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Isoparametricity Phenomenon and Kinetic Enthalpy–Entropy Compensation Effect: Experimental Evidence Obtained by Investigating Pyridine-Catalyzed Reactions of Phenyloxirane with Benzoic Acids

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Abstract—The joint effect of structure and temperature on the rate and free activation energy of reactions between phenyloxirane and substituted benzoic acids catalyzed by substituted pyridines in acetonitrile has been investigated. A correlation analysis of the results of a multifactor kinetic experiment indicates the additivity of the joint effects of structural factors (substituents X in pyridines and substituents Y in benzoic acids) and of the effects of the substituents Y and temperature. Intensive interaction (nonadditivity) is observed between the effects of the substituents X and temperature. This fact has provided experimental evidence for the existence of the enthalpy–entropy compensation aspect of the isoparametricity phenomenon: at the isoparametric temperature point (isokinetic temperature), the rate (free activation energy) of the process is independent of the structure of the substituent X because of the existence of an enthalpy–entropy compensation effect; on passing through this point, an inversion of the effect of X on the catalytic activity of pyridines takes place (isoparametricity paradox). At the isoparametric point with respect to the substituent X constant, there is no temperature effect on the reaction rate because of the activation enthalpy being close to zero. The isoparametric properties of a cross series of reactions are used to describe the mechanism of the pyridine-catalyzed opening of the oxirane ring.

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Among the variety of internal and external factors (structure, solvent, temperature, pH of the medium, pressure, etc.) that can affect chemical, physical, biological, and other processes, the temperature effects were studied in greatest detail, as is evident from the numerous publications in this field that have appeared since Arrhenius' times. Interest in the temperature dependences increased after the concept of isokinetic (isoequilibrium) relationships based on the enthalpy–entropy compensation effect was suggested [1]. From the standpoint of the formal theory of interaction [2], these relationships, which allow for the nonadditivity of joint effects of temperature and any other factor j, express more general isoparametric relationships based on the polylinearity principle (PLP). The isoparametric relationships are quantitatively characterized in terms of isoparametric points (IPPs) with respect to parameters varied. A remarkable property of these points is that, at an IPP with respect to the parameter of on factor, the quantity being correlated is insensitive to the effects of the other factor. The most significant attribute of the kinetic compensation effect is an IPP with respect to temperature, T^{IP} (isokinetic temperature T_{iso}). At the T^{IP} point, the changes in the enthalpic and entropic constituents of free activation energy under the variation of the parameter of factor j are completely counterbalanced: $\delta_j\Delta H^{\neq} = T^{\mathrm{IP}}\delta_j\Delta S^{\neq}$; accordingly, $\delta_j\Delta G^{\neq} = \delta_j\Delta H^{\neq} - T^{\mathrm{IP}}\delta_j\Delta S^{\neq} = 0$, $\Delta G_j^{\neq} =$ const, and all reactions of the series have the same rate ($\log k_{j\mathrm{T}} =$ const).

Since an IPP with respect to temperature, T^{IP}, is the most reliable test for the verity of the compensation effect, experimental realization of such a point is a challenging phenomenological problem. However, despite that there have been extensive studies on the compensation effect in chemistry, physics, biology, etc. (see, e.g., [3–16]), experimental observations of T^{IP} are very rare [6]. This experimental inaccessibility of T^{IP} casts doubt on the existence of the compensation effect and arouse discussions about the reliability of the methods used in the quantitative estimation of this effect [9–16].

The purpose of our work was to investigate the enthalpy–entropy compensation phenomenon in oxirane ring opening reactions. The specific arrangement of atoms in this ring, its strain and unsaturated character, the wide variety of reactions of oxirane substrates with compounds of different classes—the totality of these facts has evoked great interest in oxirane chemistry [17–21]. Here, we report evidence

Table 1. Rate constant k_3 data for reactions of phenyloxirane with Y-substituted benzoic acids catalyzed by X-substituted pyridines in acetonitrile at different temperatures

Y	σ_Y	X	σ_X	$k_3 \times 10^5$, L^2 mol^{-2} s^{-1}				
				279 K	295 K	308 K	323 K	343 K
3-NO_2	0.71	4-OMe	–0.27	2.26 ± 0.01	16.1 ± 0.1	63.7 ± 0.9	219 ± 2	1260 ± 20
		4-Et	–0.15	2.88 ± 0.03	15.8 ± 0.2	48 ± 2	133 ± 3	701 ± 4
		H	0	3.7 ± 0.1	15.6 ± 0.1	34.8 ± 0.1	78.8 ± 0.3	287 ± 7
		3-COOEt	0.37	7.0 ± 0.1	14.4 ± 0.2	19.2 ± 0.8	–*	–
		3-CN	0. 56	–	13.7 ± 0.2	14.9 ± 0.7	16.9 ± 0.2	–
3-Br	0.39	4-OMe	–0.27	–	7.40 ± 0.09	32 ± 2	120 ± 2	650 ± 10
		4-Et	–0.15	1.39 ± 0.03	7.20 ± 0.03	26.2 ± 0.2	80 ± 1	302 ± 6
		H	0	2.00 ± 0.01	6.99 ± 0.03	18.1 ± 0.1	45.1 ± 0.1	141 ± 2
		3-COOEt	0.37	3.7 ± 0.1	6.7 ± 0.2	10.69 ± 0.02	–	–
		3-CN	0.56	–	6.26 ± 0.07	7.0 ± 0.3	7.7 ± 0.1	–
H	0	4-OMe	–0.27	–	3.4 ± 0.1	14.9 ± 0.2	51.9 ± 0.8	292 ± 1
		4-Et	–0.15	0.692 ± 0.006	3.28 ± 0.07	11.5 ± 0.6	32 ± 1	136 ± 7
		H	0	0.894 ± 0.006	3.22 ± 0.05	8.2 ± 0.1	18.9 ± 0.2	64 ± 4
		3-COOEt	0.37	1.71 ± 0.01	3.00 ± 0.06	4.7 ± 0.1	–	–

