Isoparametricity Phenomenon in Organic Reactions: Paradoxical Reality

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Abstract: This article presents an overview of the systematic study of the difficult-to-perceive unique phenomenon of isoparametricity in nucleophilic substitution reactions at the carbonyl and benzyl electrophilic centers, as well as in nucleophilic oxirane ring-opening reactions. The conducted studies have shown that isoparametric properties of formal polylinear relations are inherent in organic reactions. Before these studies, little experimental evidence of isoparametricity was known. Non-additive multifactor effects on the kinetics and activation parameters of the considered reactions revealed a wide variety of isoparametric points in cross correlations of the structure–structure, structure–solvent, structure–temperature, and solvent–temperature types. At these points, the reacting system loses its sensitivity to the influence of the corresponding factor. Some of these points were passed through and this was accompanied by reversal of the signs of the corresponding sensitivity coefficients because of reactivity reorientation (isoparametricity paradox). The physical reality of widely discussed enthalpy-entropy compensation effect is proved in studied reactions. The prospects for further investigation of isoparametricity phenomenon are considered.

Keywords: aryloxiranes, organic acids, pyridines, kinetics, catalysis, activation parameters, compensation effect, isoparametricity.

INTRODUCTION

THE fundamental problem of reactivity in chemistry has been solved using correlation analysis for many decades. Dozens of empirical relationships successfully evaluate the influence of various external and internal factors (structure, catalyst, solvent, temperature, pressure, pH of the medium, etc.) on kinetic, activation, thermodynamic and other characteristics of chemical processes.[1–7] They demonstrate the surprising universality of the principle of linearity in the change of free energies, which Pal'm has shown is a particular case of a more general regularity - the polylinearity principle.[3] Polylinear equations are used to study chemical systems with multifactor variation in the structure of reagents and reaction conditions. These equations contain cross terms that evaluate quantitatively the nonadditive effects from various factors present together, so their predictive power is increased considerably by comparison with traditional one-parameter correlations. Polylinear equations reflect the unique latent properties of chemical processes and significantly expand the possibilities of understanding their mechanisms.[8–10] Two-parameter polylinear equations exhibit such an intriguing property as isoparametricity.[3] This term means that the coefficient of sensitivity to the effect of one of factors in one-parameter correlation, *e.g.,* α (β) in the Brönsted equation, or ρ in the Hammett equation, or the coefficient proportional to the activation energy in the Arrhenius equation, becomes zero for the special value of the parameter of another factor called the isoparametric point. In other words, at the isoparametric point for the parameter of one of the factors no influence is exerted on the correlated value of another factor.

In this context, the isoparametric points can be considered as a kind of peculiar "black holes" in a multifactorial system. At these points, the sensitivity of the system to the influence of the corresponding factor fatally disappears. After passing through these points, the signs of the sensitivity coefficients are inverted, which is called the isoparametricity paradox.[3] Because of the unusual paradoxical properties of isoparametric relationships, they are difficult to perceive. Such relationships are called "*the mysterious regularities*",[11] and the isoparametric points are called "*the magic points*".[12]

As a real phenomenon, isoparametricity is a challenge to traditional concepts in chemistry. Despite this, still little attention is paid to its study. One of the reasons is that the isoparametric points in many processes fall within the area of distant extrapolation and are unattainable experimentally.

Originally, the concept of isoparametricity arose within the framework of the formal theory of interaction,[3] but later it was found that this property is inherent in real chemical processes. The early data on isoparametricity were analyzed in a monograph,[3] but later it has been established that most of those do not inspire confidence.[13–17]

The purpose of this review is to sum up the results of the systematic study of the amazing isoparametricity phenomenon in organic reactions, to show that isoparametricity is not at all a nuance of the mathematical manipulation but it is a physical reality in numerous chemical processes. The final part is devoted to the consideration of further prospects for the study of isoparametricity.

Mathematical Aspects of Isoparametricity

The following equation is an example of the simplest polylinear dependence:

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

Here F_{00} is the magnitude of F_{ij} at randomly selected standard values of the parameters of the factors i and j, e.g., $x_i = 0$ and $x_j = 0$; q_i^0 and q_j^0 are coefficients of the sensitivity toward x_i and x_j under standard conditions ($x_j = 0$, and $x_i = 0$, respectively); q_{ij} is the cross-interaction coefficient, which reflects the perturbing (non-additive) effects of factors i and j (in this and subsequent equations, the subscripts and superscripts relate respectively to the varied and fixed factors).

Because of the cross term ($q_{ij} \neq 0$), Eq. (1) exhibits isoparametric properties.[3,18] The term means that at the isoparametric points $x_i^{IP} = -q_j^0 q_{ij}^{-1}$, or $x_j^{IP} = -q_i^0 q_{ij}^{-1}$, the magnitude F_{ij} is the same: $F_{ij}^{IP} = F_{00} - q_i^0 q_j^0 q_{ij}^{-1}$, and remains constant when x_j ($q_j^i = 0$) or x_i ($q_i^j = 0$) are varied.

Another striking feature of Eq. (1) emerges when it is presented in the form of Eq. (2).

$$F_{ij} = F_{00} + q_i^0 x_i + (q_j^0 + q_{ij} x_i) x_j \qquad (2)$$

If the parameter of the factor i is fixed ($x_i = \text{const}$), then the expression in brackets in Eq. (2) can be represented as follows:

$$q_j^i = q_j^0 + q_{ij} x_i \qquad (3)$$

Here q_j^i is the coefficient of sensitivity to the effects of the variable factor j by fixed factor i. As $q_j^i = 0$ at the isoparametric point $x_i^{IP} = -q_j^0 q_{ij}^{-1}$, the passage through that point, where on the one hand $x_i > -q_j^0 q_{ij}^{-1}$ and on the other $x_i < -q_j^0 q_{ij}^{-1}$, will be accompanied by inversion of the sign q_j^i, i.e., a reversal of the order of influence of the factor j on the correlated quantity F_{ij}. The sign inversion for the sensitivity coefficient q_j^i upon passing through the isoparametric point $x_j^{IP} = -q_i^0 q_{ij}^{-1}$ can be predicted in an analogous way.

Because of the above predictions of the intriguing properties of the polylinear relationship (1) at the isoparametric points x_i^{IP}, x_j^{IP} and after passing through them, the question arises of whether they are only a manifestation of the formal mathematical properties of such relations (the nuances of mathematical manipulations), or do they occur as a physical reality in chemical processes? The answer to this question was obtained in a systematic study of the combined effects of different factors (structure, temperature, medium polarity) in the nucleophilic substitution reactions, a report on which is presented below.

A necessary condition for isoparametricity is that the cross-interaction coefficient q_{ij} is different from zero. If $q_{ij} = 0$, i.e., there is additivity in the joint effects of factors i and j, then isoparametricity is impossible even in principle. In the two-factor case, isoparametricity can be extended to any multiparameter case if there is the same mechanism for all the types of interaction.[18] However, in fact no such reaction series have so far been identified. On the other hand, examples are known of additivity for several interaction mechanisms in the three-factor systems, and each mechanism has its own special isoparametricity conditions.[8] The mathematical features of the three-parameter polylinear equations have been considered and their use for describing real three-factor reaction series was published.[8–10,19–23]

## Isoparametricity Phenomenon in Nucleophilic Substitution Reactions

S_N2-type reactions presented in Scheme 1 turned out to be convenient for research the isoparametricity phenomenon. These reactions provide a suitable model for studying various combinations of the second-order interactions of the effects of substituents X in the nucleophile Nu, substituents Y in the hydrocarbon moiety R of the substrate, and substituents Z in the leaving group L by the formation and breaking of bonds in the transition state **A** (Scheme 2). These

$$\text{X-Nu} + \text{Y-RL-Z} \longrightarrow \text{X-Nu}^+\text{R-Y} + \text{L-Z}^-$$

Scheme 1. Nucleophilic substitution reactions between Y, Z-substituted electrophile (Y-RL-Z) and X-substituted nucleophile (X-Nu).
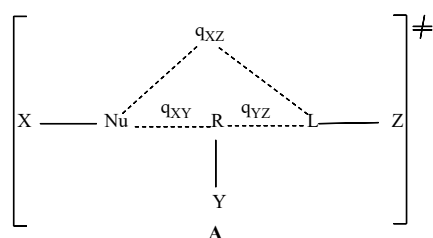
Scheme 2. Various possible combinations of the second-order interactions of the structure effects (q_{XY}, q_{YZ}, q_{XZ}) in the activation process of the A_ND_N reactions.

$$YC_6H_4\text{-}Q\text{-}L + 2XC_6H_4NH_2 \longrightarrow YC_6H_4\text{-}Q\text{-}NHC_6H_4X + XC_6H_4NH_3^+L^-$$
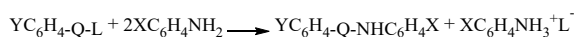
Scheme 3. Nucleophilic substitution reactions of benzoyl halides (Q = CO, L = Cl, Br), benzyl bromides (Q = CH₂, L = Br) and benzyl benzenesulfonates (Q = CH₂, L = OSO₂C₆H₄Z) with anilines.

interactions (non-additive effects) are incorporated by cross-interaction coefficients q_{XY}, q_{XZ}, and q_{YZ} in the corresponding two-parameter equations like Eq. (1).

The interaction of the effects of substituents X and Y is most clearly manifested in represented by Scheme 3 reactions of Y-substituted benzoyl (Q = CO) and benzyl (Q = CH₂) substrates with X-substituted anilines in aprotic solvents.

The combined effects of substituents X and Y on the rate of these reactions are described by Eq. (4).

$$\log k_{XY} = \log k_{HH} + \rho_X^{Y=H}\sigma_X + \rho_Y^{X=H}\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (4)$$

Table 1 contains the values of the coefficients in Eq. (4) and the values of the isoparametric points $\sigma_X^{IP} = -\rho_Y^{X=H}\rho_{XY}^{-1}$ and $\sigma_Y^{IP} = -\rho_X^{Y=H}\rho_{XY}^{-1}$, calculated for the reactions in which the isoparametricity phenomenon has been proved experimentally.[8,24–29] Here and below 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). In nine reaction series (Table 1) the isoparametric points σ_X^{IP} were realized, and in five of them (2, 4, 6, 8, 9) transitions through these points were observed. An obvious manifestation of the isoparametricity phenomenon is presented in Table 2, in which the values ρ_Y^X for the one-factor Hammett-type correlation log k_{XY} = log k_{XH} + $\rho_Y^X\sigma_Y$ in selected reaction series (Table 1) are shown to vary for several fixed substituents X in aniline. Thus, if the calculated value for σ_X^{IP} corresponds to the σ_X constant of the substituent X, then $\rho_Y^X = 0$, and after passing through the isoparametric value σ_X^{IP} in reaction series 2, 4, 6, 9, the sign of ρ_Y^X, *i.e.,* the order of the substrate reactivity, is reversed.

