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A Polylinear Regression Model Taking into Account the Cross Effects of the Structure and Temperature in the Reactions of Phenyloxirane with Benzoic Acids, Catalyzed by Pyridines: Evidence of the Isoparametricity Phenomenon

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Abstract—The joint effect of the structure and temperature on the rate of the reactions of phenyloxirane with Y-substituted benzoic acids in acetonitrile, catalyzed by X-substituted pyridines, was studied. A polylinear regression model that adequately describes the effects of cross-varied factors was calculated. Owing to intensive interaction of the effects of the substituents X and temperature, experimental evidence for the isoparametricity phenomenon was obtained.

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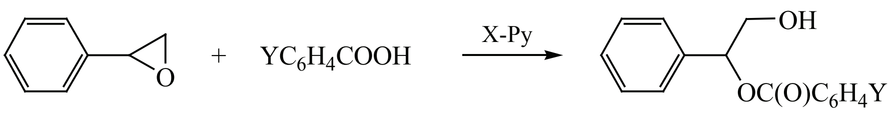
Efficient control of chemical processes requires knowledge of the quantitative relationships that take into account the joint effect of various internal and external factors (structure, solvent, temperature, pH of the medium, pressure, etc.) on their kinetic and thermodynamic characteristics. Representation of such relationships in the form of multiparameter correlations based on the polylinearity principle (PLP) is the most promising [1]. Polylinear equations (PLEs) contain cross terms taking into account nonadditivity (interaction) of the effects of mutually varied factors, whereby their predictive capabilities are significantly improved compared to traditional one-parameter correlations. Over the recent decades, PLEs have been successfully used for obtaining quantitative estimates of the rates of nucleophilic substitution reactions at various electrophilic reaction sites under multifactor conditions, as well as for interpreting their mechanisms [2–7]. Owing to interaction of the effects of the structural factors in those processes, experimental evidence for the unique isoparametricity phenomenon was obtained [1, 3, 5–7].

Isoparametricity is manifested as the zero value of the sensitivity coefficient for the effects of one of the factors in empirical one-parameter correlations, 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, at the isoparametric value of the parameter of another factor, called the isoparametric point (IPP). In other words, at the IPP for the parameter of one of the factors no influence is exerted on the correlated value of another factor. On passing through the IPP, the inversion of the signs of the corresponding sensitivity coefficients takes place (isoparametricity paradox).

Though broadening and deepening the knowledge of previously unknown properties of physicochemical systems that are in conflict with conventional chemical theory, the isoparametricity studies have received little attention so far. This is due, on the one hand, to high laboriousness of multifactor experiments, and on the other hand, to the virtual nature of the IPPs in many reaction series (RSs), because they fall into a far extrapolation region and are experimentally inaccessible. Further progress in study of the isoparametricity phenomenon may be achieved with RSs for which cross interactions involve other, along with the structural, factors. In this context, temperature deserves special attention as a universal factor characterizing the degree of hotness of the system.

For study of the joint effects of the structure and temperature we chose oxirane ring opening reactions which are of interest from both theoretical and practical viewpoints. The specific organization of the atoms in the oxirane ring, combined with its strain and unsaturated nature, are responsible for a wide variety of practically important reactions of oxirane substrates with compounds from different classes [8–10]. These reactions are widely used in organic synthesis, as well as in production of polymers, pharmaceuticals, and pesticides, and also underlie a number of biochemical processes, in particular, the physiological process of detoxification of metabolites of exogenous substances. The oxirane ring is a structural element of many biologically active substances of both synthetic and natural origin [11, 12]. We showed previously [13] that, in the reactions of aryloxiranes with arenesulfonic acids, intensive interaction of the effects of the structure of the acid reactant and the temperature is manifested, which allowed the first experimental observation of the isoparametricity phenomenon in the oxirane chemistry.

Here, we studied the joint effect of the structure and temperature on the rate of the reactions of phenyloxirane with Y-substituted arenecarboxylic (benzoic) acids (Y = H, 3-Br, 3-NO_2), catalyzed by X-substituted pyridines X-Py (X = 4-OMe, 4-Et, H, 3-COOEt, 3-CN), in acetonitrile at 279, 295, 308, 323 and 343 K, examined the isoparametric properties of the cross reaction series, and calculated a polylinear regression model of the system reactivity on the basis of the results of a multifactor kinetic experiment.