* The symbol – means the absence of experimental data.

(based on a cross correlation analysis of a multifactor kinetic experiment) for the physical reality of compensation effect and other manifestations of isoparametricity in reactions of phenyloxirane with Y-substituted benzoic acids (Y = H, 3-Br, 3-NO_2) catalyzed by substituted pyridines (X-Py; X = 4-OMe, 4-Et, H, 3-COOEt, 3-CN) in acetonitrile at 279, 295, 308, 323 and, 343 K:

$$C_6H_5CH(O)CH_2 + YC_6H_4COOH \xrightarrow{X\text{-}Py} C_6H_5CH(YC_6H_4COO)CH_2OH. \qquad (I)$$

In addition, we suggest an original explanation for the mechanism of enthalpy–entropy compensation in the catalytic opening of the oxirane ring.

EXPERIMENTAL

The products of reaction (I) are primary alcohols, namely, 2-(Y-benzoyloxy)-2-phenylethanols [22]. Acetonitrile (analytical grade) was dried and distilled from P_2O_5 and then from CaH_2. Commercial phenyloxirane (98%, Merck Chemicals) was distilled in vacuo. Benzoic acids (pure grade) were twice recrystallized from aqueous ethanol (1 : 1, vol/vol). Pyridines (pure grade or reagent grade) were distilled in vacuo.

The reaction rate was measured as a decrease in the amount of acid reactant HA, as was described in our earlier work [22]. In kinetic experiments, we used at least a tenfold excess of an oxirane substrate S over the acid reactant: $[S]_0 \gg [HA]_0 = 0.0453$–$0.090$ mol/l. The concentration of the X-Py catalyst (C) was varied between 0.00953 and 0.0473 mol/L. Under these conditions, the process rate is described by the equation $-d[HA]/dt = k_1[HA] = k_2[S]_0[HA] = k_3[S]_0[HA]C$. In all kinetic experiments, the apparent pseudo-first-order rate constant k_1 (s^{-1}) remained constant during the process until the 70–80% conversion of the acid reactant. The k_1 determination error did not exceed 5%. The rate constant k_2 (L mol^{-1} s^{-1}) was determined as $k_2 = k_1/[S]_0$. The numerical values of the apparent third-order catalytic rate constant k_3 (L^2 mol^{-2} s^{-1}) were calculated from the results of four or more experiments at different concentrations C using the linear relationship $k_2 = k_3C$ (correlation coefficient of $r \geq 0.998$), whose extrapolation to the origin of coordinates indicated the absence of a noncatalytic contribution. The accuracy of determination of kinetic and correlation parameters was estimated in terms of mean-square deviation s, which was determined statistically for the number of experimental data points n. The confidence factor in the processing of the experimental data was 0.95.

RESULTS AND DISCUSSION

The values of k_3 for the reactions examined are listed in Table 1. These data reflect the joint effect of the cross-varied factors (substituents X in pyridines, Y in benzoic acids, and temperature T) on the rate of catalytic reaction (I). Note that, at 295 K, the substituents X have a negligible effect on k_3 in all reaction series (RS's) with a fixed substituent Y in benzoic acid.

Table 2. Sensitivity coefficients ρ_X^{YT} ($r \geq 0.995$) in the Hammett equation for reactions of phenyloxirane with Y-substituted benzoic acids catalyzed by X-substituted pyridines in acetonitrile at different temperatures

Y	ρ_X^{YT}				
	279 K	295 K	308 K	323 K	343 K
3-NO_2	0.761 ± 0.009	−0.083 ± 0.003	−0.75 ± 0.04	−1.30 ± 0.07	−2.4 ± 0.1
3-Br	0.81 ± 0.08	−0.077 ± 0.009	−0.77 ± 0.04	−1.74 ± 0.04	−2.4 ± 0.1
H	0.751 ± 0.005	−0.078 ± 0.002	−0.77 ± 0.06	−1.62 ± 0.06	−2.4 ± 0.2

At a lower temperature of 279 K, k_3 increases significantly as the electron-donating properties of X weaken and the electron-withdrawing properties of X strengthen. Conversely, above 295 K the same variation of the properties of the substituent X causes a decrease in k_3, and this decrease increases with an increasing temperature. This behavior of the rate constant k_3 indicates an interaction (nonadditivity) of the effects of X and temperature in the cross RS (I). For quantitative estimation of this interaction, the results of the multifactor kinetic experiment (Table 1) were subjected to a correlation analysis.