Figure 1 shows the isoparametricity graphically in reaction series 4. The correlation lines in the coordinates of the Hammett equation for reactions of Y-substituted benzyl bromides with X-substituted anilines intersect at the nodal point. That point corresponds to 3-Cl-aniline, in which the value $\sigma_X = 0.37$ of the substituent X = 3-Cl almost coincides with the isoparametric value $\sigma_X^{IP} = 0.39$. The rates of reactions involving that aniline are the same for all benzyl bromides, so $\rho_Y^X = 0$.[27] After passing through this isoparametric point to aniline ($\sigma_X = 0$, $\rho_Y^X = 0.22$) or 5-NO₂-3-COOMe-aniline ($\sigma_X = 0.96$, $\rho_Y^X = -0.35$), there is a reversal in the order of reactivity for the benzyl bromides.

Table 1. The coefficients of Eq. (4)[(a)] for reactions of anilines (XC₆H₄(₃)NH₂) with benzoyl and benzyl substrates in aprotic media [benzene (Bz), nitrobenzene (NBz), chlorobenzene (CBz), cyclohexane (CH), dioxan (DO), DMSO, and THF].

RS[(b)]	Substrate	Solvent[(c)] (T/K)	$\rho_Y^{X=H}$	$-\rho_X^{Y=H}$	$-\rho_{XY}$	σ_X^{IP}	$-\sigma_Y^{IP}$	Refs
1	YC₆H₄COBr	Bz (25)	1.10 ± 0.07	3.00 ± 0.03	0.79 ± 0.08	1.39[(d)]	3.79	[24]
2	YC₆H₄COBr	CB:CH, 1:1 (298)	0.58 ± 0.12	3.16 ± 0.04	0.62 ± 0.13	0.94[(d)]	5.10	[25]
3	YC₆H₄COCl	CB:CH, 1:1 (298)	1.14 ± 0.06	3.32 ± 0.04	0.80 ± 0.09	1.42[(d)]	4.15	[26]
4	YC₆H₄CH₂Br	1 M DMSO in NB (313)	0.22 ± 0.04	1.40 ± 0.04	0.57 ± 0.07	0.39[(d)]	2.46	[27]
5	YC₆H₄CH₂Br	2 M DMSO in DO (313)	0.39 ± 0.03	1.22 ± 0.03	0.61 ± 0.07	0.64[(d)]	2.03	[28]
6	YC₆H₄CH₂Br	3 M DMSO in DO (313)	0.29 ± 0.03	1.24 ± 0.04	0.59 ± 0.05	0.49[(d)]	2.10	[28]
7	YC₆H₄CH₂Br	NB (313)	-0.29 ± 0.03	1.90 ± 0.03	0.48 ± 0.06	-0.60[(d)]	3.99	[29]
8	YC₆H₄CH₂Br	DO (313)	-0.39 ± 0.02	2.31 ± 0.03	1.77 ± 0.06	-0.22[(d)]	1.30	[28]
9	BBS[(e)]	DMSO:THF, 1:3 (293)	-0.25 ± 0.01	2.03 ± 0.04	0.53 ± 0.05	-0.47[(d)]	3.83	[8][(f)]

[(a)]   Cross-correlation coefficient $R \geq 0.997$.

[(b)]   Reaction series.

[(c)]   Volumetric mixtures of solvents ($v : v$) were used.

[(d)]   Experimentally observed isoparametric point.

[(e)]   YC₆H₄CH₂OSO₂C₆H₅.

[(f)]   The coefficients were calculated using the data from the indicated work.

Table 2. The values of ρ_Y^X for the reactions of X-substituted anilines with Y-substituted benzoyl and benzyl substrates [reaction series (RS) in Table 1]

Substituent X in anilines (σ_X)	ρ_Y^X [σ_X^{IP}]					
	RS 2	RS 3	RS 4	RS 6	RS 7	RS 9
4-NH₂ (−0.66)					0	0.11 ± 0.01
4-OCH₃ (−0.26)					-0.23 ± 0.04	-0.12 ± 0.01
H (0)	0.63 ± 0.09	1.03 ± 0.03	0.22 ± 0.04	0.26 ± 0.02	-0.46 ± 0.03	-0.24 ± 0.03
3-Cl (0.37)	0.42 ± 0.03	0.78 ± 0.04	0	0.12 ± 0.01	-0.62 ± 0.02	
3-NO₂ (0.70)	0.16 ± 0.02	0.53 ± 0.06	-0.14 ± 0.01	-0.16 ± 0.01		
5-NO₂-3-COOMe (0.96)	0	0.15 ± 0.01	-0.35 ± 0.06			
3,5-(NO₂)₂ (1.40)	-0.37 ± 0.04	0				
	[0.94]	[1.42]	[0.39]	[0.49]	[−0.60]	[−0.47]
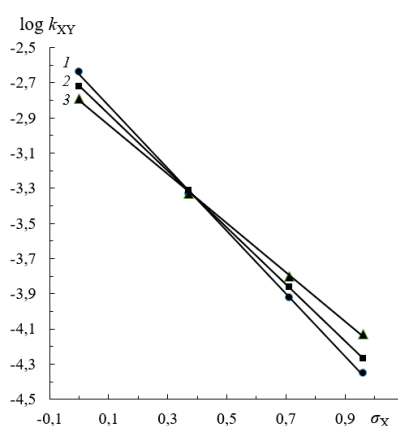
Figure 1. Transition through the isoparametric point σ_X^{IP} = 0.39 in the reactions of X-substituted anilines with Y-substituted benzyl bromides [Y = 3-NO₂ (*1*), 3-Cl (*2*), H (*3*)] in 1 M solution of DMSO in nitrobenzene at 313 K (reaction series 4 in Table 1).

The isoparametricity phenomenon in the reactions (Table 1) can be interpreted in terms of the concept of a variable transition state structure of a direct concerted S_N2 displacement ($A_N D_N$). Upon mutual cross-interaction of the structural factors the ratio between bond making and bond breaking in the activation process in a transition state is changed. At the isoparametric point σ_X^{IP} the transition state must be symmetrical (bond formation is equal to bond breaking, $\rho_Y^X = 0$), and after passing through the isoparametric values of σ_X^{IP} there is an inversion of the sign of ρ_Y^X, which is due to inversion of the substrate reactivities caused by the transition state becoming either associative (bond making is predominated, $\rho_Y^X > 0$) or dissociative (bond breaking is predominated, $\rho_Y^X < 0$). Thus, discussed above transitions through the isoparametric point σ_X^{IP} indicate that associative and dissociative nucleophilic

substitutions may occur together in a single isoparametric reaction series having a common S_N2 mechanism for all the related reactions.

As regards the isoparametric point σ_Y^{IP}, it cannot be attained experimentally in any of the reaction series given in Table 1, because this would require the introduction into the substrate of unrealistically powerful electron donor substituent Y ($\sigma_Y \leq -1.30$). At that point, where ρ_X^Y should be zero, the transition state would have an extremely prominent dissociative character with a very small degree of bond formation. It seems that it is hardly possible for such a transition state to occur on the reaction coordinate within the framework of the S_N2 mechanism.

The considered transitions through the isoparametric points σ_X^{IP} have a direct bearing on the well-known reactivity-selectivity principle,[12] according to which there is an antibate relationship between reactivity and sensitivity: a more (less) reactive system is characterized by less (more) sensitivity to structural changes in reagents. These transitions convincingly demonstrate that this principle is a particular case of the isoparametricity phenomenon. It is fulfilled only in one of the two of parts of a cross reaction series divided by an isoparametric point and is not fulfilled in its other part (see, for example, reaction series 2, 4 in Table 2, and Figure 1).

Quantitative evidence for the second-order interaction structure-structure was obtained in the reactions between benzyl bromides YC₆H₄CH₂Br and imidazoles in nitrobenzene at 313 K.[30] Eq. (5) was used to estimate the influence of structural factors on the rates of these reactions.

$$\log k_{YIm} = \log k_{st} + \rho_Y^{st}\sigma_Y + \beta_{Im}^{st}\text{p}K_{a(Im)} + q_{YIm}\sigma_Y\text{p}K_{a(Im)} \quad (5)$$

Here k_{st} is the rate constant under standard conditions (p$K_{a(Im)}$ = 0, σ_Y = 0), ρ_Y^{st} and β_{Im}^{st} are parameters

for standard reactions at $pK_{a(Im)} = 0$ and $\sigma_Y = 0$, respectively, and q_{YIm} is the cross-interaction coefficient. The values of the coefficients of Eq. (5) are given in regression, [Eq. (6)] ($R = 0.999$).

$$\log k_{YIm} = (-6.48 \pm 0.11) + (-1.23 \pm 0.23)\sigma_Y + \\ (0.53 \pm 0.02)pK_{a(Im)} + (0.17 \pm 0.04)pK_{a(Im)} \quad (6)$$

The statistical significance of $q_{YIm} = 0.17 \pm 0.04$ makes it possible to calculate isoparametric points $\sigma_Y^{IP} = -\beta_{Im}^{st}q_{YIm}^{-1} = -3.12$ and $pK_{a(Im)}^{IP} = -\rho_Y^{st}q_{YIm}^{-1} = 7.23$. The first point goes far beyond the limits of experimental attainability. The second point approximately corresponds to imidazole ($pK_{a(Im)} = 6.99$), the rate of reaction of which barely depends on the effects of the substituents Y in benzyl bromide: in a number of substituents $Y(\sigma_Y) = $ H (0), 3-Cl (0.37), 3-CN (0.56), 3-NO$_2$ (0.71) the values of $\log k_{YIm} = -2.82, -2.84, -2.82, -2.83$, so that $\rho_Y^{Im} = 0$. It should be noted that in a series of azoles ($pK_{a(Im)}$): imidazole (6.99), 4(5)-phenylimidazole (6.10), benzimidazole (5.53) and 5-NO$_2$-benzimidazole (3.48), the values of $\rho_Y^{Im} = 0, -0.17 \pm 0.01, -0.30 \pm 0.02, -0.62 \pm 0.06$. So, in the reactions involving imidazole, in which ρ_Y^{Im} is equal to zero, synchronous S$_N$2 substitution occurs with identical extends of formation and rupture of bonds in the transition state. In the rest of the reactions for which $\rho_Y^{Im} < 0$, the rapture of the bond predominates over formation.

The interaction of the effects of substituents Y and Z was observed in the reactions of anilines $XC_6H_4NH_2$ with benzyl benzenesulfonates ($YC_6H_4CH_2OSO_2C_6H_4Z$) in a volumetric mixture of DMSO and THF (1:3, $v : v$) at 293 K.[8] It was most intense in the reactions involving 4-NH$_2$-aniline (X = 4-NH$_2$) and is described by the following regression, [Eq. (7)] ($R = 0.999$):

$$\log k_{YZ} = (-0.77 \pm 0.01) + (0.11 \pm 0.02)\sigma_Y + \\ (1.95 \pm 0.03)\sigma_Z + (-0.29 \pm 0.06)\sigma_Y\sigma_Z \quad (7)$$

In these reactions it was possible not only to implement the isoparametric point $\sigma_Z^{IP} = 0.38$ for substituent Z in a leaving group of the substrate, but also to realize the transition through this point. It is accompanied by an inversion of the substrate reactivity with respect to the influence of Y substituents in benzyl moiety [$\rho_Y^Z = 0.18, 0.11, 0.02, -0.08$ if Z (σ_Z) = 4-CH$_3$ (−0.17), H (0), 4-Cl (0.23), 3-NO$_2$ (0.71)]. Therefore, depending on the effects of the substituents Z, the S$_N$2 transition state can be associative ($\rho_Y^Z > 0$), symmetrical at the isoparametric point $\sigma_Z^{IP} = 0.38$ ($\rho_Y^Z = 0$), or dissociative ($\rho_Y^Z < 0$).