(1)

EXPERIMENTAL

As solvent we used analytically pure-grade acetonitrile, which was dried and distilled successively from P_2O_5 and CaH_2. Phenyloxirane (Merck, content of the main substance no less than 98%) was vacuum-distilled. Pure-grade benzoic acids were recrystallized twice from aqueous ethanol (1 : 1). Pure- and chemically pure-grade pyridines were vacuum-distilled. The products of reactions (1) are primary alcohols, 2-(Y-benzoyloxy)-2-phenylethanols [14]. The rate of the reactions was determined from the loss of the acid reactant HA, as we described previously [14]. In the kinetic experiments we used the oxirane substrate S in no less than tenfold excess with respect to HA: $[S]_0 >> [HA]_0 = 0.062–0.090$ M. The concentration of the X-Py catalyst m was varied within 0.00953–0.0473 M. Under these conditions, the reaction rate is described by the equation $d[HA]/dt = k_1[HA] = k_2[S]_0[HA] = k_3[S]_0[HA]m$. In all the kinetic experiments the observed pseudo-first-order rate constants k_1, s^{-1}, remained unchanged during the process up to 70–80% conversions of the acid reactant. The k_1 constants were determined accurately to within 5%. The second-order rate constants k_2, L mol^{-1} s^{-1}, were obtained using the relationship $k_2 = k_1/[S]_0$. The apparent third-order catalytic rate constants k_3, L^2 mol^{-2} s^{-1}, were calculated for four or more concentrations m from the linear dependences $k_2 = k_3m$ (correlation coefficient $r \geq 0.998$), whose extrapolation to the origin indicates the absence of a noncatalytic process. The accuracy of the kinetic and correlation parameters was estimated in terms of the standard deviation SD, which was derived by the statistical method from N experimental data points. Statistical data processing was carried out using Origin 6.1 package for the confidence level of 0.95.

The rate constants k_3 listed in the table for all the reactions studied reflect the joint effect of the cross-varied factors (substituents X in the pyridines, substituents Y in the benzoic acids, temperature T) on the rate of the catalytic process (1). It is noteworthy that, at 295 K, in all the RSs with fixed substituents Y, the substituents X have negligible effect on k_3. At a lower temperature (279 K) k_3 tends to increase with weakening of the electron-donating and strengthening of the electron-accepting power of the substituents X. By contrast, at temperatures above 295 K, the identical change in the power of the substituents X causes k_3 to decrease, more intensively at higher temperatures. These changes in k_3 are indicative of interaction (nonadditivity) of the effects of the substituents X and temperature in cross RS (1). For quantitative estimation of this interaction the kinetic data were subjected to correlation analysis.

The effect of the substituents X on the rate of reactions (1) is well described by the Hammett equation

Rate constants k_3 and ρ_X^{YT} coefficients in the Hammett equation for the reactions of phenyloxirane with Y-substituted benzoic acids, catalyzed by X-substituted pyridines, in acetonitrile at different temperatures

X (σ_X)	$k_3 \times 10^5$, $L^2\,mol^{-2}\,s^{-1}$, at indicated temperature, K				
	279	295	308	323	343
Y (σ_Y) = 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 ± 0.5	–	–
3-CN (0. 56)	–	13.7 ± 0.2	14.9 ± 0.7	16.9 ± 0.2	–
ρ_X^{YT}	0.761 ± 0.009	–0.083 ± 0.003	–0.75 ± 0.04	–1.30 ± 0.07	–2.4 ± 0.1
Y (σ_Y) = 3-Br (0.39)					
4-OMe	–	7.40 ± 0.09	32 ± 2	120 ± 2	650 ± 10
4-Et	1.39 ± 0.03	7.20 ± 0.03	26.2 ± 0.2	80 ± 1	302 ± 6
H	2.00 ± 0.01	6.99 ± 0.03	18.1 ± 0.1	45.1 ± 0.1	141 ± 2
3-COOEt	3.7 ± 0.1	6.7 ± 0.2	10.69 ± 0.02	–	–
3-CN	–	6.26 ± 0.07	7.0 ± 0.3	7.7 ± 0.1	–
ρ_X^{YT}	0.81 ± 0.08	–0.077 ± 0.009	–0.77 ± 0.04	–1.74 ± 0.04	–2.4 ± 0.1
Y (σ_Y) = H (0)					
4-OMe	–	3.4 ± 0.1	14.9 ± 0.2	51.9 ± 0.8	292 ± 1
4-Et	0.692 ± 0.006	3.28 ± 0.07	11.5 ± 0.5	32 ± 1	136 ± 6
H	0.894 ± 0.006	3.22 ± 0.05	8.2 ± 0.1	18.9 ± 0.2	64 ± 3
3-COOEt	1.71 ± 0.01	3.00 ± 0.06	4.7 ± 0.1	–	–
ρ_X^{YT}	0.751 ± 0.005	–0.078 ± 0.002	–0.77 ± 0.06	–1.62 ± 0.06	–2.4 ± 0.2