One-Parameter Correlations

The effect of the substituents X on the rate of reaction (I) is described well by the Hammett equation, whose sensitivity coefficient ρ_X^{YT} (Table 2) in partial RS's at a fixed temperature and substituent Y depends strongly on temperature, which has an effect on both the value and sign of ρ_X^{YT}. This is due to the interaction between the substituent X and temperature effects in process (I). According to the PLP, the coefficient of this interaction (q_{XT}^{Y}) can be calculated via the equation $\rho_X^{YT} = \rho_X^{YT=\infty} + q_{XT}^{Y} \times 10^3/T$, in which the free term is equal to ρ_X^{YT} at $T = \infty$ (in this equation and subsequent ones, the subscripts pertain to variable factors and the superscripts pertain to fixed factors). In the RS's with fixed Y = H, 3-Br, and 3-NO_2, the sensitivity coefficient ρ_X^{YT} was calculated to be $(-16.6 \pm 0.4) + (4.9 \pm 0.1) \times 10^3/T$, $(-17.1 \pm 0.7) + (5.0 \pm 0.2) \times 10^3/T$, and $(16.0 \pm 0.7) + (4.7 \pm 0.2) \times 10^3/T$, respectively ($r \geq 0.991$). The statistical significance of the coefficient q_{XT}^{Y} suggests that it is necessary to take into account the interaction between the substituent X and temperature effects in reaction (I). Note that the substituent Y has no effect on q_{XT}^{Y}, suggesting that there is no ternary interaction of the effects of X, Y, and temperature T ($q_{XYT} = 0$). Therefore the binary interactions between the effects of X and Y and between the effects of Y and temperature must not affect the catalytic process either ($\rho_{XY}^{T} = 0$, $q_{YT}^{X} = 0$). This is confirmed by the fact that, as calculated from data presented in Table 1, the sensitivity ρ_Y^{XT} toward the effects of Y in partial RS's with fixed X and different constant temperatures varies in a narrow range ($\rho_Y^{XT} = 0.86$–0.96, $r \geq 0.992$).

The temperature effect on the rate of reaction (I) was estimated using the Eyring equation:

$$\log(k_3/T) = A_{T=\infty}^{XY} + B_T^{XY} \times 10^3/T, \tag{1}$$

where $A_{T=\infty}^{XY} = \log(k_B/h) + \Delta S_{XY}^{\neq}/2.3R$, $B_T^{XY} = -\Delta H_{XY}^{\neq}/2.3R$, k_B is the Boltzmann constant, h is the Planck constant, and R is the gas constant. Equation (1) involves no transmission coefficient, which is usually taken to be unity for heterolytic reactions. Table 3 lists the coefficients of Eq. (1) for all partial RS's and the activation enthalpy ($\Delta H_{XY}^{\neq}$) and activation entropy ($\Delta S_{XY}^{\neq}$) values calculated using these coefficients. The existence of interaction between the substituent X and temperature effects in the cross RS (I) is indicated by the linearity of the $B_T^{XY} = B_T^{HY} + q_{XT}^{Y}\sigma_X$ relationship (σ is the substituent constant in the Hammett equation), which, for the fixed substituents Y = H, 3-Br, and 3-NO_2, is given by the equations $B_T^{XY} = (-2.71 \pm 0.03) + (4.2 \pm 0.1)\sigma_X$, $B_T^{XY} = (-2.74 \pm 0.06) + (4.4 \pm 0.2)\sigma_X$, and $B_T^{XY} = (-2.75 \pm 0.04) + (4.5 \pm 0.1)\sigma_X$, respectively ($r \geq 0.998$). The cross interaction coefficients q_{XT}^{Y} in these equations have the values calculated above. The absence of an effect of Y on the interaction coefficients is further evidence that $q_{XYT} = 0$. As for the activation parameters $\Delta H_{XY}^{\neq}$ and $\Delta S_{XY}^{\neq}$, they are linearly correlated as substituents X are varied. For the above series of fixed substituents Y, this correlation is given by the following equations:

$$\Delta H_{XY}^{\neq} = (97.8 \pm 0.6) \times 10^3 + (296 \pm 3)\Delta S_{XY}^{\neq} \quad (s = 438,\ r = 0.999,\ n = 4), \tag{2}$$

$$\Delta H_{XY}^{\neq} = (95.6 \pm 0.3) \times 10^3 + (294 \pm 2)\Delta S_{XY}^{\neq} \quad (s = 351,\ r = 0.999,\ n = 5), \tag{3}$$

$$\Delta H_{XY}^{\neq} = (93.4 \pm 0.3) \times 10^3 + (293 \pm 1)\Delta S_{XY}^{\neq} \quad (s = 289,\ r = 0.999,\ n = 5). \tag{4}$$