In reactions (Scheme 3), not only the interaction of structure effects, but also other types of second-order interaction were found. Thus, an intense interaction of the effects of temperature and the medium polarity was identified in the reaction of 3,5-dinitrobenzoyl chloride with 3-fluoroaniline in volumetric mixtures of chlorobenzene with cyclohexane ($v : v$) 1 : 10, 1 : 3, 1 : 1, 3 : 1.[31] To analyze the effects of temperature on the reaction rate at a fixed parameter of the second factor j, the Eyring equation in logarithmic form was used:

$$\log(k_{ji}T^{-1}) = A_{T=\infty}^j + B_T^j T^{-1} \quad (8)$$

Here $A_{T=\infty}^j = \log(k_B h^{-1}) + \Delta S_j^{\neq}(2.3R)^{-1}$, $B_T^j = -\Delta H_j^{\neq}(2.3R)^{-1}$ (k_B – is the Boltzmann constant, h is the Plank constant, and R is the gas constant). Eq. (8) lacks the transmission factor, which is usually taken to be 1 for heterolytic reactions. The coefficients $A_{T=\infty}^j$ and B_T^j were used to calculate the activation entropy $\Delta S_j^{\neq}$ and the activation enthalpy $\Delta H_j^{\neq}$ of the reactions.

Eq. (9) describes the combined influence of the temperature and polarity of the medium on the rate of the reaction under consideration.

$$\log k_{ST} = \log k_{G\infty} + p_S^{T=\infty}P_S + b_T^G(10^3 T^{-1}) + q_{ST}P_S(10^3 T^{-1}) \quad (9)$$

Here, $P_S = [(\varepsilon - 1)(2\varepsilon + 1)^{-1}]_S$ is solvent polarity parameter, where ε is the dielectric constant of solvent S, the indices G and ∞ refer respectively to the standard medium (gas phase, $\varepsilon = 1$, $P_S = 0$) and standard temperature ($T = \infty$ K, $10^3 T^{-1} = 0$).

The joint effects of the variable factors on the reaction rate are evaluated by the regression, [Eq. (10)] ($R = 0.981$).

$$\log k_{ST} = (-10.0 \pm 3.1) + (37.3 \pm 9.7)P_S + \\ (2.70 \pm 0.97)(10^3 T^{-1}) + (-11.6 \pm 0.9)P_S(10^3 T^{-1}) \quad (10)$$

The isoparametric attributes of this regression are the isoparametric points for the temperature $10^3 T^{IP-1} = -p_S^{T=\infty}q_{ST}^{-1} = 3.215$ ($T^{IP} = 311$ K), the medium polarity $P_S^{IP} = -b_T^G q_{ST}^{-1} = 0.23$, and the value of $\log k_{ST}^{IP} = \log k_{G\infty} - p_S^{T=\infty}b_T^G q_{ST}^{-1} = -1.32$ at these points. The isoparametric points turned out to be experimentally achievable. With the regularities of isoparametric dependencies, at these points the reaction rate should not depend on the influence of the corresponding variable factor. Thus, the value of the sensitivity coefficient p_S^T to the medium polarity P_S in one parameter correlation $\log k_{ST} = \log k_{GT} + p_S^T P_S$ becomes equal to zero at a temperature of 313 K, which almost coincides with the isoparametric value $T^{IP} = 311$ K: p_S^T ($T / $ K) = −3.84 (283), −2.88 (290), −2.09 (298), 0 (313). On the

other hand, the sensitivity to the effect of temperature, estimated by the coefficient b_T^S in the Arrhenius-type equation $\log k_{ST} = \log k_{S\infty} + b_T^S (10^3 T^{-1})$, decreases with the transition to less polar media and becomes equal to zero in a mixture of chlorobenzene with cyclohexane (1 : 10), for which the value P_S = 0.236 practically coincides with the isoparametric value P_S^{IP} = 0.233: b_T^S (chlorobenzene : cyclohexane, P_S) = 1.36 (3 : 1, 0.353), 1,04 (1 : 1, 0.322), 0.50 (1 : 3, 0.275), 0 (1 : 10, 0.236).

A graphic illustration of the implementation of the isoparametric points T^{IP} and P_S^{IP} is shown in Figure 2. The correlation lines in the coordinates of the Arrhenius equation intersect at one point where the rate of the reaction does not depend on a change in the medium polarity ($p_S^T = 0$). The coordinates of this point correspond to isoparametric values of $\log k_{ST}^{IP}$ = −1.32 and $10^3(T^{IP} / K)^{-1}$ = 3.21. In addition, a decrease in the angular slopes of the correlation lines *4*, *3*, *2*, *1* to zero with a decrease in the medium polarity upon transition to a mixture of chlorobenzene with cyclohexane (1 : 10, P_S = 0.236) indicates the implementation of the isoparametric point P_S^{IP} = 0.233, where there is no effect of temperature on the reaction rate ($b_T^S = 0$).

Unusual for S_N2 processes an increase in the reaction rate with a decrease in the medium polarity ($p_S^T < 0$) is associated with the formation of the cyclic transition state **B** with a hydrogen bond between the leaving group (L = Cl) and the hydrogen atom of the amino group of 3-F-aniline (Scheme 4). In the formation in low-polar organic solvents of such a transition state due to the H-bond, the leaving group is not the chloride anion Cl⁻, but the energetically favorable electrically neutral HCl molecule. Since both the
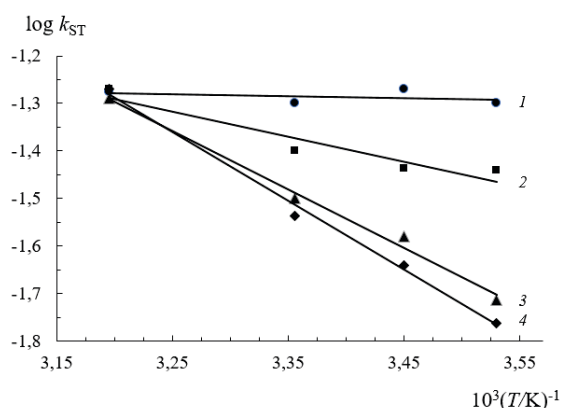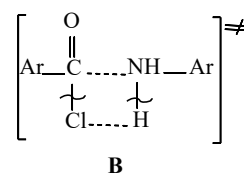
Scheme 4. Cyclic transition state **B** with the formation of a hydrogen bond in a low polar medium.

medium polarity and the temperature affect the strength of the H-bond in transition state **B**, this circumstance is the reason for the intense interaction of the effects of these factors and the clear manifestation of the isoparametric properties of this reaction.

The cyclic structure of the transition state **B** is consistent with the small values of the enthalpy of activation ($\Delta H_S^{\neq}$) and large absolute values of the entropy of activation ($\Delta S_S^{\neq}$): in mixtures of chlorobenzene with cyclohexane 3 : 1, 1 : 1, 1 : 3, 1 : 10 $\Delta H_S^{\neq}/(\text{kJ mol}^{-1})$ = 25.4, 19.9, 8.95, 0 and $\Delta S_S^{\neq}/(\text{J mol}^{-1} \text{ K}^{-1})$ = −194, −214, −248, −277. A consequence of the interaction of the effects of medium polarity and temperature is the compensation relationship in the change in enthalpy $\Delta H_S^{\neq}$ and entropy $\Delta S_S^{\neq}$ of activation as a function of variable medium polarity: $\Delta H_S^{\neq}$ = (86 ± 1)10³ + (309 ± 5)$\Delta S_S^{\neq}$. The slope in this relationship evaluates the value T_{iso} = 309 K, which is consistent with the T^{IP} = 311 K calculated from Eq. (10).
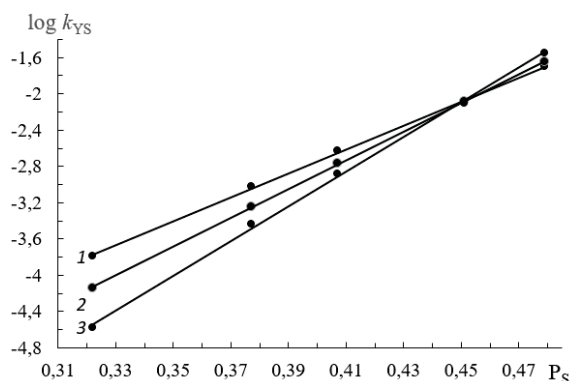
Arguments in favor of the formation of a cyclic transition state with H-bond in the reactions of aroyl chlorides with anilines in low polar media (chlorobenzene-cyclohexane mixtures) are also discussed.[26]

The intense interaction of the effects of the structure and polarity of the medium is manifested in the reactions of Y-substituted benzyl bromides with *n*-butylamine in nitrobenzene, chlorobenzene, and binary volumetric mixtures of chlorobenzene with nitrobenzene and cyclohexane at 313 K.[32] The joint influence of these factors on the rate of reactions is described by Eq. (11), the coefficients of which are presented in regression, Eq. (12) (R = 0.999).

$$\log k_{YS} = \log k_{HG} + \rho_Y^G \sigma_Y + p_S^{Y=H} P_S + q_{YS} \sigma_Y P_S \qquad (11)$$

$$\log k_{YS} = (-7.94 \pm 0.08) + (4.0 \pm 0.2)\sigma_Y + (13.0 \pm 0.2)P_S + (8.9 \pm 0.4)\sigma_Y P_S \qquad (12)$$

Regression, Eq. (12), displays isoparametric proper-ties that are quantitatively characterized by the isopara-metric points for the constant of substituent Y, σ_Y^{IP} = $-p_S^{Y=H} q_{YS}^{-1}$ = −1.47, and for the medium polarity P_S^{IP} = $-\rho_Y^G q_{YS}^{-1}$ = 0.449. In the isoparametric point σ_Y^{IP} the rate of

Figure 2. Intersection of the correlation lines in the coordinates of the Arrhenius equation at $10^3(T / K)^{-1}$ = 3.19 (T = 313 K) near the isoparametric point $10^3(T^{IP} / K)^{-1}$ = 3.21 (T^{IP} = 311 K) in the reaction of 3,5-dinitrobenzoyl chloride with 3-fluoroaniline in volumetric mixtures of chlorobenzene with cyclohexane ($v : v$, P_S): 1 : 10, 2.34 (*1*), 1 : 3, 2.83 (*2*), 1 : 1, 3.71 (*3*), 3 : 1, 4.60 (*4*).[31]

