-1} = 3.42$ [$T_{(Z)}^{Y} = 292$ K (Y = H)] and for the constant of the substituent Z $\sigma_{Z(T)}^{Y} = -q_T^{00}q_{ZT}^{-1} = 0.63$ (Y = H). Both points turned out to be experimentally attainable. At the isoparametric point $\sigma_{Z(T)}^{Y}$ the rate of the process should be temperature independent. The reactions involving 3-CN-pyridine, for which the constant $\sigma_Z = 0.56$ for the substituent Z = 3-CN is little different from the isoparametric value $\sigma_{Z(T)}^{Y} = 0.63$, exhibit low sensitivity to temperature effects. These reactions are characterized by near-zero slopes of the B_T^{YZ} in the Arrhenius equation $\log k_{YZT} = \log k_{YZT=\infty} + B_T^{YZ}(10^3\,T^{-1})$ ($r \geq 0.995$): B_T^{YZ} (Z =3-CN) = –0.30 ± 0.02 (Y = 3-Br), –0.31 ± 0.03 (Y = 3-NO$_2$).[18] Consequently, the apparent activation energies $Ea^{YZ} = -2.303RB_T^{YZ}10^3$ (R = 8.314 J mol^{-1} K^{-1} is gas constant) are low: 5.73 and 5.9 kJ mol^{-1} respectivily, and the rate of the process will be determined by the entropic factor ($\Delta G_{ZT}^{\neq Y} = -T\Delta S_Z^{\neq Y}$). In the reactions catalyzed by 3-CN-pyridine, the contribution of the entropy term to the activation free energy exceeds 96 % at 298 K.[8] The above indicates that when the considered isoparametric point $\sigma_{Z(T)}^{Y}$ is reached, the catalytic process occurs without an activation barrier.

In the reactions under consideration, a passage through the isoparametric point $(T_{(Z)}^{Y})^{-1}10^3 = 3.42$ [$T_{(Z)}^{Y}$ = 292 K (Y = H)] with varied temperatures was realized. In this case, an inversion of the sign of the sensitivity coefficient ρ_Z^{YT} to the effects of substituents Z was observed. This situation is demonstrated in Figure 5 for the reaction involving benzoic acid (Y = H). The values of ρ_Z^{YT} (T) at different temperatures change as follows ($r \geq 0.996$): 0.751 ± 0.009 (279 K), –0.078 ± 0.002 (295 K), –0.77 ± 0.06 (308 K), –1.62 ± 0.06 (323 K), –2.4 ± 0.2 (343 K).[19] The opposite signs of ρ_Z^{YT} after passing through the isoparametric point $T_{(Z)}^{Y}$ = 292 K indicate a reversal of the order of the catalytic activity of pyridines, which is convincing evidence of the isoparametricity paradox experimentally observed when the temperature changes from 279 to 343 K. Such situations are extremely rare in chemical processes. The isoparametric properties of this cross-reaction series are described in more detail in a recent publication.[8]

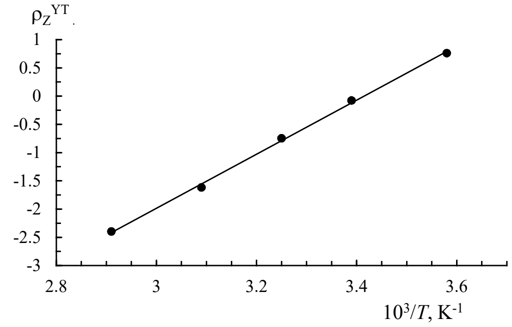


Figure 5. Change in the sign of the coefficient ρ_Z^{YT} (Y = H) after passing through the isoparametric point $(T_{(Z)}^{Y})^{-1}10^3$ = 3.42 in the reaction of phenyloxirane with benzoic acid catalyzed by Z-substituted pyridines.

3. Effects of Structure and Medium Polarity

The combined effects of structure and medium polarity were studied in the reactions of Y-substituted benzoyl chlorides with X-substituted anilines in chlorobenzene, nitrobenzene, and volumetric mixtures of chlorobenzene with nitrobenzene ($v : v$) 9 : 1, 3 : 1, 1 : 1 at 298 K (Scheme 5).[20]

$$\text{Y-C}_6\text{H}_m\text{COCl} + 2\ \text{X-C}_6\text{H}_m\text{NH}_2 \xrightarrow{S} \text{Y-C}_6\text{H}_m\text{CONHC}_6\text{H}_m\text{-X} + \text{X-C}_6\text{H}_m\text{NH}_3^+\text{Cl}^-$$