Table 3. Coefficients of Eq. (1) and the activation parameters $\Delta H^{\neq}_{XY}$ and $\Delta S^{\neq}_{XY}$ for reactions of phenyloxirane with Y-substituted benzoic acids catalyzed by X-substituted pyridines in acetonitrile

Y	X	$A^{XY}_{T=\infty}$	$-B^{XY}_{T}$	*r*	*s*	$\Delta S^{\neq}_{XY}$, J mol^{-1} K^{-1}	$\Delta H^{\neq}_{XY}$, kJ/mol
3-NO_2	4-OMe	7.2 ± 0.3	3.99 ± 0.09	0.999	0.048	−60	76
	4-Et	5.3 ± 0.3	3.42 ± 0.09	0.999	0.048	−96	65
	H	2.7 ± 0.3	2.66 ± 0.09	0.998	0.048	−146	51
	3-COOEt	−2.2 ± 0.7	1.2 ± 0.2	0.986	0.049	−240	23
	3-CN	−5.7 ± 0.1	0.17 ± 0.02	0.995	0.0034	−308	3.3
3-Br	4-OMe	6.9 ± 0.3	3.96 ± 0.09	0.999	0.034	−66	76
	4-Et	4.9 ± 0.3	3.4 ± 0.1	0.998	0.053	−104	65
	H	2.3 ± 0.1	2.65 ± 0.03	0.999	0.017	−153	51
	3-COOEt	−2.33 ± 0.02	1.272 ± 0.006	0.999	0.0015	−242	24
	3-CN	−6.08 ±0.08	0.17 ± 0.02	0.991	0.0048	−314	3.3
H	4-OMe	6.2 ± 0.7	3.9 ± 0.2	0.997	0.076	−79	74
	4-Et	4.3 ± 0.2	3.32 ± 0.07	0.999	0.035	−115	64
	H	2.0 ± 0.1	2.65 ± 0.05	0.999	0.025	−159	51
	3-COOEt	−2.98 ± 0.05	1.18 ± 0.02	0.999	0.0037	−255	22

The slope coefficients of these equations are equal to the temperature IP (T^{IP}) values, which vary only slightly from one substituent Y to another and, very importantly, do not go beyond the temperature range examined, which is 289–343 K. According to the enthalpy–entropy compensation conception, reaction system (I) at these T^{IP} values is isokinetic; that is, the rate of the process is independent of the substituent X in the pyridine molecule ($\rho^{YT}_{X} = 0$). It is this fact that is indicated by the data listed in Table 2: at 295 K, a temperature close to the T^{IP} values calculated via Eqs. (2)–(4), the sensitivity ρ^{YT}_{X} toward the electronic effects of X is close to zero at any fixed Y.

Note that, according to the data presented in Table 3, cross reaction system (I) is isoenthalpic with respect to the substituents Y in the acid reactant. At a fixed substituent X, the activation enthalpy $\Delta H^{\neq}_{XY}$ is practically independent of substituent Y. Thus, the substituents Y exerts an effect on the free activation energy and, accordingly, on the rate of the process only when the activation entropy changes. In all partial reaction series with a fixed X, $\Delta S^{\neq}_{XY}$ is a linear function of σ_Y; for example, for X = H, $\Delta S^{\neq}_{XY} = (-159.3 \pm 0.9) + (18 \pm 1)\sigma_Y$ ($r = 0.995$). The isoenthalpic character of reactions (I) with respect to the substituents Y is due to the absence of interactions between the effects of these substituents and temperature ($q^{X}_{YT} = 0$).

Multiparametric Correlations

From the formal standpoint, the joint effect of the substituents X and Y and temperature *T* on the rate of reactions (I) can be estimated, with allowance made for the cross interactions of all of the three variable factors, by using the following polylinear equation applicable to the three-parameter variant of PLP [2]:

$$\begin{aligned}\log k_3 = {} & \log k_3^{\mathrm{st}} + \rho^{\mathrm{st}}_{X}\sigma_X + \rho^{\mathrm{st}}_{Y}\sigma_Y + b^{\mathrm{st}}_{T} \times 10^3/T \\ & + \rho^{\mathrm{st}}_{XY}\sigma_X\sigma_Y + q^{\mathrm{st}}_{XT}\sigma_X \times 10^3/T \\ & + q^{\mathrm{st}}_{YT}\sigma_Y \times 10^3/T + q_{XYT}\sigma_X\sigma_Y \times 10^3/T,\end{aligned} \quad (5)$$

where k_3^{st} is the rate constant under standard conditions ($\sigma_X = \sigma_Y = 0$, $T = \infty$); ρ^{st}_{X}, ρ^{st}_{Y}, and b^{st}_{T} are the parameters of the standard reactions at $\sigma_Y = 0$ and $T = \infty$, $\sigma_X = 0$ and $T = \infty$, and $\sigma_X = \sigma_Y = 0$, respectively; ρ^{st}_{XY}, q^{st}_{XT}, and q^{st}_{YT} are the binary interaction coefficients in the standard reaction series ($T = \infty$, $\sigma_Y = 0$, and $\sigma_X = 0$, respectively); q_{XYT} is the ternary cross interaction coefficient. By processing the results of the multifactor kinetic experiment (Table 1) using Eq. (1), we obtained the polylinear regression