Figure 3. Transition through the isoparametric point P_S^{IP} = 0.449 in the reactions of Y-substituted benzyl bromides [Y = H (*1*), 3-Cl (*2*), 3-NO$_2$ (*3*)] with n-butylamine in nitrobenzene, chlorobenzene, and volumetric binary mixtures of chlorobenzene with nitrobenzene and cyclohexane at 313 K.[32]

the process should not depend on the medium polarity (p_S^Y = 0). However, this point cannot be realized because of the deficit of powerful electron-donor substituents Y in benzyl bromide with σ_Y = −1.47. As for the isoparametric point P_S^{IP} = 0.449, it falls in the experimental range of variation of the medium polarity P_S = 0.322 to 0.479 which made it possible to carry out the transition through this point, accompanied by inversion of the sign of the sensitivity coefficient ρ_Y^S: in a series of such solvents as nitrobenzene, nitrobenzene : chlorobenzene (1 : 1), (1 : 9), chlorobenzene, chlorobenzene : cyclohexane (1 : 1) the values of ρ_Y^S (P_S) are respectively equal to 0.21 ± 0.05 (0.479), 0 (0.451), −0.37 ± 0.03 (0.407), −0.60 ± 0.02 (0.377), −1.18 ± 0.20 (0.322). This unique situation is illustrated by Figure 3. Inversion of the sign of the sensitivity coefficient ρ_Y^S in this reaction series is due to the change in the S$_N$2 transition state from associative (ρ_Y^S > 0) through symmetrical (ρ_Y^S = 0) to dissociative (ρ_Y^S < 0) and conversely, in response to the joint effects of the structural factors and the medium polarity.

Isoparametricity Phenomenon in Oxirane Ring Opening Reactions. Enthalpy-Entropy Compensation Effect

The interactions structure-structure and structure-temperature types were clearly manifested in reactions of X-substituted 2-aryloxiranes **1a**–**1c** [X = H (**1a**), 4-NO$_2$ (**1b**), 3,5-(NO$_2$)$_2$ (**1c**)] and symmetrically X-substituted trans-2,3-
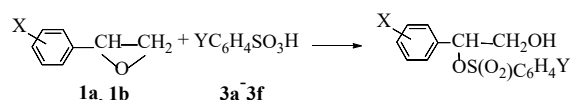
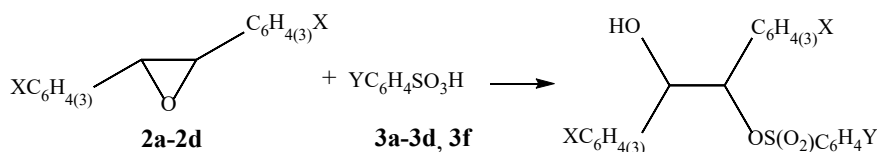**Scheme 5.** Reactions of 2-aryloxiranes **1** with arenesulfonic acids **3**.

diaryloxiranes **2a**–**2d** [X = H (**2a**), 3-Br (**2b**), 4-NO$_2$ (**2c**), 3-Br-5-NO$_2$ (**2d**)] with Y- substituted arenesulfonic acids **3a**-**3f** [Y = 4-OCH$_3$ (**3a**), 4-CH$_3$ (**3b**), H (**3c**), 4-Cl (**3d**), 4-Br (**3e**), 3-NO$_2$ (**3f**)] (Schemes 5, 6).[33–37] In these reactions, convincing experimental evidence for the phenomenon of isoparametricity was obtained. Of particular importance is the proof of the physical reality of such a special aspect of isoparametricity as an enthalpy-entropy compensation effect, which has been the subject of hot debate by scientists for many decades.[38–43] In reactions with the participation of oxiranes **1a**, **1b** α-ring opening occurs with the formation of primary alcohols.[33] Secondary alcohol products of β-ring opening form in reactions of oxirane **1c** with strong electron acceptor substituents [X = 3,5-(NO$_2$)$_2$].[34]

Intense interaction of the effects of the structure appears in the reactions of X-substituted oxiranes **2a**–**2d** with Y-substituted acids **3a**–**3d**, **3f** in the mixture of dioxane with 1,2-dichloroethane (7 : 3, *v* : *v*) at 265 K (Scheme 6).[36] Mutual effects of the substituents X and Y were estimated by Eq. (13).

$$\log k_{XY} = \log k_{HH} + \lambda_X^{st}\tau_X + \rho_Y^{st}\sigma_Y + q_{XY}\tau_X\sigma_Y \qquad (13)$$

Here, k_{HH} is the rate constant of the standard reaction (X = H, τ_X = 0, Y = H, σ_Y = 0), λ_X^{st} and ρ_Y^{st} are the coefficients of sensitivity of the standard reaction (Y = H, X = H, respectively). Substituent constant $\tau_X = \log k_{HH} - \log k_{XH}$ is a quantitative characteristic of total effects of substituents X in oxiranes **2a**–**2d** (values of τ_X for X = H in **2a**, 3-Br in **2b**, 4-NO$_2$ in **2c**, 3-Br-5-NO$_2$ in **2d** are equal to 0, 2.02, 3.47, and 4.38, respectively).[36] The treatment of the results of the multifactor kinetic experiment using Eq. (13) gives the polylinear regression, Eq. (14) (R = 0.999).

$$\log k_{XY} = (-1.24 \pm 0.01) + (-0.999 \pm 0.002)\tau_X + (1.61 \pm 0.04)\sigma_Y + (-0.34 \pm 0.01)\tau_X\sigma_Y \qquad (14)$$
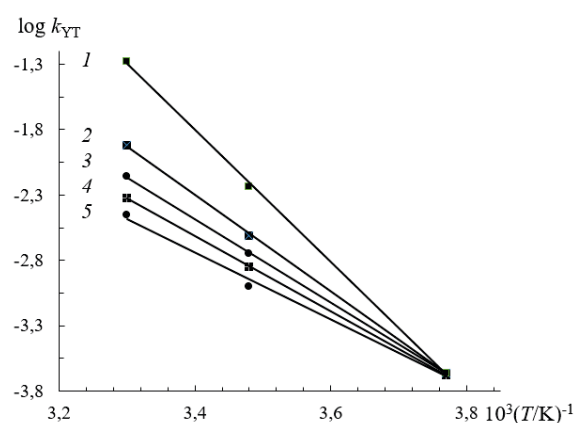

Scheme 6. Reactions of 2,3-diaryloxiranes **2** with arenesulfonic acids **3**.
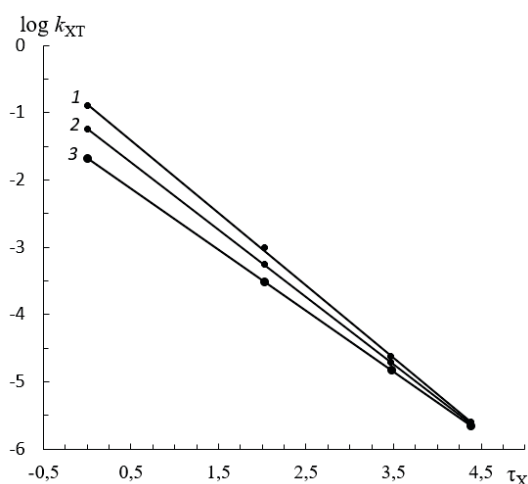
Figure 4. Intersection of the correlation lines at $\tau_X = 4.38$ near the isoparametric point $\tau_X^{IP} = 4.73$ in the reactions of oxiranes (τ_X) **2a** (0), **2b** (2.02), **2c** (3.47), **2d** (4.38) with arenesulfonic acids **3d** (1), **3c** (2), and **3a** (3) in the dioxane − 1,2-dichloroethane mixture (7:3, $v : v$) at 265 K.[36]

Quantitative characteristics of the regression are the isoparametric points for substituent X ($\tau_X^{IP} = -\rho_Y^{st}q_{XY}^{-1} = 4.73$) and Y ($\sigma_Y^{IP} = -\lambda_X^{st}q_{XY}^{-1} = -2.94$). The calculated points fall in the range of low reactivity of the system ($\log k_{XY}^{IP} = \log k_{HH} - \lambda_X^{st}\rho_Y^{st}q_{XY}^{-1} = -5.97$). Experimentally, it is impossible to reach the point $\sigma_Y^{IP} = -2.94$, at which the reaction rate would be independent on substituent X in oxirane **2** ($\lambda_X^Y = 0$), because of the absence of such strong electron donor substituents Y. At the same time, the isoparametric point $\tau_X^{IP} = 4.73$ for substituent X is almost reached in the case of oxirane **2d**, for which the total value $\tau_X = 4.38$ of the substituents X = 3-Br-5-NO$_2$ is close to the isoparametric point τ_X^{IP}. At this point the effects of the substituents Y in acid **3** should not appear, which is confirmed by a decrease in ρ_Y^X (X, τ_X) = 1.57 ± 0.02 (H, 0), 1.00 ± 0.04 (3-Br, 2.02),

Figure 5. Intersection of the correlation lines in the coordinates of the Arrhenius equation at $10^3(T/K)^{-1} = 3.77$ ($T = 265$ K) near the isoparametric point $10^3(T^{IP}/K)^{-1} = 3.80$ ($T^{IP} = 263$ K) in the reactions of oxirane **1c** with arenesulfonic acids **3f** (1), **3d** (2), **3c** (3), **3b** (4), **3a** (5) (reaction series 1 in Table 3).

0.50 ± 0.03 (3-NO$_2$, 3.47), 0.10 ± 0.05 (3-Br-5-NO$_2$, 4.38) with an increase in the electron withdrawing properties of the substituents X.[36,37] Figure 4 explicitly demonstrates intersection of correlation dependencies of $\log k_{XY}$ on τ_X for different fixed substituents Y close to the isoparametric point τ_X^{IP}.

As noted above, in the reactions of oxirane substrates with acidic reagents, there is an intense interaction between the effects of structure and temperature. To assess the joint effects of substituents Y and temperature T on the rate of the reactions of acids **3** with oxiranes **1** and **2**, Eq. (15) was used.

$$\log k_{YT} = \log k_{HT=\infty} + \rho_Y^{T=\infty}\sigma_Y + q_T^{Y=H}(10^3\,T^{-1}) + q_{YT}\sigma_Y(10^3\,T^{-1}) \tag{15}$$

Table 3. The coefficients of Eqs. (15)[a], (16)[a] and the values of the isoparametric points for the reactions of oxiranes **1** and **2** with acids **3** at different temperatures [dioxan (DO), diglyme (DG), acetonitrile (AN), 1,2-dichloroethane (1,2-DCE)].

