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THE REACTIVITY OF N-PHENYLANTHRANILIC ACIDS DERIVATIVES. XXV.* KINETIC PARAMETERS OF ACTIVATION AND ISOPARAMETRICITY OF THE REACTION OF THE ALKALINE HYDROLYSIS OF METHYL ESTERS OF SUBSTITUTED 4,5-DIMETHOXY-N-PHENYLANTHRANILIC ACIDS IN THE BINARY DIOXANE-WATER SOLVENT

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Key words: N-phenylanthranilic acid; methyl esters; reactivity; thermodynamic parameters of activation; thermodynamic parameters of activation; isoparametricity of reactions; enthalpy control

Kinetics of the alkaline hydrolysis reaction of methyl esters of substituted 4,5-dimethoxy-N-phenylanthranilic acids has been studied in the binary solvent of dioxane-water at 55, 75, 85°C. It has been found that at each experimental temperatures lgk_T *dependence on the nature and position of substitutes in a non-anthranilic fragment of the molecule is described by the Hammett equation. It has been demonstrated that introduction of electrodonor substituents in the molecule of ester assists increasing of the activation energy and free activation energy. The activation entropy for all substances is significant and high according to the absolute value, which indicates the* $B_{AC}2$ *mechanism of the reaction with formation of high-symmetrical intermediates. The analysis of the numerous kinetic and activation parameters has shown isokinetics of the reaction with the enthalpy type of control. It has been experimentally found that the compounds synthesized show the anti-inflammatory, analgesic, diuretic, bacteriostatic activities.*

РЕАКЦІЙНА ЗДАТНІСТЬ ПОХІДНИХ N-ФЕНІЛАНТРАНІЛОВИХ КИСЛОТ. XXV. КІНЕТИЧНІ ПАРАМЕТРИ АКТИВАЦІЇ ТА ІЗОПАРАМЕТРИЧНІСТЬ РЕАКЦІЇ ЛУЖНОГО ГІДРОЛІЗУ МЕТИЛОВИХ ЕСТЕРІВ ЗАМІЩЕНИХ 4,5-ДИМЕТОКСИ-N-ФЕНІЛАНТРАНІЛОВИХ КИСЛОТ У БІНАРНОМУ РОЗЧИННИКУ ДІОКСАН-ВОДА

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Ключові слова: *N-фенілантранілова кислота; метилові естери; реакційна здатність; термодинамічні параметри активації; ізопараметричність реакції; ентальпійний контроль*

Досліджено кінетику реакції лужного гідролізу метилових естерів заміщених 4,5-диметокси-N-фенілантранілових кислот у бінарному розчиннику діоксан – вода при температурах 55, 75, 85°С. Встановлено, що при всіх досліджених температурах залежність lgk_T *від природи і положення заступників у неантраніловому фрагменті молекули описується рівнянням Гамета. Показано, що введення електронодонорних замісників у молекулу естеру сприяє підвищенню енергії активації і вільної енергії активації. Ентропія активації для всіх речовин від'ємна та велика за абсолютним значенням, що вказує на* $B_{AC}2$ *механізм реакції з утворенням високосиметричних інтермедіантів. Аналіз численних кінетичних і активаційних параметрів показав ізокінетичність реакції з ентальпійним типом контролю. Експериментально встановлено, що синтезовані речовини виявляють протизапальну, аналгетичну, діуретичну, бактеріостатичну активність.*

РЕАКЦИОННАЯ СПОСОБНОСТЬ ПРОИЗВОДНЫХ N-ФЕНИЛАНТРАНИЛОВЫХ КИСЛОТ. XXV. КИНЕТИЧЕСКИЕ ПАРАМЕТРЫ АКТИВАЦИИ И ИЗОПАРАМЕТРИЧНОСТЬ РЕАКЦИИ ЩЕЛОЧНОГО ГИДРОЛИЗА МЕТИЛОВЫХ ЭФИРОВ ЗАМЕЩЕННЫХ 4,5-ДИМЕТОКСИ-N-ФЕНИЛАНТРАНИЛОВЫХ КИСЛОТ

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Ключевые слова: *N-фенилантраниловая кислота; метиловый эфир; реакционная способность; термодинамические параметры активации; изопараметричность реакции; энтальпийный контроль*