$$\begin{aligned}\log k_3 = {} & (5.1 \pm 0.2) + (-15.6 \pm 0.7)\sigma_X + (1.2 \pm 0.3)\sigma_Y \\ & + (-2.83 \pm 0.05) \times 10^3/T + (0.4 \pm 1.4)\sigma_X\sigma_Y \\ & + (4.6 \pm 0.2)\sigma_X \times 10^3/T + (-0.08 \pm 0.09)\sigma_Y \\ & \times 10^3/T + (-0.1 \pm 0.4)\sigma_X\sigma_Y \times 10^3/T\end{aligned} \quad (6)$$

($s = 0.0367$; multiple correlation coefficient, $r = 0.998$; $n = 58$; Fisher's test value, $F = 3260$).

As would be expected, the statistically insignificant coefficients in regression (6) are the above-considered

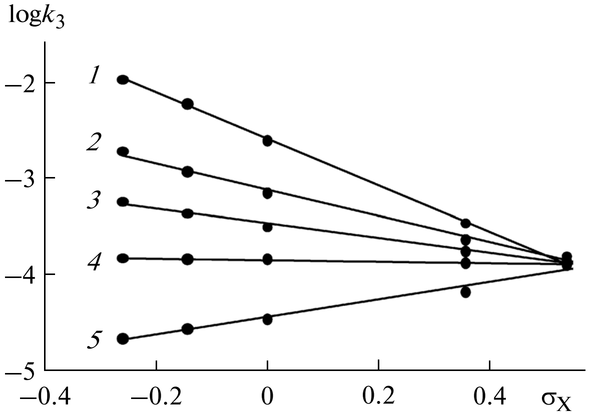


Fig. 1. log k_3 versus σ_X for the reaction between phenyloxirane and 3-nitrobenzoic acid catalyzed by X-substituted pyridines in acetonitrile at different temperatures: (*1*) 343, (*2*) 323, (*3*) 308, (*4*) 295, and (*5*) 279 K. The values of log k_3 for the reaction involving 3-COOEt-pyridine at 323 and 343 K and for the reaction involving 3-CN-pyridine at 279 and 343 K were calculated via Eq. (7).

cross interaction coefficients ρ_{XY}, q_{YT}, and q_{XYT}. In the processing of the kinetic data, elimination of the cross terms with these statistically unreliable coefficients from Eq. (5) yielded regression (7), which adequately describes the reactivity of system (I), taking into account the additive effects of the substituents Y and temperature and the nonadditive effects of the substituents X and temperature:

$$\begin{gathered}\log k_3 = (5.18 \pm 0.08) + (-15.4 \pm 0.3)\sigma_X \\ + (0.91 \pm 0.02)\sigma_Y + (-2.85 \pm 0.02) \times 10^3/T \\ + (4.5 \pm 0.1)\sigma_X \times 10^3/T \\ (s = 0.0362,\ r = 0.998,\ n = 58,\ F = 6226).\end{gathered} \tag{7}$$

Regression (7) is characterized by two IP points, one with respect to the constant of the substituent X ($\sigma_X^{IP} = -b_T^{st}/q_{XT} = 0.63$) and the other with respect to inverse temperature ($10^3/T^{IP} = -\rho_X^{st}/q_{XT} = 3.42$, $T^{IP} = 293$ K), and by the isoparametric value $\log k_3^{IP} = \log k_3^{st} - \rho_X^{st} b_T^{st}/q_{XT} = -4.57$, which is a component of the effective quantity $\log k_3 = \log k_3^{IP} + \rho_Y^{st}\sigma_Y = -4.57 + (0.91 \pm 0.02)\sigma_Y$ (at a standard value of $\sigma_Y = 0$ (Y = H), $\log k_3 = \log k_3^{IP}$).

At the $\sigma_X^{IP} = 0.63$ point, the rate constant of the process (log k_3) should be temperature-independent. The data presented in Fig. 1 indicate a decrease in sensitivity to the effect of temperature for the reaction involving 3-nitrobenzoic acid and show that the σ_X^{IP} point is approached upon passing from electron-donating substituents X to electron-withdrawing ones in pyridine. In the presence of 3-CN-pyridine, for which the constant of the X = 3-CN substituent, $\sigma_X =$ 0.56, differs little from the isoparametric value $\sigma_X^{IP} =$ 0.63, the reactions are low-sensitive to temperature. They are characterized by near-zero values of the slope coefficient B_T^{XY} in Eq. (1) and by small values of effective activation enthalpy (Table 3). According to the equations obtained for the reactions involving 3-Br- and 3-NO_2-benzoic acids in the presence of 3-CN-pyridine, $\Delta H^{\neq}_{XY} = (52.4 \pm 0.8) + (-85 \pm 2)\sigma_X$ ($r = 0.999$) and $\Delta H^{\neq}_{XY} = (52 \pm 1) + (-85 \pm 3)\sigma_X$ ($r = 0.998$) and, at σ_X values of 0.62 and 0.61, respectively, which are practically equal to $\sigma_X^{IP} = 0.63$, $\Delta H^{\neq}_{XY} = 0$. At this IP point, the free activation energy ($\Delta G^{\neq}_{XYT} = -T\Delta S^{\neq}_Y$) and, accordingly, the rate of the process, will be determined only by the entropic factor (see below).