RS[b]	Oxirane	Acids	Solvent[c]	$\log k_{HT=\infty}$	$\rho_Y^{T=\infty}$	$q_T^{Y=H}$	q_{YT}	σ_Y^{IP}	T^{IP} K	Refs
1	**1c**	**3a–3d**, **3f**	DO:DG, 1:1	8.4 ± 0.2	9.5 ± 0.6	−3.21 ± 0.07	−2.5 ± 0.2	−1.28	263[d]	[34]
2	**1b**	**3a–3c**, **3e**	DO	10.4 ± 0.3	21 ± 1	−3.4 ± 0.1	−5.8 ± 0.4	−0.59	276	[33]
3	**2d**	**3a–3d**	DO:1,2−DCE, 7:3	11.7 ± 0.1	8.4 ± 0.7	−4.61 ± 0.04	−2.2 ± 0.2	−2.09	262[d]	[37]
				$\Delta G_{HT=0}^{\neq}$	$Q_Y^{T=0}$	$Q_T^{Y=H}$	Q_{YT}	$\sigma_Y^{IP(G)}$	$T^{IP(G)}$ K	
1G	**1c**	**3a–3d**, **3f**	DO:DG, 1:1	60.7 ± 1	41 ± 2	0.084 ± 0.003	−0.16 ± 0.01	0.54[d]	263[d]	[34]
3G	**2d**	**3a–3d**	DO:1,2−DCE, 7:3	83 ± 1	47 ± 5	0.036 ± 0.003	−0.18 ± 0.02	0.20[d]	261[d]	[37]
4G	**2c**	**3a–3d**, **3f**	DO:1,2−DCE, 7:3	67 ± 1	39 ± 3	0.083 ± 0.004	−0.16 ± 0.01	0.52[d]	244	[35]

[a]   Cross-correlation coefficient $R \geq 0.995$.
[b]   Reaction series.
[c]   Volumetric mixtures of solvents ($v : v$) were used.
[d]   Experimentally observed isoparametric point.

The coefficients of Eq. (15) and the isoparametric point values calculated for the parameters of the variable factors $\sigma_Y^{IP} = -q_T^{Y=H}q_{YT}^{-1}$ and $T^{IP-1} = -\rho_Y^{T=\infty}(q_{YT}10^3)^{-1}$ [$T^{IP} = -q_{YT}10^3(\rho_Y^{T=\infty})^{-1}$] are given for reaction series 1–3 in Table 3. In reaction series 1, 3 an experimental implementation of the isoparametric points T^{IP} was carried out. Their values are close to the temperature of 265 K in an experiment. At this temperature, in accordance with the regularities of isoparametric dependences, there should be no sensitivity of the process to the effects of substituents Y. Indeed, in these reaction series, the values ρ_Y^T tend to zero with decreasing temperature to 265 K: 1.18 ± 0.05 (303 K), 0.81 ± 0.01 (287 K), 0 (265 K); 1.01 ± 0.09 (298 K), 0.50 ± 0.04 (281 K), 0.10 ± 0.05 (265 K).[34,37] Figure 5 shows the intersection of the correlation lines in the coordinates of the Arrhenius equation with the fixed substituents Y near the isoparametric point T^{IP} = 263 K in reaction series 1.

In rection series 2, the implementation of the formally available T^{IP} = 276 K turned out to be impossible due to the solid state of the used solvent (dioxane, T_{mp} = 284.7 K).

At the isoparametric point σ_Y^{IP}, the rate of the process should not depend on the temperature ($q_T^Y = 0$), and according to Eq. (8) activation enthalpy $\Delta H_Y^{\neq}$ must be equal to zero [$B_T^j (B_T^Y) = 0$, $\Delta H_j^{\neq} (\Delta H_Y^{\neq}) = 0$)]. However, this point cannot be implemented in reaction series 1–3 due to the lack of strong electron-donating substituents Y.

In terms of activation parameters, the interaction between the effects of structure and temperature can be analyzed using the following multilinear relation:

$$\Delta G_{YT}^{\neq} = \Delta G_{HT=0}^{\neq} + Q_Y^{T=0}\sigma_Y + Q_T^{Y=H}T + Q_{YT}\sigma_Y T \tag{16}$$

Table 3 shows the coefficients of Eq. (16) for reaction series 1G, 3G, 4G with experimentally implemented isoparametric points $\sigma_Y^{IP(G)} = -Q_T^{Y=H}Q_{YT}^{-1}$ and $T^{IP(G)} = -Q_Y^{T=0}Q_{YT}^{-1}$. The values of the isoparametric point for temperature $T^{IP(G)}$ in reaction series 1G, 3G consistent with the above calculated values T^{IP} for the reaction series 1, 3 in Table 3. At these points, the activation free energy $\Delta G_{YT}^{\neq IP}$ does not depend on the effects of substituents Y. The reason for the disappearance of the effects Y on the isoparametric value $\Delta G_{YT}^{\neq IP}$ at $T^{IP(G)}$ is the enthalpy-entropy compensation effect, *i.e.* the complete compensation of the variation of enthalpy and entropy components in activation free energy: $\delta_Y\Delta H_Y^{\neq} = T^{IP(G)}\delta_Y\Delta S_Y^{\neq}$; as a result, $\delta_Y\Delta G_{YT}^{\neq IP} = \delta_Y\Delta H_Y^{\neq} - T^{IP(G)}\delta_Y\Delta S_Y^{\neq} = 0$, $\Delta G_{YT}^{\neq IP}$ = const, and isokinetic phenomenon occurs (k_{YT} = const, $\rho_Y^T = 0$). The enthalpy-entropy compensation effect is realized in reaction series 1G, 3G at a temperature of 265 K in an experiment close to $T^{IP(G)}$ = 263, 261 K. For example, at this temperature the values $\Delta G_{YT}^{\neq}$ are almost the same for the reactions of acids **3a**, **3b**, **3c**, and **3d** in reaction series 3G:

93.3, 92.8, 93.3, and 93.1 kJ mol⁻¹; that is, they remain practically invariable with different substituents Y in the acidic reagent ($\rho_Y^T = 0$). In reaction series 3G the values of the sensitivity coefficient Q_Y^T to the effects of Y tend to zero as the temperature decreases to 265 K: Q_Y^T (T/K) = −5.1 ± 0.7 (298), -2.9 ± 0.3 (281), and 0 (265). According to the polylinearity principle, the following relationship between Q_Y^T and T is valid: $Q_Y^T = (41 ± 4) + (−0.155 ± 0.005)T$ (r = 0.995), whose slope coincides with the cross interaction coefficient Q_{YT} = −0.18 for reaction series 3G. From this equation it follows that the sensitivity of $\Delta G_{YT}^{\neq}$ to the influence of the substituents Y disappears ($Q_Y^T = 0$) at a temperature of 264 K, corresponding to its isoparametric value $T^{IP(G)}$ = 261 K.
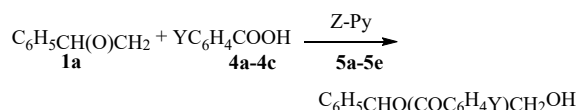
The isoparametric points $\sigma_Y^{IP(G)}$ for the substituent Y were realized in the reaction series 1G, 3G, and 4G. They fall in the experimental range of variation of σ_Y (Y) = −0.27 (4-OMe) to 0.71 (4-NO₂). A remarkable feature of these points is that the free activation energy $\Delta G_{YT}^{\neq IP}$ at them does not depend on temperature, that is possible if in the expression $\Delta G_{YT}^{\neq IP} = \Delta H_Y^{\neq} - T\Delta S_Y^{\neq}$ the activation entropy $\Delta S_Y^{\neq} = 0$ and the free activation energy is determined only by the enthalpy term ($\Delta G_{YT}^{\neq IP} = \Delta H_Y^{\neq}$). Such a unique situation is confirmed, for example, by the equation $\Delta S_Y^{\neq} = (−87 ± 1) + (187 ± 3)\sigma_Y$ (r = 0.999) for reaction series 4G, from which it follows that $\Delta S_Y^{\neq} = 0$ at the value σ_Y = 0.47, which corresponds to the value $\sigma_Y^{IP(G)}$ = 0.52. In reaction series 1G, 3G, 4G it was possible not only to demonstrate a rare case of realization of the isoparametric points for the structural parameter $\sigma_Y^{IP(G)}$, but also to realize unique transitions through these points, when the substituents Y were varied. The transition through the isoparametric point $\sigma_Y^{IP(G)}$ = 0.54 in reaction series 1G is shown in Figure 6. According to the regularities of isoparametric dependences, such transitions are accompanied by an inversion of the sign of the activation entropy $\Delta S_Y^{\neq}$. For example, in reaction series 4G this phenomenon is observed when passing through $\sigma_Y^{IP(G)}$ = 0.52 in the series of acids **2a−2d**,

$\Delta G_{YT}^{\#}$/kJ mol⁻¹
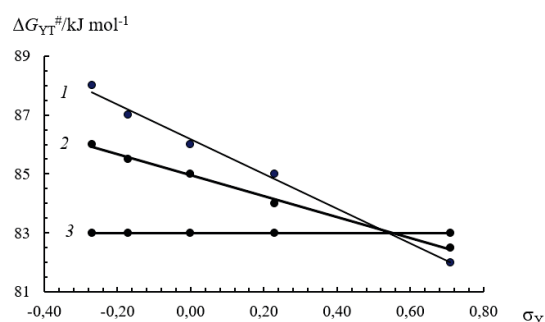
Figure 6. Transition through the isoparametric point $\sigma_Y^{IP(G)}$ = 0.54 in the reactions of oxirane **1c** with acids **3** (Y, σ_Y): **3a** (4-OMe, −0.27), **3b** (4-Me, −0.17), **3c** (H, 0), **3d** (4-Cl, 0.23), **3f** (4-NO₂, 0.71) at T/K = 303 (*1*), 287 (*2*), and 265 (*3*) (reaction series 1G in Table 3).

$\Delta G_{YT}^{\neq}/\text{kJ mol}^{-1}$
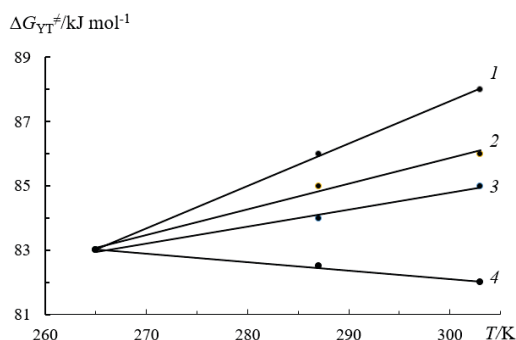
Figure 7. Inversion of the temperature effect on the free activation energy $\Delta G_{YT}^{\neq}$ after passing through the isoparametric point $\sigma_Y^{\text{IP(G)}} = 0.54$ in the reactions of oxirane **1c** with acids **3** (Y, σ_Y): **3a** (4-OCH₃, -0.27) (*1*), **3c** (H, 0) (*2*), **3d** (4-Cl, 0.23) (*3*), **3f** (3-NO₂, 0.71) (*4*) (reaction series 1G in Table 3).

$$C_6H_5CH(O)CH_2 + YC_6H_4COOH \xrightarrow[\textbf{5a-5e}]{\text{Z-Py}}$$
$$\underset{\textbf{1a}}{} \qquad \underset{\textbf{4a-4c}}{}$$
$$C_6H_5CHO(COC_6H_4Y)CH_2OH$$

Scheme 7. Reactions of oxirane **1a** with arenecarboxylic acids **4** catalyzed by pyridines (Z-Py) **5**.