$$\begin{aligned}&\text{Y}\ (\sigma_\text{Y}) = \text{H}\ (0), \text{3-Cl}\ (0.37), \text{3-NO}_2\ (0.71)\ (\text{m} = 4); \text{3,5-Me}_2\ (-0.14)\ (\text{m} = 3).\\ &\text{X}\ (\sigma_\text{X}) = \text{H}\ (0), \text{3-COOMe}\ (0.26), \text{3-F}\ (0.35), \text{3-NO}_2\ (0.71)\ (m = 4);\\ &\qquad \text{3-NO}_2\text{-5-COOMe}\ (0.97)\ (m = 3).\end{aligned}$$

Scheme 5. Reactions of Y-substituted benzoyl chlorides with X-substituted anilines in chlorobenzene, nitrobenzene, and their volumetric mixtures.

The second-order interactions of the effects of the variable factors were estimated by Eqs. (36 – 38) that consider the combined effects of substituents X and Y at a fixed solvent S, substituents X and solvents S at a fixed substituent Y, substituents Y and solvents S at a fixed substituent X.

$$\log k_{XYS} = \log k_{00S} + \rho_X^{0S}\sigma_X + \rho_Y^{0S}\sigma_Y + \rho_{XY}^{S}\sigma_X\sigma_Y, \qquad (36)$$

$$\log k_{XYS} = \log k_{0YG} + \rho_X^{YG}\sigma_X + q_S^{0Y}P_S + q_{XS}^{Y}\sigma_X P_S, \qquad (37)$$

$$\log k_{XYS} = \log k_{X0G} + \rho_Y^{XG}\sigma_Y + q_S^{X0}P_S + q_{YS}^{X}\sigma_Y P_S. \qquad (38)$$

In Eqs. (37), (38) $P_S = [(\varepsilon_S - 1)(2\varepsilon_S + 1)^{-1}]$ is solvent polarity parameter, where ε_S is the dielectric constant of solvent S; the index G refers to the standard medium (gas phase, ε_S = 1, P_S = 0). The values P_S of chlorobenzene, nitrobenzene, and mixtures of chlorobenzene with nitrobenzene 9 : 1, 3 : 1, 1 : 1 are equal to 0.377, 0.479, 0.407, 0.434, 0.451, respectively.[20,21] The results of processing kinetic data[20] using Eqs. (36 – 38) are given in Table 5. They show the manifestation of all types of second-order interactions (ρ_{XY}^{T}, q_{XT}^{Y}, q_{YT}^{X}) in cross-reaction series. However, despite this, not a single isoparametric point was implemented in the experiment. Moreover, the isoparametric points $P_{S(X)}^{Y}$ in reaction series 6 – 9 have no physical meaning at all, since the range of variation of the function P_S is limited to the interval from 0 (gas phase) to ~0.5 (most polar medium). At the same time, the isoparametric points $P_{S(Y)}^{X}$ = 0.15 – 0.25 in reaction series 10 – 14 correspond to fully accessible low-polarity solvents, such as the mixture of chlorobenzene with cyclohexane (1 : 10), for which P_S = 0.236.[21] However, it was not possible to implement these points due to the non-observance of Eq. (38) when passing to media less polar than chlorobenzene (P_S = 0.377).[21]

The polylinear Eq. (39) was used to consider the combined effects of three variable factors on the rate of the reactions under consideration.

$$\log k_{XYS} = \log k_{00G} + \rho_X^{0G}\sigma_X + \rho_Y^{0G}\sigma_Y + q_S^{00}P_S + \rho_{XY}^{G}\sigma_X\sigma_Y + q_{XS}^{0}\sigma_X P_S + q_{YS}^{0}\sigma_Y P_S + q_{XYS}\sigma_X\sigma_Y P_S \qquad (39)$$

When processing the results of a multifactor kinetic experiment[20] using Eq. (39), the polylinear regression, Eq. (40), was obtained.

$$\log k_{XYS} = (-6.66 \pm 0.02) + (-4.9 \pm 0.7)\sigma_X + (-1.5 \pm 0.1)\sigma_Y + (11 \pm 1)P_S + (-1.37 \pm 0.03)\sigma_X\sigma_Y + (4.6 \pm 0.8)\sigma_X P_S + (6.5 \pm 0.7)\sigma_Y P_S + (2.0 \pm 0.3)\sigma_X\sigma_Y P_S \qquad (40)$$

$S = 0.069$, $R = 0.998$, $n = 99$.