As for the $T^{IP} = 292$ K point, it is in agreement with values calculated from compensation relationships (2)–(4) and, as was noted above, is within the temperature range examined. At this IP point, the substituent X in pyridine should not affect the rate of the process ($\rho_X^{YT} = 0$), and this is confirmed by the near-zero values of ρ_X^{YT} (Table 2) for the reactions of all Y-substituted benzoic acids at 295 K, a temperature close to T^{IP}. Note that a passage through the T^{IP} point was carried out in cross RS (I), The observed reversal of the sign of the sensitivity ρ_X^{YT} to the effects of X for all fixed substituents Y is a manifestation of the isoparametricity paradox, specifically, the inversion of the order of substituent X effects on the catalytic activity of pyridines on passing through the T^{IP} point. A graphical illustration of the isoparametricity paradox is presented in Fig. 1 in the coordinates of the Hammett equation.

Since the nonadditive effects of only temperature and substituents X in pyridine show themselves in cross RS (I), polylinear regression (8) was calculated for quantitative estimation of the joint effect of these factors and substituents Y in benzoic acids. In this regression, we used the $\Delta G^{\neq}_{XYT} = \Delta H^{\neq}_{XY} - T\Delta S^{\neq}_{XY}$ values calculated from the $\Delta H^{\neq}_{XY}$ $\Delta S^{\neq}_{XY}$ values presented in Table 3:

$$\begin{gathered}\Delta G^{\neq}_{XYZ} = (54.6 \pm 0.8) \\ +(-82 \pm 3)\sigma_X + (-5.0 \pm 0.2)\sigma_Y \\ + (0.146 \pm 0.003)T + (0.279 \pm 0.008)\sigma_X T \\ (s = 0.471,\ r = 0.990,\ n = 70,\ F = 1562).\end{gathered} \tag{8}$$

The isoparametric characteristics of regression (8) are the temperature IP point, $T^{IP(G)} = 294$ K, which is in agreement with the earlier calculated T^{IP} values; the IP point with respect to the constant of the substituent X, $\sigma_X^{IP(G)} = -0.52$, which differs radically from the value calculated via Eq. (7), $\sigma_X^{IP} = 0.63$; isoparametric value of $\Delta G^{\neq IP}_{XYT} = 97.5$, which is a component of the effective value $\Delta G^{\neq}_{XYT} = 97.5 + (-5.0 \pm 0.2)\sigma_Y$. At the $\sigma_X^{IP(G)}$ point, $\Delta G^{\neq IP}_{XYT}$ should be temperature-independent, which will be possible if, in the $\Delta G^{\neq IP}_{XYT} = \Delta H^{\neq}_{XY} - T\Delta S^{\neq}_{XY}$ expression, the activation entropy is $\Delta S^{\neq}_{XY} = 0$ and $\Delta G^{\neq IP}_{XYT}$ is determined only by the enthalpic term, $\Delta G^{\neq IP}_{XYT} = \Delta H^{\neq}_{XY} = 97.5$ kJ/mol, whose value is in agreement with the free terms in Eqs. (2)–(4). This is also confirmed by the equations derived from the data presented in Table 3 for the reactions of 3-Br- and 3-NO_2-benzoic acids: $\Delta S^{\neq}_{XY} = (-146 \pm 4) + (-288 \pm 12)\sigma_X$ ($r = 0.997$) and $\Delta S^{\neq}_{XY} = (-140 \pm 3) + (-292 \pm 9)\sigma_X$ ($r = 0.998$), according to which $\Delta S^{\neq}_{XY} = 0$ at σ_X values of –0.51 and –0.48, respectively, which differ only slightly from $\sigma_X^{IP(G)} = -0.52$.