Исследована кинетика реакции щелочного гидролиза метиловых эфиров замещенных 4,5-диметокси-N-фенилантраниловых кислот в бинарном растворителе диоксан-вода при температурах 55, 75, 85°С. Установлено, что при всех исследованных температурах зависимость lgk_T *от природы и положения заместителей в неантраниловом фрагменте молекулы описывается уравнением Гамета. Показано, что введение электронодонорных заместителей в молекулу эфира способствует повышению энергии активации и свободной энергии активации. Энтропия активации для всех веществ отрицательна и велика по абсолютным значениям, что указывает на* $B_{AC}2$ *механизм реакции с образованием высокосимметричного интермедианта. Анализ многочисленных кинетических и активационных параметров показал изокинетичность реакции с энтальпийным типом контроля. Экспериментально установлено, что синтезированные вещества проявляют противовоспалительную, анальгетическую, диуретическую, бактериостатическую активность.*

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* Report XXIV see [15]

The long-time investigations in the range of N-phenylanthranilic acids (N-PAA) and their derivatives by researchers of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine, Institute of Pharmacology and Toxicology of the Ukrainian Academy of Medical Sciences and the National University of Pharmacy led to creation of effective medicines (mefenamic acid and its sodium salt, difluorant, antral) widely used in medical practice as anti-inflammatory, antipsoriatic and hepatoprotective medicines [5, 6]. Data of scientific research of domestic and foreign scientists indicate that derivatives of N-PAA have a wide synthetic and pharmacological potential [1-3, 6, 10, 14, 16, 17]. These circumstances caused the necessity of synthesis of methyl esters 4,5-dimetoxy-N-PAA and study their reactivity. It should be noted that the reaction of alkaline hydrolysis of N-PAA esters is one of the possible ways of their metabolism in the organism and is of a great scientific and practical interest for researchers in the field of organic synthesis and pharmacological research. Esters of N-PAA are also initial substances for obtaining the corresponding alkyl-, aryl-, heterylamides, hydrazides and their derivatives. To continue the study of kinetics of the alkaline hydrolysis reaction [15] of biologically active methylic esters of 4,5-dimethoxy-N-phenylanthranilic acids in the binary solvent of dioxane-water (60 vol.% of dioxane) by the equation according to the scheme 1, the constants of the reaction rate have been determined at the temperatures of 55, 75 and 85°C (Scheme 1).

Analysis of the results obtained proves that at all experimental temperatures the influence of the nature and position of substituents in a non-anthranilic fragment of the molecule is similar: acceptor substituents accelerate the reaction due to delocalization of the charge in relation to the anion, and donor substituents causes the opposite effect; it allows to assume the course of the alkaline hydrolysis reaction of methyl esters of 4,5-dimethoxy-N-phenylanthranilic acids (1-9) by $B_{AC}2$ mechanism.

According to the Hammett's equation the quantitative estimation of the influence of the nature and position of substituents upon the constants of the reaction rate at 55, 75, 85°C has been performed.

$$\lg k_{328} = (-4.801 \pm 0.007) + (0.996 \pm 0.029)\sigma \quad (1)$$
$$n=9 \qquad r=0.997 \qquad S=4.7\cdot10^{-2}$$

$$\lg k_{348} = (-4.317 \pm 0.005) + (0.883 \pm 0.029)\sigma \quad (2)$$
$$n=9 \qquad r=0.998 \qquad S=3.7\cdot10^{-2}$$

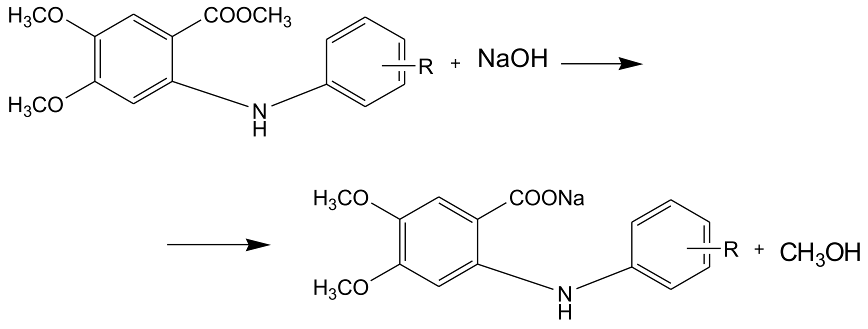
$$\lg k_{358} = (-4.062 \pm 0.004) + (0.844 \pm 0.015)\sigma \quad (3)$$
$$n=9 \qquad r=0.998 \qquad S=2.5\cdot10^{-2}$$

The correlative equations obtained have convincing statistical characteristics. The little values of the reaction parameter (ρ) at all experimental temperatures testify its slight sensitivity to the influence of substituents, it reduces with increase of the reaction temperature. It is interesting that the values of the reaction parameter practically coincide (within the experimental error) with ρ of β-dialkylaminethyl esters of 4-nitro-, 4-nitro-5-chloro- and 4-sulfamoil-N-PAA [7, 11-13]. The positive values of ρ testify of $B_{AC}2$ mechanism of the reaction (Scheme 2).