All regression coefficients are statistically significant, including the third-order interaction coefficient (q_{XYS} = 2.0 ± 0.3). It should be noted that none of the nine critical values of this regression ($\sigma_{X(Y)}^{CV} = -1.09$, $\sigma_{Y(X)}^{CV} = -3.58$, $\sigma_{X(S)}^{CV} = -2.39$, $\sigma_{Y(S)}^{CV} = -2.39$, $P_{S(X)}^{CV} = 1.06$, $P_{S(Y)}^{CV} = 0.23$, $\sigma_{X(YS)}^{CV} = -3.25$, $\sigma_{Y(XS)}^{CV} = -2.3$, $P_{S(XY)}^{CV} = 0.68$) was implemented.

4. Effects of Structure, Temperature, and Medium Polarity

The joint effects of structure, temperature, and medium polarity were studied in reactions of Y-substituted benzyl bromides with *n*-butylamine in chlorobenzene, nitrobenzene, volumetric mixtures of chlorobenzene with nitrobenzene 9 : 1, 1 : 1 at 313, 323, 333 K, and in the mixture of chlorobenzene with cyclohexane 1 : 1 at 313 K (Scheme 6).[22,23]

$$\text{Y-C}_6\text{H}_4\text{CH}_2\text{Br} + 2\ n\text{-BuNH}_2 \xrightarrow{S,\ T} \text{Y-C}_6\text{H}_4\text{CH}_2\text{NHBu-}n + n\text{-BuNH}_3^{+}\text{Br}^{-}$$

$$\text{Y}\,(\sigma_Y) = \text{H}\,(0), \text{3-Cl}\,(0.37), \text{3-Br}\,(0.39), \text{3-CN}\,(0.56), \text{3-NO}_2\,(0.71).$$
$$T = 313, 323, 333\text{ K}.$$

Scheme 6. Reactions of Y-substituted benzyl bromides with *n*-butylamine in chlorobenzene, nitrobenzene, and their volumetric mixtures at different temperatures.

Eq. (41) was used to consider the cumulative effects of the variable factors on the rate of these reactions.

$$\log k_{YST} = \log k_{0NB0} + \rho_Y^{NB0}\sigma_Y + q_S^{00}V_S + q_T^{0NB}\tau_T + q_{YS}^{0}\sigma_Y V_S + q_{YT}^{NB}\sigma_Y\tau_T + q_{ST}^{0}V_S\tau_T + q_{YST}\sigma_Y V_S\tau_T \qquad (41)$$

In Eq. (41), nitrobenzene (index NB) is chosen as the standard medium, and the standard temperature is taken to be 313 K. In this regard, $V_S = P_S - P_{NB}$ (P_S is the solvent polarity parameter), $\tau_T = (T^{-1} - 313^{-1})10^3$. For nitrobenzene, mixtures of nitrobenzene with chlorobenzene 1 : 1 and 1 : 9, chlorobenzene and mixture of chlorobenzene with cyclohexane 1 : 1, the V_S values are 0, –0.028, –0.072, –0.102, and –0.157, respectively.[22,23]

When calculating the kinetic data[22,23] using Eq. (41), the regression, Eq. (42), was obtained.

$$\log k_{YST} = (-1.73 \pm 0.02) + (0.22 \pm 0.05)\sigma_Y + (12.8 \pm 0.3)V_S + (-2.32 \pm 0.22)\tau_T + (8.56 \pm 0.60)\sigma_Y V_S + (0.31 \pm 0.44)\sigma_Y\tau_T + (-5.14 \pm 2.93)V_S\tau_T + (9.21 \pm 5.93)\sigma_Y V_S\tau_T, \qquad (42)$$

$$S = 0.044,\ R = 0.999,\ n = 55.$$

In regression, Eq. (42), there is a statistically insignificant coefficient at the cross term $(0.31 \pm 0.44)\sigma_Y\tau_T$, which considers the joint effects of structure and temperature. In addition, the coefficients at the cross terms estimating the combined effects of the medium polarity

Table 5. The coefficients of Eqs. (36 – 38)(a) and the isoparametric points $x_{i(j)}^{h}$ for two-factor cross-reaction series including the reactions of Y-substituted benzoyl chlorides $\text{Y-C}_6\text{H}_4\text{COCl}$ with X-substitutes anilines $\text{X-C}_6\text{H}_{4(3)}\text{NH}_2$ in chlorobenzene (CB), nitrobenzene (NB), and volumetric mixtures of CB with NB (*v* : *v*) at 298 K.[20]