2f: $\Delta S_Y^{\neq}/(\text{kJ mol}^{-1}\text{ K}^{-1})$ (Y, σ_Y) = −140 (4-OMe, −0.27), −119 (4-Me, −0.17), −85 (H, 0), −42 (4-Cl, 0.23), 44 (3-NO₂, 0.71). The inversion of the sign of the activation entropy causes the reversal of the effect of temperature on the value of $\Delta G_{YT}^{\neq}$. Figure 7 illustrates this unique situation.

A striking manifestation of the isoparametricity phenomenon is observed in the reactions of oxirane **1a** with Y-substituted arenecarboxylic acids **4a–4c** [Y = H (**4a**), 3-Br (**4b**), 3-NO₂ (**4c**)] catalyzed by Z-substituted pyridines (Z-Py) **5a–5e** [Z = 4-OMe (**5a**), 4-Et (**5b**), H (**5c**), 3-COOEt (**5d**), 3-CN (**5e**) (Scheme 7).[44,45]

Eq. (17) was used to describe the joint effect of temperature and substituents Z in catalyst **5** on the rate of these reactions.

$$\log k_{ZT} = \log k_{HT=\infty} + \rho_Z^{T=\infty}\sigma_Z + q_T^{Z=H}(10^3\,T^{-1}) + q_{ZT}\sigma_Z(10^3\,T^{-1}) \tag{17}$$

The coefficients of Eq. (17) for reaction series 1–3 in which the isoparametric points $\sigma_Z^{\text{IP}} = -q_T^{Z=H}q_{ZT}^{-1}$ and $T^{\text{IP}} = -q_{ZT}10^3(\rho_Z^{T=\infty})^{-1}$ were implemented, are given in Table 4. The isoparametric points with respect to temperature T^{IP} correspond to the slopes of compensation dependences (18)–(20) in the change in the activation enthalpy $\Delta H_Z^{\neq}$ and entropy $\Delta S_Z^{\neq}$ under the influence of substituents Z in catalyst **5a–5e** in the series of acids **4a**, **4b**, **4c** ($r = 0.999$).[44].

$$\Delta H_Z^{\neq} = (97.8 \pm 0.6) \cdot 10^3 + (293 \pm 3)\Delta S_Z^{\neq} \tag{18}$$

$$\Delta H_Z^{\neq} = (95.6 \pm 0.3) \cdot 10^3 + (294 \pm 2)\Delta S_Z^{\neq} \tag{19}$$

$$\Delta H_Z^{\neq} = (93.4 \pm 0.3) \cdot 10^3 + (293 \pm 1)\Delta S_Z^{\neq} \tag{20}$$

In these reaction series, the values of the isoparametric points T^{IP} do not go beyond the temperature range 279 to 343 K in an experiment, which indicates physical reality of these points. Table 5 shows that, according to the concept of enthalpy-entropy compensation, at an experimenttal temperature of 295 K, corresponding to these points, the sensitivity coefficient ρ_Z^T to the effects of substituents Z in pyridines **5a–5e** in the reactions of oxirane **1** with acids **4a–4c** in acetonitrile approaches zero, *i.e.*, the reactions under consideration become isokinetic. The opposite signs of ρ_Z^T after passing through the isoparametric points T^{IP} 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

Table 4. The coefficients of Eqs. (17)[(a)], (21)[(a)] and the values of the isoparametric points for the reactions of oxirane **1a** with acids **4a-4c** catalyzed by pyridines (Pys) **5a-5e** in acetonitrile at different temperatures.

RS[(b)]	Acid	Pys	$\log k_{HT=\infty}$	$\rho_Z^{T=\infty}$	$q_T^{Z=H}$	q_{ZT}	σ_Z^{IP}	T^{IP} K	Refs
1	**4a**	**5a–5d**	5.0 ± 0.1	-15.6 ± 0.8	-2.81 ± 0.04	4.6 ± 0.2	0.61	295[(c)]	[44][(d)]
2	**4b**	**5a–5e**	5.6 ± 0.1	-15.5 ± 0.5	-2.86 ± 0.04	4.5 ± 0.2	0.62[(c)]	295[(c)]	[44][(d)]
3	**4c**	**5a–5e**	5.6 ± 0.2	-16.9 ± 0.8	-2.80 ± 0.06	5.0 ± 0.2	0.56[(c)]	296[(c)]	[45]
			$\Delta G_{HT=0}^{\neq}$	$Q_Z^{T=0}$	$Q_T^{Z=H}$	Q_{ZT}	$\sigma_Z^{\text{IP(G)}}$	$T^{\text{IP(G)}}$ K	
1G	**4a**	**5a–5d**	53 ± 1	-81 ± 6	0.150 ± 0.005	0.27 ± 0.02	−0.56	300[(c)]	[44][(d)]
2G	**4b**	**5a–5e**	52 ± 2	-80 ± 4	0.148 ± 0.005	0.27 ± 0.01	−0.55	296[(c)]	[44][(d)]
3G	**4c**	**5a–5e**	53 ± 1	-86 ± 3	0.138 ± 0.003	0.29 ± 0.01	−0.48	296[(c)]	[45]

(a) Cross-correlation coefficient $R \geq 0.996$.

(b) Reaction series.

(c) Experimentally observed isoparametric point.

(d) The coefficients were calculated using the data from the indicated work.
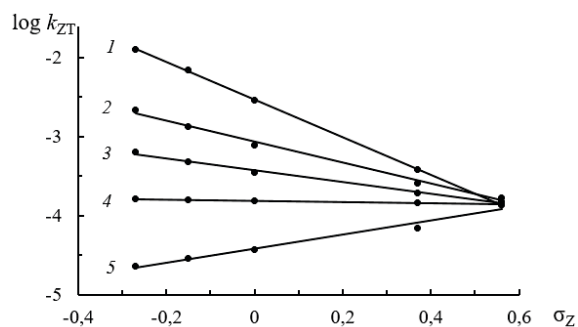
Figure 8. Temperature-induced reversal of the order of the catalytic activity of pyridines **5a-5e** in reaction of oxirane **1a** with acid **4c** at the temperature T/K: 343 (*1*), 323 (*2*), 308 (*3*), 295 (*4*), 279 (*5*) (reaction series 3 in Table 4).

Table 5. Values ρ_Z^T ($r \geq 0.995$) in the Hammett type equation (log k_{ZT} = log $k_{HT=\infty} + \rho_Z^T \sigma_Z$) for catalyzed by pyridines **7a–7e** reactions of oxirane **1a** with arenecarboxylic acids **4** (Scheme 6) in acetonitrile at different temperatures.[45]

acid	ρ_Z^T				
(Y)	279 K	295 K	308 K	323 K	343 K
4a (H)	0.751 ± 0.005	-0.078 ± 0.002	-0.77 ± 0.06	-1.62 ± 0.06	-2.4 ± 0.2
4b (3-Br)	0.81 ± 0.08	-0.077 ± 0.009	-0.77 ± 0.04	-1.74 ± 0.04	-2.4 ± 0.1
4c (3-NO₂)	0.761 ± 0.009	-0.083 ± 0.003	-0.75 ± 0.04	-1.30 ± 0.07	-2.4 ± 0.1

from 279 to 343 K. A graphical illustration of this paradox in reaction series 3 is shown in Figure 8.

As for the isoparametric points σ_Z^{IP}, they are implemented in reaction series 2 and 3 in the reactions involving pyridine **5e** (Z = 3-CN, σ_Z = 0.56). At these points the rate of the catalytic process should not depend on the temperature (q_T^Z = 0), and according to Eq. (8) activation enthalpy $\Delta H_Z^{\neq}$ must be equal to zero [B_T^j (B_T^Z) = 0, $\Delta H_j^{\neq}$ ($\Delta H_Y^{\neq}$) = 0)]. As can be seen in Figure 8, the temperature factor has no effect on the rate of the catalytic process (reaction series 3) at $\sigma_Z = \sigma_Z^{IP}$ = 0.56. In the reaction series 2, for example, the values of the sensitivity coefficient q_T^Z to the effects of temperature approach zero in the series of pyridines **5a-5e** (Z, σ_Z): –3.96 ± 0.09 [**5a** (4-OMe, -0.27)], –3.40 ± 0.09 [**5b** (4-Et, –0.15)], –2.65 ± 0.03 [**5c** (H, 0)], –1.27 ± 0.01 [**5d** (3-COOEt, 0.37)], –0.17 ± 0.02 [**5e** (3-CN, 0.56)].[44] In this series of pyridines activation enthalpy and entropy are changed as follows: $\Delta H_Z^{\neq}$/(kJ mol⁻¹) = 76, 65, 51, 23, 3.3; $\Delta S_Z^{\neq}$/(J mol⁻¹ K⁻¹) = –66, –104, –153, –242, –314. According to the equations obtained for the reactions of oxirane **1a** with acids **4b** and **4c** in the presence of pyridine **5e**, $\Delta H_Z^{\neq}$ = (52.4 ± 0.8) + (–85 ± 2)σ_Z (r = 0.999) and $\Delta H_Z^{\neq}$ = (52 ± 1) + (–85 ± 3)σ_Z (r = 0.998), the activation enthalpy $\Delta H_Z^{\neq}$ = 0 at σ_Z values of 0.62 and 0.61, respectively, which
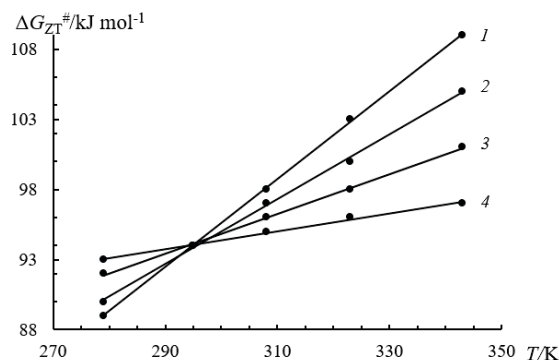
Figure 9. Transition through the isoparametric point $T^{IP(G)}$ = 296 K in the reaction between oxirane **1a** and acid **4c** catalyzed by pyridines **5a** (*4*), **5c** (*3*), **5d** (*2*), **5e** (*1*) in acetonitrile (reaction series 3G in Table 4).

are practically equal to the values of the isoparametric points σ_Z^{IP} in reaction series 2 and 3. At these points, the free activation energy and, accordingly, the rate of the catalytic process, will be determined only by the entropic factor ($\Delta G_{ZT}^{\neq IP}$ = $-T\Delta S_Z^{\neq}$). In the reactions catalyzed by pyridine **5e**, the contribution of the entropy term to the activation free energy at 298 K exceeds 96 %. The above indicates that when the considered isoparametric points σ_Z^{IP} are reached, the catalytic process occurs without an activation barrier.