Table 1

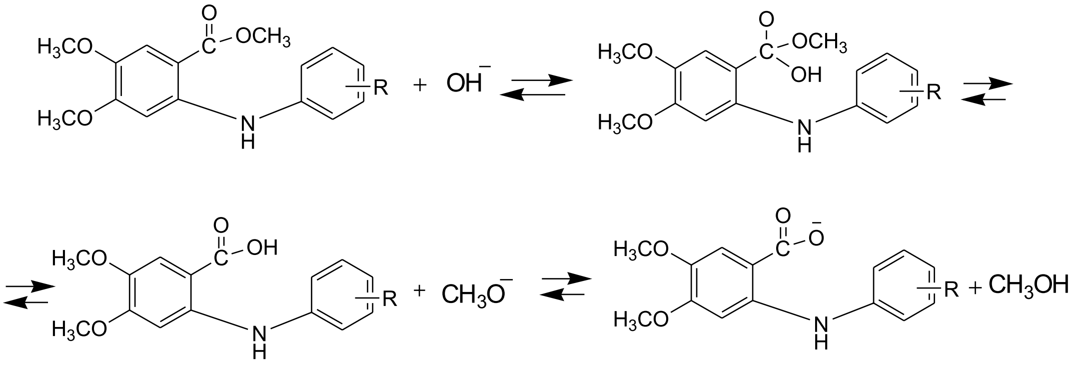
The constants (k) of the alkaline hydrolysis reaction rate of methyl esters of substituted 4,5-dimethoxy-N-phenylanthranilic acids at various temperatures

Compound	$k \cdot 10^5$, $l \cdot mol^{-1} \cdot s^{-1}$ at T, k		
	328	348	358
1	1.63±0.03	4.46±0.03	8.69±0.05
2	1.10±0.04	3.44±0.02	6.16±0.04
3	1.03±0.03	3.44±0.03	6.02±0.04
4	0.94±0.03	2.99±0.03	5.54±0.03
5	0.88±0.02	2.81±0.04	5.15±0.04
6	0.83±0.04	2.67±0.03	5.02±0.02
7	0.71±0.03	2.54±0.04	4.68±0.02
8	2.62±0.02	7.80±0.05	13.24±0.07
9	2.67±0.02	7.85±0.05	13.95±0.06



where: R = H (1), 2'-CH_3 (2), 4'-CH_3 (3), 3',4'-$(CH_3)_2$ (4), 4'-OCH_3 (5), 4'-OC_2H_5 (6), 4'-OC_3H_7 (7), 4'-Cl (8), 4'-Br (9)

Scheme 1



Scheme 2

The temperature dependence of constants of the reaction rates can be explained by the Arrenius equation:

$$\ln k = \ln A \frac{E_A}{RT} \qquad (4).$$

The values of the activation energy (E_A) and the logarithm of the predexaponential factor ($\ln A$) calculated according to equation (4) are presented in Table 2. These data show that addition of electrodonor substituents to the molecule of ester naturally leads to increase of the energy barrier and value E_A, respectively. The acceptor substituents cause the opposite effect. Correlation of E_A and $\ln A$ with Hammet σ-constants is statistically unreliable.

According to the Eiring's equation [9] enthalpy ($\Delta H^{\neq}$) and enthropy ($\Delta S^{\neq}$) of activation have been calculated:

$$\ln\frac{k}{T}\cdot\frac{h}{K}=\frac{\Delta S^{\neq}}{R}-\frac{1}{RT}\cdot\Delta H^{\neq}, \qquad (5)$$

where: h – is the Plank's constant; K – is the Bolthman's constant; R – is the universal gas constant; T – is the absolute temperature.

Free energy of activation ($\Delta G^{\neq}$) has been calculated according to the second principle of thermodynamics. The data obtained are presented in Table 3.