$$\log k_3 = \log k_3^{st} + \rho_X^{YT}\sigma_X, \qquad (2)$$

where k_3^{st} is the rate constant at temperature T with the substituent Y under standard conditions (X = H, $\sigma_X = 0$), and ρ_X^{YT}, coefficient of sensitivity to the effects of the substituents X (from here on, the sub- and superscripts refer to the varied and fixed factors, respectively).

The ρ_X^{YT} coefficients (see table) for partial RSs depend on the temperature which affects not only the magnitude but also the sign of ρ_X^{YT}. The reason is the above-mentioned interaction of the effects of the X substituents and temperature in reaction (1). According to the PLP, the cross-interaction coefficient q_X^{YT} can be calculated using the linear dependence $\rho_X^{YT} = \rho_X^{YT=\infty} + q_X^{YT} \times 10^3/T$, which is represented in the series of the fixed substituents Y = H, 3-Br, 3-NO_2 by the equations ($r \geq 0.991$) $\rho_X^{YT} = (-16.6 \pm 0.4) + (4.9 \pm 0.1) \times 10^3/T$, $\rho_X^{YT} = (-17.1 \pm 0.7) + (5.0 \pm 0.2) \times 10^3/T$, and $\rho_X^{YT} = (16.0 \pm 0.7) + (4.7 \pm 0.2) \times 10^3/T$, respectively. As seen from these equations, q_X^{YT} is unaffected by the substituents Y, which fact suggests the lack of pair interactions of the effects of X and Y ($\rho_X^{YT} = 0$), on the one hand, and of the effects of Y and temperature, on the other ($q_X^{YT} = 0$), as well as of the ternary interaction of the effects of the substituents X and Y and temperature T ($q_X^{YT} = 0$). The lack of these interactions is responsible for a narrow range of variation of the parameters of sensitivity ρ_Y^{XT} to the effects of the substituents Y, calculated using the tabulated data, in the equation $\log k_3 = \log k_3^{st} + \rho_Y^{XT}\sigma_Y$ for partial reactions in the case of different fixed substituents X and different fixed temperatures T ($\rho_Y^{XT} = 0.86–0.96$, $r \geq 0.992$).

In the general case, according to the PLP, the joint effect of the substituents X and Y and temperature T on the rate of reactions (1), taking into account the cross-interaction of the effects of all the three varied factors, should be estimated using the PLE:

$$\log k_3 = \log k_3^{st} + \rho_X^{st}\sigma_X + \rho_Y^{st}\sigma_Y + B_T^{st} \times 10^3/T + \rho_{XY}^{st}\sigma_X\sigma_Y$$
$$+ q_{XT}^{st}\sigma_X \times 10^3/T + q_{YT}^{st}\sigma_Y \times 10^3/T + q_{XYT}\sigma_X\sigma_Y \times 10^3/T, \quad (3)$$

where k_3^{st} is the rate constant under standard conditions ($\sigma_X = \sigma_Y = 0$, $T = \infty$ K); ρ_X^{st}, ρ_Y^{st}, and B_T^{st}, parameters of the standard reactions at $\sigma_Y = 0$ and $T = \infty$ K, $\sigma_X = 0$ and $T = \infty$ K, and $\sigma_X = \sigma_Y = 0$, respectively; ρ_{XY}^{st}, q_{XT}^{st}, and q_{YT}^{st}, pair interaction coefficients in the standard reaction series (at $T = \infty$ K, $\sigma_Y = 0$, and $\sigma_X = 0$, respectively); and q_{XYT}, triple cross-interaction coefficient.