At the $T^{IP(G)} = 294$ K point, $\Delta G^{\neq IP}_{XYT}$ should not depend on the effects of the substituents X, and this is confirmed by the fact that $\Delta G^{\neq IP}_{XYT}$ at 295 K, a temperature close to $T^{IP(G)}$, remains constant as X is varied. For example, for the reactions of 3-NO_2-benzoic acid with the pyridines X-Py with X = 4-OMe, 4-Et, H, 3-COOEt, and 3-CN, the $\Delta G^{\neq}_{XYT}$, calculated from data listed in Table 3 is 93.7, 93.3, 94.1, 93.8, and 94.1, respectively; that is, it remains almost invariable. The absence of an effect of X on $\Delta G^{\neq}_{XYT}$ is the enthalpy–entropy compensation effect, $\delta_X\Delta H^{\neq}_{XY} = T^{IP(G)}\delta_X\Delta S^{\neq}_{XY}$, owing to which $\delta_X\Delta G^{\neq IP}_{XYT} = 0$ and $\Delta G^{\neq IP}_{XYT} = \text{const}$. Since $T^{IP(G)}$ is within the temperature range examined, we have an opportunity to experimentally observe the passage of the system through this IP point. Figure 2 illustrates the associated isoparametricity paradox, which consists in the inversion of the order of changes in free activation energy under the variation of the substituents X in pyridine or, in other words, reversal of the sign of the coefficient of sensitivity a_X^{YT} ($r \geq 0.980$) toward the effects of the substituents X in pyridine ($\Delta G^{\neq}_{XYT} = \Delta G^{\neq}_{HYT} + a_X^{YT}\sigma_X$ equation) in the temperature range considered. For example, for the reactions involving 3-NO_2-benzoic acid, a_X^{YT} at 279, 295, 308, 323, and 343 K is -4.9 ± 0.2, 0, 3.4 ± 0.2, 7.7 ± 0.9, and 14 ± 1, respectively.

Dividing the left- and right-hand-sides of regression (8) by temperature T turns the regression into the isoparametric relationship

$$\begin{aligned}\Delta G^{\neq}_{XYT}/T &= (0.146 \pm 0.003) \\ &+ (-5.0 \pm 0.2)\sigma_Y/T + (0.279 \pm 0.008)\sigma_X \\ &+ (54.6 \pm 0.8)/T + (-82 \pm 3)\sigma_X/T,\end{aligned} \tag{9}$$

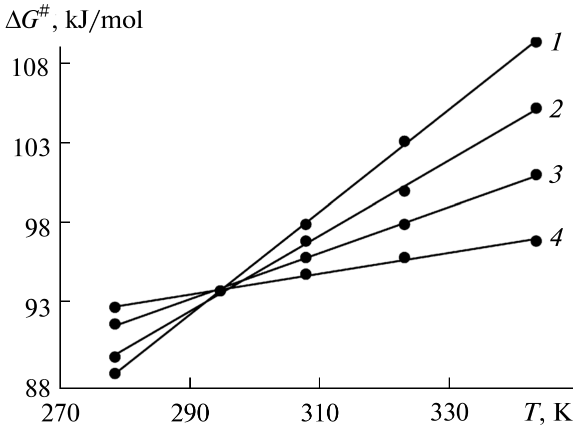


Fig. 2. Temperature dependence of free activation energy for the reaction between phenyloxirane and 3-nitrobenzoic acid catalyzed by X-substituted pyridines in acetonitrile. X = (*1*) 3-CN, (*2*) 3-COOEt, (*3*) H, and (*4*) 4-OCH_3.

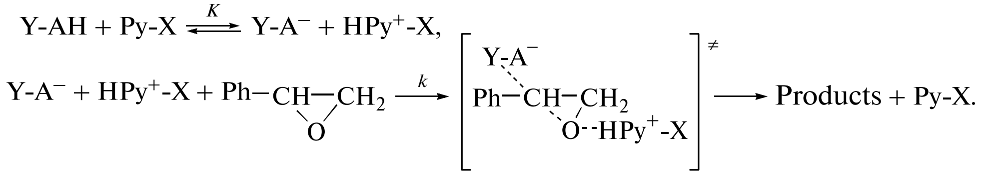
from which we obtain $1/T^{IP} = -0.279/-82 = 0.0034$ and $T^{IP} = 294$ K; from the constant of the substituent X, we obtain $\sigma_X^{IP} = -54.6/-82 = 0.67$. These IP points are in agreement with the values calculated using regression (7). At the $\sigma_X^{IP} = 0.67$ point, $\Delta G^{\neq IP}_{XYT}/T$ should not depend on temperature. This will be possible if, in the expression $\Delta G^{\neq IP}_{XYT}/T = \Delta H^{\neq}_{XY}/T - \Delta S^{\neq}_{XY}$, the enthalpic term is zero, $\Delta H^{\neq}_{XY} = 0$. In other words, we again arrive at the above conclusion that the activation energy at this IP point is completely determined by the entropic term: $\Delta G^{\neq IP}_{XYT}/T = \Delta S^{\neq}_{XY}$ ($\Delta S^{\neq IP}_{XYT} = -T\Delta S^{\neq}_{XY}$).

Thus, the above cross correlation analysis of the results of the multifactor kinetic experiment demonstrated that the kinetic enthalpy–entropy compensation effect is, in essence, a particular case of isoparametricity. The quantitative characteristics of the compensation phenomenon are three IP points in which reaction system (I) acquires special, "magic" properties. It was mentioned above that, at the temperature IP point, $T^{IP} = 292$ K ($T^{IP(G)} = 294$ K), the effect of the substituents X on $\Delta G^{\neq}_{XYT}$, and, accordingly, on the reaction rate disappears ($\rho^{T}_{XY} = 0$) owing to enthalpy–entropy compensation. In addition, because of the dual nature of $\Delta G^{\neq}_{XYT}$, within the compensation effect reaction system van pass from its special state associated with the $\sigma_X^{IP} = 0.63$ (0.67) point, in which there is no contribution from the enthalpic factor to the free activation energy ($\Delta H^{\neq}_{XY} = 0$), to the equally interesting state associated with the $\sigma_X^{IP(G)} = -0.52$ point, in which there is no contribution from the entropic factor ($\Delta S^{\neq}_{XY} = 0$). We proved the physical reality of the IP points with respect to the reaction temperature