Table 2

Kinetic parameters of activation (E_A and ln A) of the alkaline hydrolysis reaction of methyl esters of 4,5-dimethoxy-N-phenylanthranilic acids

Compound	E_A, kJ · mol^{-1}	*ln* A	r	s
1	49.4±0.3	7.14±0.10	0.994	0.175
2	52.0±0.2	7.69±0.10	0.995	0.170
3	50.4±0.4	7.15±0.13	0.991	0.224
4	53.3±0.3	8.03±0.09	0.996	0.156
5	53.4±0.3	7.98±0.09	0.997	0.148
6	54.0±0.3	8.15±0.10	0.996	0.158
7	54.9±0.3	8.41±0.11	0.994	0.193
8	47.7±0.3	7.03±0.10	0.995	0.159
9	48.0±0.3	7.16±0.12	0.993	0.190

The activation entropy for all compounds is inseparable, and it additionally proves the reaction $B_{AC}2$ mechanism. High absolute values of $\Delta S^{\neq}$ indicate a high symmetric structure of the intermediate to be formed. Addition of acceptor substituents to the molecule causes increase of the absolute value of $\Delta S^{\neq}$ and decrease of $\Delta H^{\neq}$. The $\Delta H^{\neq}$ values are small. This fact testifies coincidence of the reaction series. Correla-

Table 3

Thermodynamic parameters of activation ($\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta G^{\neq}$) of the alkaline hydrolysis reaction of methyl esters of 4,5-dimethoxy-N-phenylanthranilic acids

Compound	$\Delta G^{\neq}$, kG · mol^{-1}					$\Delta H^{\neq}$, kG · mol^{-1}	$\Delta S^{\neq}$, kG · mol^{-1}	r	s	T $\Delta S^{\neq}$, kG · mol^{-1}				
	318K	328K	338K	348K	358K					318K	328K	338K	348K	358K
1	108.6	110.5	112.5	114.4	116.4	46.6±0.3	-194.9±8.9	0.994	0.173	-62.0	-63.9	-65.9	-67.8	-69.8
2	109.7	111.6	113.5	115.4	117.3	49.2±0.3	-190.3±8.6	0.995	0.168	-60.5	-62.4	-64.3	-66.2	-68-1
3	109.5	111.5	119.4	115.4	117.3	47.6±0.4	-194.8±11.4	0.990	0.222	-61.9	-63.9	-65.8	-67.8	-69.7
4	110.1	112.0	113.9	115.7	117.6	50.5±0.3	-187.5±7.9	0.996	0.486	-59.6	-61.5	-63.4	-65.2	-67.1
5	110.4	112.2	114.1	116.0	117.9	50.6±0.3	-187.9±7.5	0.996	0.462	-59.8	-61.6	-63.5	-65.4	-67.3
6	110.5	112.3	114.2	116.1	117.9	51.2±0.3	-186.4±8.0	0.996	0.157	-59.3	-61.1	-63.0	-64.9	-66.7
7	110.7	112.5	114.4	116.2	118.1	52.1±0.3	-184.3±8.0	0.994	0.192	-58.6	-60.4	-62.3	-64.1	-66.0
8	107.2	109.1	111.1	113.0	111.1	44.9±0.3	-195.8±8.0	0.995	0.157	-62.3	-64.2	-66.2	-68.1	-70.1
9	107.1	109.1	111.0	113.0	114.9	45.2±0.3	-194.7±9.5	0.993	0.185	-61.9	-63.9	-65.8	-67.8	-69.7

Table 4

Determination of isokinetic temperature. The correlation parameters of equation $y = a + bx$ of dependence of kinetic and activation parameters of the alkaline hydrolysis reaction of methyl esters of 4,5-dimethoxy-N-phenylanthranilic acids and isokinetics of temperatures β

χ	y	a	b	r	s	β, K
$\lg K_{318}$	$\Delta H^{\neq}$	$(12.6 \pm 1.2) \cdot 10^3$	$(-9.1 \pm 0.5) \cdot 10^3$	0.964	190	615
$\lg K_{328}$	$\Delta H^{\neq}$	$(13.2 \pm 1.4) \cdot 10^3$	$(-9.1 \pm 0.7) \cdot 10^3$	0.952	230	625
$\lg K_{338}$	$\Delta H^{\neq}$	$(14.6 \pm 1.6) \cdot 10^3$	$(-10.1 \pm 0.8) \cdot 10^3$	0.942	425	608
$\lg K_{348}$	$\Delta H^{\neq}$	$(14.9 \pm 1.7) \cdot 10^3$	$(-10.1 \pm 0.8) \cdot 10^3$	0.944	249	629
$\lg K_{358}$	$\Delta H^{\neq}$	$(16.6 \pm 1.8) \cdot 10^3$	$(-9.2 \pm 0.8) \cdot 10^3$	0.943	252	610
$\Delta S^{\neq}$	$\Delta H^{\neq}$	$(383 \pm 28) \cdot 10^2$	585 ± 31	0.963	49	585
1/T	ρ	-0.890 ± 0.08	618 ± 26	0.997	$1.27 \cdot 10^{-2}$	618

tions of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ with Hammet σ-constants are statistically insignificant. It is interesting to note that enthalpy and entropy contributions to $\Delta G^{\neq}$ are similar.