By processing the results of the multifactor kinetic experiment using Eq. (3), a polylinear regression was calculated (R is the multiple correlation coefficient, and F, Fisher's exact test):

$$\log k_3 = (5.1 \pm 0.2) + (-15.6 \pm 0.7)\sigma_X + (1.2 \pm 0.3)\sigma_Y$$
$$+ (-2.83 \pm 0.05) \times 10^3/T + (0.4 \pm 1.4)\sigma_X\sigma_Y$$
$$+ (4.6 \pm 0.2)\sigma_X \times 10^3/T + (-0.08 \pm 0.09)\sigma_Y \times 10^3/T$$
$$+ (-0.1 \pm 0.4)\sigma_X\sigma_Y \times 10^3/T,$$
$$R = 0.998,\ SD = 0.0367,\ N = 58,\ \mathrm{F} = 3260. \quad (4)$$

As might be expected, in regression (4) the already discussed ρ_{XY}, q_{YT}, and q_{XYT} coefficients are statistically insignificant. After exclusion of the cross-terms with these coefficients, PLE (3) is simplified to the form

$$\log k_3 = \log k_3^{st} + \rho_X^{st}\sigma_X + \rho_Y^{st}\sigma_Y + B_T^{st} \times 10^3/\mathrm{T}$$
$$+ q_{XT}\sigma_X \times 10^3/T. \quad (5)$$

Processing the kinetic data by Eq. (5) gave

$$\log k_3 = (5.18 \pm 0.08) + (-15.4 \pm 0.3)\sigma_X$$
$$+ (0.91 \pm 0.02)\sigma_Y + (-2.85 \pm 0.02) \times 10^3/T$$
$$+ (4.5 \pm 0.1)\sigma_X \times 10^3/T,$$
$$R = 0.998,\ SD = 0.0362,\ N = 58,\ \mathrm{F} = 6226. \quad (6)$$

The statistical characteristics of regression (6) are indicative of high reliability of all its coefficients. The adequacy of the rate constants $\log k_3^{calc}$, calculated using this regression, to the experimental $\log k_3^{exp}$ data is demonstrated by Eq. (7) in which the slope is virtually equal to the expected unity:

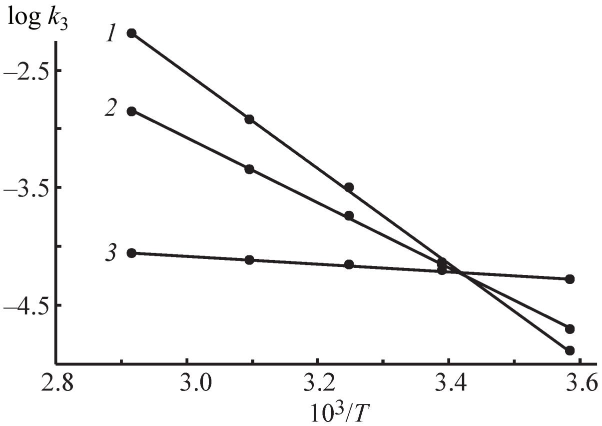
$$\log k_3^{calc} = (0.029 \pm 0.026) + (1.004 \pm 0.007)k_3^{exp},$$
$$r = 0.999,\ SD = 0.0379,\ N = 58. \quad (7)$$

Elimination from Eq. (7) of the statistically insignificant intercept term gives $\log k_3^{calc} = (1.004 \pm 0.007)k_3^{exp}$, which relationship demonstrates an excellent agreement between the calculated and experimental $\log k_3$ values.

Owing to the statistically significant coefficient at the cross-member ($q_{XT} = -2.85 \pm 0.02$), regression (6) is isoparametric. It is characterized by two IPPs, namely, that for the constant of the substituent X, $\sigma_X^{IP} = -B_T^{st}/q_{XT} = 0.63$, and that for the reciprocal of the temperature $10^3/T^{IP} = -\rho_X^{st}/q_{XT} = 3.42$, $T^{IP} = 292$ K, as well as by isoparametric value $\log k_3^{IP} = \log k_3^{st} - \rho_X^{st}B_T^{st}/q_{XT} = -4.57$, identical for the both IPPs. It should be noted that $\log k_3^{IP}$ is part of the apparent $\log k_3 = \log k_3^{IP} + \rho_Y^{st}\sigma_Y = -4.57 + (0.91 \pm 0.02)\sigma_Y$ value, and only at the standard value $\sigma_Y = 0$ (Y = H) $\log k_3 = \log k_3^{IP}$.