(T^{IP}) and structural parameter (σ_X^{IP}) and carried out a passage through the former point; that is, we demonstrated the isoparametricity paradox, which is rarely observed in experiments. In a recent study [6], we have proved the existence of an IP point with respect to the structural parameter for reactions of 3,5-dinitrophenyloxirane with Y-substituted arenesulfonic acids: $\sigma_Y^{IP(G)} = 0.54$, where $\Delta S_Y^{\neq} = 0$. We experimentally brought the reaction system through this point and observed a reversal of the sign of $\Delta S_Y^{\neq}$.

Mechanistic Aspects

The fact that the kinetic and activation parameters of all reactions in RS (I) obey partial and cross PLP correlations is evidence of a uniform interaction between the nonadditive effects of substituents X in pyridines and temperature within the single mechanism of the catalytic process. In reaction system (I), the Py-X pyridines enhance the nucleophilic properties of the acid reactant Y-AH (Y-substituted benzoic acid) by means of acid–base interactions: Y-AH + Py-X $\rightleftarrows$ Y-AH···Py-X $\rightleftarrows$ Y-A$^-$···HPy$^+$-X $\rightleftarrows$ Y-A$^-$// HPy$^+$-X $\rightleftarrows$ Y-A$^-$ + HPy$^+$-X. Among the H-complexes and ionic intermediates that are possible in the equilibrium system in acetonitrile, a highly polar solvent ($\varepsilon = 37.5$), the strongest catalytic effect can be ensured by free ions, namely, the carboxylate anion Y-A$^-$ = Y-$C_6H_4COO^-$ and the pyridinium cation HPy$^+$-X. The involvement of dissociated benzoic acids (benzoic, 4-chlorobenzoic, etc.) in oxirane ring opening in methyl ethyl ketone was considered by other authors [22]. The isoparametric properties of cross RS (I) and, in particular, the enthalpy–entropy compensation effect due to these properties are consistent with the following mechanism of the catalytic action of pyridines, which can be viewed as a nucleophilic mechanism with electrophilic assistance:



According to this mechanism, the catalytic reactions are third-order (first-order with respect to each of the participants—oxirane substrate, acid reactant, and pyridine catalyst). It follows from the scheme of the mechanism that the catalytic rate constant k_3 is an effective quantity ($k_3 = Kk$). Accordingly, the sensitivity parameter with respect to the substituents X in pyridines, ρ_X^{YT}, is a composite quantity ($\rho_X^{YT} = \rho_1 + \rho_2$; $\rho_1 < 0$ at the first stage—pyridine protonation yielding a nucleophile, namely, the benzoate anion Y-A$^-$; $\rho_2 > 0$ at the second, rate-limiting stage—electrophilic assistance of the pyridinium cation HPy$^+$-X to the opening of the oxirane ring). At the T^{IP} point, where $\rho_X^{YT} = 0$, the opposing effects of the substituents X at the first and second stage are exactly balanced ($|\rho_1| = \rho_2$) and reaction system is isokinetic ($\delta_X \log k_3^{IP} = 0$, k_3^{IP} = const). This is due to the enthalpy–entropy compensation effect, specifically, the equality of the enthalpic and entropic contributions to the change in free activation energy at the T^{IP} point. The data presented in Table 2 demonstrate that, above T^{IP}, $\rho_X^{YT} < 0$ and, therefore, $|\rho_1| > \rho_2$, with the absolute value of ρ_X^{YT} increasing markedly with an increasing temperature. This behavior of ρ_X^{YT} is due to the fact that the hydrogen bond O···H in the transition state of the second stage weakens with an increasing temperature (ρ_2 decreases) and the extent of pyridine protonation at the first stage increases ($|\rho_1|$ grows). Conversely, below T^{IP} the coefficient ρ_X^{YT} has a positive value ($\rho_X^{YT} > 0$, $|\rho_1| < \rho_2$), which is unnatural of pyridines. This is due to the fact that the hydrogen bond in the transition state strengthens (ρ_2 increases) as the temperature decreases relative to T^{IP}, which enhances the electrophilic assistance of the pyridinium cation to oxirane ring opening.

Thus, using oxirane ring opening as an example, we demonstrated that the realization of IP points with respect to temperature and with respect to the parameters of other factors and, very importantly, experimental passage through these points provide a novel insight into still poorly understood, hidden properties of cross reaction series in which enthalpy–entropy compensation takes place. It is this scenario of investigating the compensation effect that seems to us most promising. Neglect of multifactor experiments in the investigation of the compensation effect will not allow one to obtain statistically reliable compensation relationships. For this reason, the compensation effect is often referred to as a statistical phantom.

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