The non-additive effects of the structure and temperature on the free activation energy of catalyzed by Z-Py **5a–5e** reactions of oxirane **1a** with acids **4a–4c** can be analyzed using [Eq. (21)].

$$\Delta G_{ZT}^{\neq} = \Delta G_{HT=0}^{\neq} + Q_Z^{T=0}\sigma_Z + Q_T^{Z=H}T + Q_{ZT}\sigma_Z T \qquad (21)$$

Table 4 shows the coefficients of this equation for reaction series 1G–3G with experimentally implemented isoparametric points for temperature $T^{IP(G)}$. Their values coincide with the values of the isoparametric points T^{IP} ($T^{IP} \approx T^{IP(G)}$). At these points, the influence of substituents Z on the free activation energy $\Delta G_{ZT}^{\neq}$ disappears due to enthalpy-entropy compensation. Thus, in reaction series 3G at a temperature of 295 K, close to the isoparametric temperature of 296 K, the value of $\Delta G_{ZT}^{\neq}$ becomes unchanged with varying substituent Z in pyridines **5a - 5e**: $\Delta G_{ZT=295}^{\neq}$/(kJ mol⁻¹) = 94, 94, 94, 94, 94.[44] Figure 9 shows the transition through $T^{IP(G)}$ = 296 K in reaction series 3G, accompanied by the reversal of the catalytic activity of pyridines.

In isoparametric points $\sigma_Z^{IP(G)}$, the value $\Delta G_{ZT}^{\neq IP}$ should not depend on temperature due to the equality of activation entropy to zero (at $\Delta S_Z^{\neq}$ = 0 $\Delta G_{ZT}^{\neq IP}$ = $\Delta H_{ZT}^{\neq}$). However, these points were not implemented in the experiment.

Thus, the above cross correlation analysis of the joint structure-temperature effects in oxirane ring opening reactions shows that the kinetic enthalpy-entropy compensation effect is, in essence, a particular case of isoparametricity. The quantitative characteristics of the compensation phenomenon are three isoparametric points: $T^{IP} \approx T^{IP(G)}$, $\sigma_{Y(Z)}{}^{IP}$, and $\sigma_{Y(Z)}{}^{IP(G)}$ in which the cross-reaction series acquire special "magic" properties. It was mentioned above that, at the isoparametric points T^{IP} ($T^{IP(G)}$) the influence of the substituents Y in acids **3** and Z in catalyst **5** on the free activation energy $\Delta G_{YT}{}^{\neq}$, $\Delta G_{ZT}{}^{\neq}$ and, accordingly, on the reaction rate disappears ($\rho_Y = 0$, $\rho_Z = 0$) owing to enthalpy–entropy compensation.

It should be noted that the insignificant changes in the free activation energy in the considered cross-reaction series under the influence of structural factors conceal dramatic changes in the enthalpy and entropy of activation due to the enthalpy-entropy compensation effect. Because of the dual nature of the free activation energy, within the enthalpy-entropy compensation effect the considered cross-reaction series pass from special state associated with the isoparametric points $\sigma_Y{}^{IP}$ and $\sigma_Z{}^{IP}$, in which there is no contribution from the enthalpic factor to the free activation energy ($\Delta H_{Y(Z)}{}^{\neq} = 0$, $\Delta G_{Y(Z)}{}^{\neq} = -T\Delta S_{Y(Z)}{}^{\neq}$), to the equally interesting state associated with the isoparametric points $\sigma_Y{}^{IP(G)}$ and $\sigma_Z{}^{IP(G)}$, in which there is no contribution from the entropic factor ($\Delta S_{Y(Z)}{}^{\neq} = 0$, $\Delta G_{Y(Z)}{}^{\neq} = \Delta H_{Y(Z)}{}^{\neq}$). The physical reality of all these isoparametric points has been proved, moreover, transitions through them have been made, that is, the paradox of isoparametricity has been demonstrated. Between these extremal states, the reacting systems are controlled by the compensation in the change in the enthalpy and entropy of activation when the structure of the acids **3** (substituent Y) or catalyst **5** (substituent Z) are varied.

The isoparametric points for temperature T^{IP} (T_{iso}) and $T^{IP(G)}$ (T_{com}) are widely discussed as a quantitative characteristic of the isokinetic (isoequilibrium) phenomenon and enthalpy-entropy compensation effect, however, the isoparametric points of the same importance, such as $\sigma_Y{}^{IP}$, $\sigma_Z{}^{IP}$, $\sigma_Y{}^{IP(G)}$ and $\sigma_Z{}^{IP(G)}$, for the parameter of another variable factor do not usually attract any attention of researchers. Here it was shown that such points contain worthy of attention information about the hidden properties of the reacting systems.

It should be noted that ignoring multifactor experiments in the study of the enthalpy-entropy compensation effect does not allow obtaining statistically reliable characteristics of compensation dependencies. The enthalpy–entropy compensation derived from a plot ΔH against ΔS appears often to be a phantom due to random errors in kinetic data that generate an apparent compensation effe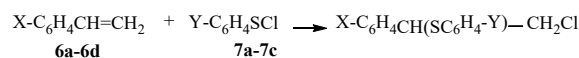ct (sometimes termed the statistical compensation effect). Moreover, false compensation dependences can arise since the activation parameters are mutually dependent because of their determination from the same experimental data. This topic is constantly debated in dozens of publications since the 1960s. In some of them, the existence of any real compensation effect was derided (see, for example, simulation of a random compensation dependence with the use of telephone numbers).[46] Critics call the enthalpy-entropy compensation effect "*a phantom phenomenon*," "*a computational (statistical) artifact*," "*a false (meaningless) compensation*," and so on.

The reviewed cross-reaction series have shown that consensus in disputes concerning enthalpy–entropy compensation can be reached based on the theory of interactions,[3] according to which the enthalpy-entropy compensation effect is a specific aspect of isoparametricity. It is not difficult to conclude that multifactor experiments performed with a cross variation of temperature and any other factor, and utilization of the methodology of the polylinearity principle for the correlation analysis of the results of such experiments will allow to avoid confusion with the statistical artifacts and get reliable evidence of the compensation phenomenon in all its manifestations in various fields of natural sciences.

Further Study of the Isoparametricity Phenomenon

This article shows that the nucleophilic substitution reactions at the different electrophilic centers are promising for the experimental investigation of the isoparametricity phenomenon in all its aspects. The great variety of nucleophilic substitution reactions opens limitless possibilities of researching this phenomenon. New interesting discoveries should be expected with further investigation of the cross effects of structure, catalyst, temperature, medium and other internal and external factors on the rate and activation parameters of ring opening reactions of aromatic substituted derivatives of small heterocycles such as oxiranes, thiiranes, aziridines, oxetanes and others.

Promising for the study of isoparametricity are the reactions of electrophilic addition (Ad$_E$) of the strong electrophiles like arylsulphenyl halides, arenesulfonic acids and others to such unsaturated compounds as 1-aryl-, 1,1-diaryl-, 1,2-diaryl-ethylenes, 1-aryl-, 1,2-diaryl-acetylenes, etc.[47] Effective interaction of the structural factors is expected in these reactions, as evidenced by the reactions of X-substituted 1-arylethylenes **6a**–**6d** [X = 4-OMe (**6a**),

$$X\text{-}C_6H_4CH{=}CH_2 \;+\; Y\text{-}C_6H_4SCl \longrightarrow X\text{-}C_6H_4CH(SC_6H_4\text{-}Y)\text{---}CH_2Cl$$
$$\textbf{6a-6d} \qquad\qquad \textbf{7a-7c}$$

Scheme 8. Reactions of 1-arylethylenes **6** with arylsulphenyl chlorides **7**.

4-Me (**6b**), H (**6c**), 3-NO$_2$ (**1d**)] with Y-substituted arylsulphenyl chlorides **7a-7c** [Y = 4-Me (**7a**), H (**7b**), 4-NO$_2$ (**7c**)] in AcOH at 298 K (Scheme 8).[48]
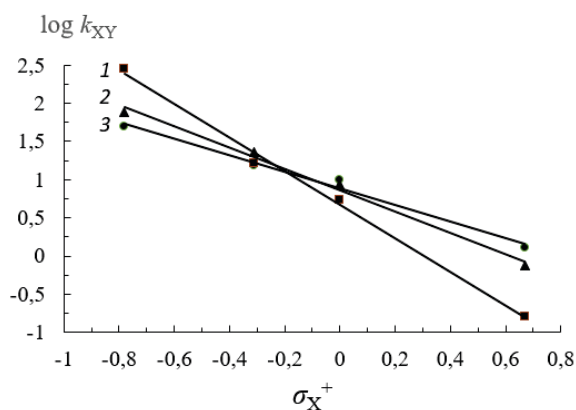
The combined effects of the substituents X and Y on the rate of these reactions are described by Eq. (22), whose coefficients are presented in regression, Eq. (23) (R = 0.990).

$$\log k_{XY} = \log k_{HH} + \rho_X^{Y=H}\sigma_X^+ + \rho_Y^{X=H}\sigma_Y + \rho_{XY}\sigma_X^+\sigma_Y \quad (22)$$

$$\log k_{XY} = (0.93 \pm 0.03) + (-1.45 \pm 0.07)\sigma_X^+ +$$
$$(-0.18 \pm 0.07)\sigma_Y + (-1.2 \pm 0.1)\sigma_X^+\sigma_Y \quad (23)$$

The isoparametric characteristics of considered reactions are the isoparametric points $\sigma_X^{+IP} = -\rho_Y^{X=H}\rho_{XY}^{-1} = -0.15$ and $\sigma_Y^{IP} = -\rho_X^{Y=H}\rho_{XY}^{-1} = -1.21$ as well as $\log k_{XY}^{IP} = \log k_{HH} - \rho_X^{Y=H}\rho_Y^{X=H}\rho_{XY}^{-1} = 1.15$ at these points. The isoparametric point σ_Y^{IP} cannot be implemented due to the lack of strong electron-donating substituents Y. Along with this, the isoparametric point σ_X^{+IP} falls within the range of variation of the constants σ_X^+ of substituents X in alkenes **6a–6d**: −0.78 (X = 4-OMe) to 0.67 (X = 4-NO$_2$). At this point, the influence of substituents Y on the rate of the process should disappear ($\rho_Y^X = 0$), and after passing this point, the sign of ρ_Y^X should be reversed, which is actually observed: ρ_Y^X, $r \geq$ 0.996 (X, σ_X^+) = 0.77 ± 0.05, (4-OMe, −0.78), 0 (4-Me, −0.31), −0.220 ± 0.03, (H, 0), −0.93 ± 0.08, (3-NO$_2$, 0.69). Figure 10 demonstrates the transition through the isoparametric point $\sigma_X^{+IP} = -0.15$ in these reactions.