At the IPP $\sigma_X^{IP} = 0.63$ the rate of the process ($\log k_3$) should be temperature-independent. The figure illustrates a decrease in sensitivity to the effect of temperature in the reaction involving 3-bromobenzoic acid, with the IPP σ_X^{IP} being approached on changing from electron-donating to electron-accepting substituent X in pyridine. The reactions involving 3-CN-pyridine, for which the constant $\sigma_X = 0.56$ in the case of the substituent X = 3-CN is little different from the isoparametric value $\sigma_X^{IP} = 0.63$, exhibit low sensitivity to the effect of the temperature. These reactions are characterized by close to zero slopes B_T^{XY} in the Arrhenius equation $\log k_3 = A^{XY}_{T=\infty} + \mathrm{B}_T^{XY}\times 10^3/T$ ($r \geq 0.995$): Y = 3-Br, $\log k_3 = (-3.17 \pm 0.06) + (-0.30 \pm 0.02) \times 10^3/T$; Y = 3-NO$_2$, $\log k_3 = (-2.8 \pm 0.1) + (-0.31 \pm 0.03) \times 10^3/T$. As a consequence, the apparent activation energies $E_a^{XY} = -2.303\mathrm{R} \times B_T^{XY}\times 10^3$ (R is gas constant) are low: 5.7 and 5.9 kJ mol^{-1}, respectively.

As to the IPP for temperature $T^{IP} = 292$ K, its realization in experiment is clearly demonstrated by the figure, in which it appears as the intersection point of the family of the correlation straight lines in the Arrhenius equa-



Variation of log k_3 (see table) with $10^3/T$ (T, K) for the reaction of phenyloxirane with 3-bromobenzoic acid in acetonitrile, catalyzed by X-substituted pyridines: X = (*1*) 4-OMe, (*2*) H, and (*3*) 3-CN. The log k_3 values for the reaction involving 3-CN-pyridine at 279 and 343 K were calculated by Eq. (6).

tion coordinates for partial reaction series with fixed substituents X in pyridine. At this IPP, substituents X have no effect on the rate of the process ($\rho^{YT} = 0$). We came very close to this IPP in the experiment at a close to isoparametric temperature of 295 K. For all the fixed substituents Y, the ρ_X^{YT} values for the reactions at this temperature are slightly different from zero (see table). It should be emphasized that, in the case of cross RS (1), a passage through IPP T^{IP} with varied temperature was realized, which is an extremely rare situation in chemical processes. The observed inversion of the sign of the parameter of sensitivity ρ_X^{YT} to the effects of the substituents X demonstrates the isoparametricity paradox, namely, reversal of the order of the effect of the substituents X on the catalytic activity of the pyridines on passing through the T^{IP}.

Thus, the joint effects of the structure and temperature in cross RS (1) are adequately described by polylinear regression model (6) which takes into account both the additive contribution from the effects of the cross-varied factors to the rate of the process and the nonadditive effects of the temperature and substituents X in pyridine. The use of this polyilinear model, taking into account its isoparametric properties, allows very accurate prediction of the reactivity of the phenyloxirane-benzoic acid-pyridine catalyst systems for any set of parameters of the varied factors.

CONCLUSIONS

(1) Processing the multifactor kinetic experiment data enabled calculation of a polylinear regression model that adequately describes the effect of cross-varied factors (structure, temperature) on the rate of the reactions of phenyloxirane with benzoic acids, catalyzed by pyridines.

(2) The interaction of the effects of the substituents X in pyridine and of the temperature was revealed, whereby experimental evidence for the isoparametricity phenomenon was provided: At the isoparametric point for temperature T^{IP} (isokinetic temperature) the rate of the reactions studied is independent of the structure of the substituents X, and on passing through this point the order of the effect of X on the catalytic activity of the pyridines is reversed (isoparametricity paradox). At the isoparametric point σ_X^{IP} for the constant of the substituent X the temperature has a negligible effect on the rate of the process.

(3) It was shown that the multifactor experiments and cross-correlation analysis of their results enable identification of previously unknown fundamental properties of cross reaction series, such as nonadditivity of the joint effects of the varied factors, the isoparametricity phenomenon, and the isoparametricity paradox. The knowledge of these properties allows the use of quantitative approaches to designing optimal conditions for organic reactions, in particular, for oxirane ring opening reactions. Using the polylinear model of the reactivity of the phenyloxirane-benzoic acid-pyridine catalyst systems at different temperatures, it is possible to predict with high reliability the rate of the catalytic process for any given set of parameters of the varied factors.

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