RS(b)	Fixed *S* (P_S)	log k_{00S}	ρ_X^{0S}	ρ_Y^{0S}	ρ_{XY}^{S}	$\sigma_{X(Y)}^{S}$	$\sigma_{Y(X)}^{S}$
1	CB (0.377)	−1.20 ± 0.03	−3.23 ± 0.05	0.88 ± 0.04	−0.57 ± 0.09	1.54	−5.67
2	CB : NB = 9 : 1 (0.407)	−0.91 ± 0.03	−2.95 ± 0.05	1.25 ± 0.05	−0.51 ± 0.09	2.45	−5.78
3	CB : NB = 3 : 1 (0.434)	−0.61 ± 0.04	−2.86 ± 0.06	1.42 ± 0.08	−0.44 ± 0.09	3.23	−6.50
4	CB : NB = 1 : 1 (0.451)	−0.36 ± 0.03	−2.74 ± 0.06	1.39 ± 0.07	−0.39 ± 0.01	3.56	−7.02
5	NB (0.479)	0.02 ± 0.01	−2.72 ± 0.09	1.36 ± 0.06	−0.30 ± 0.02	4.53	−9.07
RS	Fixed Y (σ_Y)	log k_{0YG}	ρ_X^{YG}	q_S^{0Y}	q_{XS}^{Y}	$\sigma_{X(S)}^{Y}$	$P_{S(X)}^{Y}$
6	3,5-(CH_3)$_2$ (−0.14)	−5.6 ± 0.1	−5.0 ± 0.2	11.7 ± 0.3	4.8 ± 0.5	−2.44	1.04
7	H (0)	−5.6 ± 0.1	−4.9 ± 0.2	11.7 ± 0.2	4.6 ± 0.5	−2.54	1.06
8	3-Cl (0.37)	−5.7 ± 0.1	−4.7 ± 0.3	12.0 ± 0.3	4.1 ± 0.6	−2.93	1.15
9	3-NO_2 (0.71)	−6.3 ± 0.2	−4.4 ± 0.3	13.2 ± 0.4	3.5 ± 0.7	−3.77	1.26
RS	Fixed X (σ_X)	log k_{X0G}	ρ_Y^{XG}	q_S^{X0}	q_{YS}^{X}	$\sigma_{Y(T)}^{X}$	$P_{S(Y)}^{X}$
10	H (0)	−5.6 ± 0.1	−2.0 ± 0.3	11.7 ± 0.3	8.1 ± 0.6	−1.44	0.25
11	3-$COOCH_3$ (0.26)	−5.6 ± 0.1	−1.72 ± 0.02	13.9 ± 0.3	7.4 ± 0.5	−1.88	0.23
12	3-F (0.34)	−6.4 ± 0.1	−1.4 ± 0.3	13.6 ± 0.3	6.9 ± 0.6	−1.97	0.20
13	3-NO_2 (0.71)	−5.7 ± 0.1	−1.4 ± 0.2	12.0 ± 0.3	5.7 ± 0.5	−2.10	0.25
14	3-NO_2-5-$COOCH_3$ (0.97)	−6.6 ± 0.1	−0.72 ± 0.02	13.9 ± 0.3	4.7 ± 0.6	−2.96	0.15

(a) Cross-correlation coefficient $R \geq 0.995$.

(b) Reaction series.

and temperature (q_{ST}^0) and all three factors (q_{YST}) are determined with large errors. The exclusion of these cross terms leads to an expression, Eq. (43).

$$\log k_{YST} = (-1.72 \pm 0.02) + (0.21 \pm 0.03)\sigma_Y + (13.1 \pm 0.2)V_S + (-2.11 \pm 0.22)\tau_T + (8.04 \pm 0.47)\sigma_Y V_S \qquad (43)$$

$S = 0.044$, $R = 0.999$, $n = 55$.