Numerous processes in chemistry, physics, biology, pharmacology, etc. are associated with the formation of the H-bonds.[49–51] They have great prospects for the manifestation of isoparametricity. Since the strength of the H-bond is affected by many factors, such as temperature [increase (decrease) in temperature weakens (strengthens)

H-bonding], medium [decrease (increase) in medium polarity promotes (prevents) the formation of H-bond], structure of hydrogen bond donors and hydrogen bond acceptors, etc., various combinations of second-order interactions of their effects are possible in H-bond formation processes. This is evidenced by the considered above reaction of 3,5-dinitrobenzoyl chloride with 3-fluoraniline in which there is an intense interaction of temperature and medium polarity effects [$q_{ST} = -11.6 \pm 0.9$ in Eq. (10)] due to the formation of cyclic transition state **B** with a hydrogen bond (Scheme 4).

The interaction of structural effects was found in the formation of H-bonds between X-substituted phenols and Y-substituted pyridines in carbon tetrachloride at 298 K.[52] The joint effects of substituents X and Y on the complexation constants were estimated by Eq. (24).

$$\log K_{XY} = 1.76 + 1.08\sigma_X - 1.35\sigma_Y - 0.57\sigma_X\sigma_Y \quad (24)$$

None of the isoparametric points in this reaction series ($\sigma_X^{IP} = -2.37$, $\sigma_Y^{IP} = 1.89$) were realized.

If we look at the problem of isoparametricity more broadly, we can conclude that this property should be inherent to any process, the quantitative characteristics of which depend on the non-additive effects of at least two factors in accordance with the principle of polylinearity. Therefore, the study of intriguing isoparametric properties of the different processes in animate and inanimate nature seems to be a promising area of research for scientists in various fields of knowledge.

Figure 10. Transition through the isoparametric point $\sigma_X^{+IP} = -0.15$ in the reactions of 1-arylethylenes **6** with arylsulphenyl chlorides **7a** (*3*), **7b** (*2*), **7c** (*1*) in AcOH at 298 K.[48]

REFERENCES

[1]   N. Chapman, J. Shorter, Eds. Advances in Linear Free Energy Relationships, Plenum Press, New York, **1972**, 481.
https://doi.org/10.1007/978-1-4615-8660-9

[2]   C. D. Johnson, The Hammett Equation, UP, Cambridge, **1973**, 196.

[3]   V. A. Pal'm, Osnovy kolichestvennoi teorii organicheskikh reaktsii, Khimiya, Leningrad, **1977**, pp. 35–54, 260–276, 310–314.

[4]   N. B. Chapman, J. Shorter, Eds. Correlation Analysis: Recent Advances, Plenum Press, New York, **1978**, 541. https://doi.org/10.1007/978-1-4615-8831-3

[5] J. Shorter, Correlation Analysis of Organic Reactivity, with Particular Reference to Multiple Regression, John Wiley and Sons Inc., Somerset, NJ, **1982**, 235

[6] A. Williams, Free Energy Relationships in Organic and Bioorganic Chemistry, RSC, Cambridge, **2003**, 298. https://doi.org/10.1039/9781847550927

[7] C. Reichardt, T. Welton, Solvents and Solvent Effects in Organic Chemistry, Wiley-VCH, Weinheim, **2010**, 718. https://doi.org/10.1002/anie.201105531

[8] I. V. Shpanko, Kim S.I., H. J. Koh, I. Lee, *Bull. Korean Chem. Soc.* **1995**, *16*, 533–538.

[9] I. V. Shpan'ko, *Theor. Exp. Chem.* **1999**, *35*, 63–74. https://doi.org/10.1007/BF02511491

[10] I. V. Shpan'ko, *Theor. Exp. Chem.* **2001**, *37*, 265–282. https://doi.org/10.1023/A:1013879231709

[11] A. I. Lesnikovich, S. V. Levchik, *J. Therm. Anal.* **1985**, *30*, 237–262. https://doi.org/10.1007/BF02128134

[12] Exner, O., *J. Chem. Soc., Perkin Trans.* 2. **1993**, 973–979. https://doi.org/10.1039/P29930000973

[13] Ya. Kh. Riikoya, Kh. R. Timotkheus, V. A. Pal'm, *Reakts. Sposobnost' Org. Soedin*. **1977,** *14*, 522–540.

[14] V. Pal'm, S. Kaasik, *Org. React.* **1996**, *30*, 73–83.

[15] B. V. Gidaspov, P. A. Ivanov, S. A. Pivovarov, V. F. Selivanov, *Reakts. Sposobnost' Org. Soedin.* **1971**, *8*, 49–61.

[16] S. A. Pivovarov, V. F. Selivanov, B. V. Gidaspov, *Reakts. Sposobnost' Org. Soedin.* **1975**, *12*, 307–328.

[17] S. A. Pivovarov, V. F. Selivanov, B. I. Istomin, B. V. Gidaspov, *Reakts. Sposobnost' Org. Soedin.* **1975**, *12*, 367–382.

[18] V. A. Pal'm, B. I. Istomin, *Reakts. Sposobnost' Org. Soedin.* **1969**, *6*, 427–437.

[19] B. I. Istomin, S. A. Pivovarov, V. F. Selivanov, *Reakts. Sposobnost' Org. Soedin*. **1975**, *12*, 289–300.

[20] I. V. Shpan'ko, E. E. Likhomanenko, L. M. Litvinenko, A. N. Goncharov, *Zh. Org. Khim.* **1985**, *21*, 1432–1438.

[21] I. V. Shpan'ko, A. N. Goncharov, L. M. Litvinenko, *Zh. Org. Khim*. **1988**, *24*, 761–766.

[22] I. V. Shpan'ko, I. M. Serebryakov, A. P. Korostylov, *Zh. Org. Khim.* **1988**, *24*, 1358–1365.

[23] I. V. Shpan'ko, I. V. Sadovaya*, ARKIVOC.* **2019**, *6*, 93–104. https://doi.org/10.24820/ark.5550190.p010.924

[24] I. V. Shpan'ko, G. D. Titskii, L. M. Litvinenko, M. A. Eremeev, *Reakts. Sposobnost' Org. Soedin.* **1973**, *10*, 187–202.

[25] I. V. Shpan'ko, A. N. Goncharov, E. V. Chetverova, E. E. Likhomanenko, *Zh. Org. Khim.* **1986**, *22*, 1432–1438.

[26] A. N. Goncharov, I. V. Shpan'ko, E. V. Chetverova, E. E. Likhomanenko, *Ukr. Khim. Zh.* **1986**, *52*, 1077–1082.

[27] A. N. Goncharov, I. V. Shpan'ko, A. P. Korostylev, *Zh. Org. Khim.* **1981**, *17*, 972–978.

[28] I. V. Shpan'ko, *Zh. Org. Khim*. **1998**, *34*, 1063–1066.

[29] I. V. Shpan'ko, L. M. Litvinenko, A. P. Korostylev, *Dokl. Akad. Nauk SSSR.* **1977**, *234*, 1358–1361.

[30] I. V. Shpan'ko, *Mendeleev Commun*. **1997**, *7*, 237–238. https://doi.org/10.1070/MC1997v007n06ABEH000818

[31] I. V. Shpan'ko, A. N. Goncharov, *Zh. Org. Khim.* **1987**, *23*, 2591–2596.

[32] A. P. Korostylev, L. M. Litvinenko, I. V. Shpan'ko, *Dokl. Akad. Nauk SSSR.* **1978**, *242*, 121–124.

[33] I. V. Shpan'ko, I. V. Sadovaya, *Theor. Exp. Chem.* **2000**, *36*, 338–341. https://doi.org/10.1023/A:1005272628953

[34] I. V, Shpan'ko, I. V. Sadovaya, *Theor. Exp. Chem*. **2010**, *46*, 176–181. https://doi.org/10.1007/s11237-010-9136-z

[35] I. V. Shpan'ko, I.V Sadovaya, *Russ. J. Phys. Chem. A.* **2016**, *90*, 2332–2338. https://doi.org/10.1134/S0036024416120268

[36] I. V. Shpan'ko, I.V. Sadovaya, *Russ. J. Gen. Chem*. **2017**, *87*, 2552–2557. https://doi.org/10.1134/S107036321711007X

[37] I. V. Shpan'ko, I. V. Sadovaya, *Reac. Kinet. Mech. Cat*. **2018**, *123*, 473–484. https://doi.org/10.1007/s11144-017-1340-6

[38] J. E. Leffler, E. Grunwald, *Rates and Equilibrium of Organic Reactions*, New York: John Wiley and Sons Inc., **1963**, 458.

[39] L. Liu, Q.-X. Guo, *Chem. Rev.* **2001**, *101*, 673–696. https://doi.org/10.1021/cr990416z

[40] J. Norwisz, T. J. Musielak, *Therm. Anal. Calorim.* **2007**, *88*, 751–755. https://doi.org/10.1007/s10973-006-8139-4

[41] P. J. Barrie, *Phys. Chem. Chem. Phys.* **2012**, *14*. 327–336. https://doi.org/ 10.1039/ c1cp22667c

[42] A. Mianowski, T. Radko, T. Siudyga, *Reac. Kinet. Mech. Cat.* **2021**, *132*, 37–58. https://doi.org/10.1007/s11144-020-01898-2

[43] V. N.Sapunov, E. A. Saveljev, M. S. Voronov, M. Valtiner, W. Linert, *Thermo.* **2021**, *1*, 45–60. https://doi.org/10.3390/thermo1010004

[44] V. Shpan'ko, I. V. Sadovaya, *Kinet. Catal.* **2014,** *55*, 56–63. https://doi.org/10.1134/S002315841401011X

[45] I. V. Shpan'ko, I.V. Sadovaya, *Russ. J. Phys. Chem.* **2013**, *87*, 1955–1959. https://doi.org/10.1134/S0036024413120224

[46] G. C. McBane, *J. Chem. Educ.* **1998**, *75*, 919–922. https://doi.org/10.1021/ed075p919

[47] L. Rasteikiene, D. Greiciute, M. G. Lin'kova, I. L. Knunyants, *Russ Chem. Rev.* **1977**, *46*, 548–564. https://doi.org/10.1070/RC1977v046n06ABEH002155

[48] I. V. Bodrikov, A. V. Borisov, L. V. Chumakov, N. S. Zefirov, W. A. Smit, *Tetrahedron Letters*, **1980**, *21*, 115–118. https://doi.org/10.1016/S0040-4039(00)93638-4

[49] Sławomir J. Grabowski, Eds. *Hydrogen Bonding - New Insights*, Springer Dordrecht, **2006**, 524. https://doi.org/10.1007/978-1-4020-4853-1

[50] Gastone Gilli, Paola Gilli, *The Nature of the Hydrogen Bond: Outline of a Comprehensive Hydrogen Bond Theory*, **2009**, OUP Oxford, 317.

[51] G. A Jeffrey, W. Saenger, *Hydrogen bonding in biological structures*, **2012**, Springer Science & Business Media, 569. https://doi.org/10.1007/978-3-642-85135-3

[52] D. Clotman, J. P. Muller, *Th. Zeegers-Huyskens, Bull. Soc. Chim. Belg*. **1970**, *79*, 689–697. https://doi.org/10.1002/bscb.19700791112]