For control of isokinetic correlation existence in the experimental reaction series the following correlations were examined: $\Delta H^{\neq} - \lg k_T$, $\Delta H^{\neq} - \Delta S^{\neq}$, $\rho - 1/T$ (Table 4). All of them appeared to be statistically significant. The values of isokinetic temperature β calculated from these dependencies are close to values β calculated independently (Table 5) according to the equation below:

$$\lg k_{T_2} = const + \chi \lg K_{T_1} \qquad (6).$$

The value β is higher than the interval of the temperature under study, and it testifies the enthalpy type of control of the alkaline hydrolysis reaction of methyl esters of 4,5-dimethoxy-N-phenylanthranilic acids.

Based on the PASS programme the computer prognosis of possible types of biological activity of 9 methyl esters of 4,5-dimethoxy-N-phenylanthranilic acids synthesized for the first time has been conducted. It has been found experimentally that the substances synthesized reveal the anti-inflammatory, analgetic, diuretic, bacteriostatic and fungistatic activity. According to the classification of Sidorov K.K. the compounds synthesized when introduced intragastrically belong to low toxic reagents (DL_{50}=1500-2000 mg/kg). A number of regularities of the "structure–activity–toxicity" relationship have been determined.

Table 5

Determination of isokinetic temperature β. The correlation parameters of equation $\lg K_{T_2} = const + x \lg K_{T_1}$ of the alkaline hydrolysis reaction of methyl esters of 4,5-dimethoxy-N-phenylanthranilic acids

Temperature, K		X	r	s	β, K
T_1	T_2				
318	328	0.9359	0.994	$6.87 \cdot 10^{-2}$	607
318	338	0.8759	0.996	$5.16 \cdot 10^{-2}$	608
318	348	0.8318	0.997	$4.37 \cdot 10^{-2}$	575
318	358	0.7926	0.996	$4.72 \cdot 10^{-2}$	622
328	338	0.9249	0.991	$7.77 \cdot 10^{-2}$	575
328	348	0.8798	0.923	$6.30 \cdot 10^{-2}$	541
328	358	0.8201	0.997	$3.78 \cdot 10^{-2}$	628
338	348	0.9206	0.995	$5.24 \cdot 10^{-2}$	613
338	358	0.8614	0.996	$4.08 \cdot 10^{-2}$	566
348	358	0.9503	0.970	$4.40 \cdot 10^{-2}$	610

Experimental Part

The synthesis of methyl esters of 4,5-dimethoxy-N-phenylanthranilic acid (1-9) was carried out by Fisher esterification in the medium of absolute methanol in the presence of concentrated sulfuric acid [8, 10]. The compounds (1-9) obtained were three times recrystallized from methanol and dried at 105°C up to the constant weight. The structure of the compounds synthesized was confirmed by elemental analysis, IR- and NMP-spectroscopy. The purity was controlled by the method of thin-layer chromatography in the methanol – hexane mixture (1:3).

Kinetic measurements were conducted by the screening methods [7]. The sodium hydroxide concentration in the solution was determined by potentiometric titration on an EV-74 ionomer using the standard aqueous solution of HCl. The kinetics of the reaction was studied at 55, 75 and 85°C. Experiments were repeated three times, including 6-8 measurements of each (the depth of reproduction being at least 80%). The accuracy of the results obtained was assessed by means of the methods of mathematical statistics for small sets (at 0.95% confidence interval) [4].

Conclusions

1. Kinetics of the alkaline hydrolysis reaction of methyl esters of substituted 4,5-dimethoxy-N-phenylanthranilic acids has been studied in the binary solvent of dioxane-water at the temperatures of 55, 75 and 85°C.

2. The influence of the nature and position of substituents in a non-anthranylic fragment of the molecule upon the numerous kinetic (lgk_{318}, lgk_{328}, lgk_{338}, lgk_{348}, lgk_{358}) and activation ($\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta G^{\neq}$, lnA) parameters of the alkaline hydrolysis reaction has been analyzed.

3. Numerous tests have proven isokinetics of the alkaline hydrolysis reaction of methyl esters of 4,5-dimethoxy-N-phenylanthranilic acids with the enthalpy type of control, and its $B_{AC}2$ mechanism has been confirmed with formation of a high symmetrical intermediate.

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