Due to the intensive interaction of the effects of the structure and the medium polarity ($q_{YS}^0 = 8.04 \pm 0.47$), Eq. (43) exhibits isoparametric properties. Its attributes are isoparametric points for the constant of substituent Y, $\sigma_{Y(S)}^T$ (T = 313 K) $= -q_S^{00}(q_{YS}^0)^{-1} = -1.63$, and for the parameter of the medium polarity $V_{S(Y)}^T$ (T = 313 K) $= -\rho_Y^{NB0}(q_{YS}^0)^{-1} = -0.026$). At the first point the rate of the process should not depend on the medium polarity ($\rho_S^{YT} = 0$). However, this point cannot be realized because of the deficit of powerful electron-donor substituents Y in benzyl bromide. The isoparametric point $V_{S(Y)}^T = -0.026$ falls in the experimental range of variation of the introduced medium polarity parameter V_S [from 0 (nitrobenzene) to –0.157 (the mixture of chlorobenzene with cyclohexane 1 : 1)]. This point corresponds to a mixture of nitrobenzene with chlorobenzene 1 : 1 ($V_S = -0.028$) in which the rate of the process is independent of the substituents Y ($\rho_Y^{ST} = 0$). As shown in Figure 6, in the cross-reaction series it was possible to make a transition through this point, accompanied by an inversion of the sign of the sensitivity coefficient ρ_Y^{ST}. In the series of such solvents as nitrobenzene, mixtures of nitrobenzene with chlorobenzene 1 : 1, 1 : 9, chlorobenzene, and the mixture of chlorobenzene with cyclohexane 1 : 1, the values of ρ_Y^{ST} (T = 313 K) are respectively equal to 0.20 ± 0.04 ($V_S = 0$), 0 ($V_S = -0.028$), –0.49 ± 0.03 ($V_S = -0.072$), –0.60 ± 0.03 ($V_S = -0.102$), –1.19 ± 0.09 ($V_S = -0.157$).[22]

Thus, the intensive manifestation of the interaction between the effects of structure and polarity of the medium allowed to realize a unique transition through the isoparametric point $V_{S(Y)}^T$ with respect to the polarity of the medium, at which there is a change in the order of influence of substituents Y on the rate of the process.

CONCLUSION

The study of the combined effects of three factors on the rates and activation parameters of the organic reactions has led to the establishment of previously unknown unique properties of the cross-reaction series. The second-order interactions of the effects of variable factors provide experimental evidence for the isoparametricity phenomenon, the attributes of which are the isoparametric points relative to the parameters of variables and the paradox of isoparametricity. The third-order interactions are manifested in the implementation of the non-interaction phenomenon: at the critical values of the parameters of the variable factors, corresponding terms of three-parameter relationships evaluating second-order interactions disappear. Moreover, the mathematically predicted change in the sign of the second-order cross-interaction coefficient has been experimentally proven after passing such critical values.

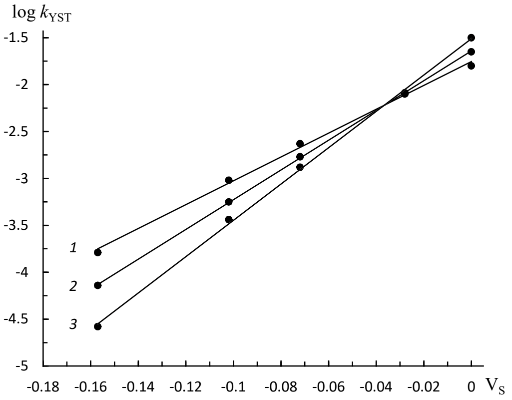


Figure 6. Transition through the isoparametric point $V_{S(Y)}^T = -0.026$ (T = 313 K) in the reactions of Y-substituted benzyl bromides [Y = H (*1*), 3-Cl (*2*), 3-NO$_2$ (*3*)] with n-butylamine in nitrobenzene (V_S = 0), chlorobenzene ($V_S = -0.102$), and volumetric mixtures of chlorobenzene with nitrobenzene 1 : 1 ($V_S = -0.028$), 1 : 9 ($V_S = -0.072$), and chlorobenzene with cyclohexane 1 : 1 ($V_S = -0.157$).[22]

Knowledge of these poorly studied latent properties of three-factor cross-reaction series expands our notions on quantitative regularities of organic reactivity. In this context, interesting new discoveries should be expected in subsequent studies of chemical systems with multifactorial variations in the structure of reagents and reaction conditions. These studies will promote the further development of a quantitative theory of organic reactions. The results of the investigation of organic reactions under multi-factorial conditions discussed in this article conclusively show that one-factor correlations, still traditionally popular among many researchers in various fields of natural sciences, may be questionable for interpretation since their results can change dramatically when moving to various levels of fixed factors. Before interpreting one-factor correlations, it is necessary to make sure that their sensitivity parameters are not influenced by other factors. This means that it is necessary to carry out at least a two-factor analysis of the system being studied.

In conclusion, it should be noted that for a more complete knowledge of the properties of chemical, physical, biological, and other systems, they should be studied under multifactorial conditions.

Acknowledgments. The author is grateful to the co-authors of joint publications cited here and thanks the Ministry of Education and Science of the Ukraine, the Vasyl' Stus Donetsk National University and the Inha University (the Republic of Korea) for financial support.

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