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; 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 substituents in a non-anthranilic fragment of the molecule is described by the Hammett equation. It has been demonstrated that introduction of electron donor 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 $B_{2n}^2$ 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.

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

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Ключові слова: N-фенілантраніловая кислота; метиловий ефір; реакційна здатність; термодинамічні параметри активації; ізопараметричність реакції; ентальпійний контроль

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

реакційна здатність похідних n-фенілантранілових кислот. ххv. 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-фенілантранілове кислото; метиловий ефір; 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 залежність $lgk_T$ від природи і положення заступників у неантраніловому фрагменті молекули описується рівнянням Гаммета. показано, що введення електронодонорних замісників у молекулу ефіру сприяє підвищенню енергії активації і вільної енергії активації. ентропія активації для всіх речовин від’ємна та велика за абсолютним значенням, що вказує на $B_{2n}^2$ механізм реакції з утворенням високосиметричних інтермедіантів. аналіз численних кінетичних і активационних параметрів показав ізокінетичність реакції з ентальпійним типом контролю. експериментально встановлено, що синтезовані речовини виявляють протизапальну, аналгетичну, диуретичну, бактеріостатичну активність.
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-dimethoxy-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 methyl 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-anthrаниlic 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 cause 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_AO2 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.

\[
\begin{align*}
\text{lg} k_{328} &= (-4.801 \pm 0.007) + (0.996 \pm 0.029) \sigma \quad (1) \\
\text{lg} k_{348} &= (-4.317 \pm 0.005) + (0.883 \pm 0.029) \sigma \quad (2) \\
\text{lg} k_{358} &= (-4.062 \pm 0.004) + (0.844 \pm 0.015) \sigma \quad (3)
\end{align*}
\]

\[n=9 \quad r=0.997 \quad S=4.7 \cdot 10^{-2}\]

\[n=9 \quad r=0.998 \quad S=3.7 \cdot 10^{-2}\]

\[n=9 \quad r=0.998 \quad S=2.5 \cdot 10^{-2}\]

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 \(\rho\) of \(\beta\)-dialkylaminemethyl esters of 4-nitro-, 4-nitro-5-chloro- and 4-sulfamoil-N-PAA [7, 11-13]. The positive values of \(\rho\) testify of \(B_AO2\) mechanism of the reaction (Scheme 2).

Table 1

| 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                      |

Scheme 1

where: R = H (1), 2’-CH₃ (2), 4’-CH₃ (3), 3’,4’-(CH₂)₃ (4), 4’-OCH₃ (5), 4’-OC₂H₅ (6), 4’-OC₂H₅ (7), 4’-Cl (8), 4’-Br (9)
The temperature dependence of constants of the reaction rates can be explained by the Arrhenius equation:

$$\ln k = \ln A \frac{E_A}{RT}$$  \hspace{1cm} (4).$$

The values of the activation energy ($E_A$) and the logarithm of the predexponential 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 $\sigma$-constants is statistically unreliable.

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

$$\ln \frac{k}{h} = \frac{\Delta S^\circ}{R} - \frac{1}{RT} \cdot \Delta H^\circ,$$  \hspace{1cm} (5)

where: $h$ is the Planck's constant; $K$ is the Boltzman's constant; $R$ is the universal gas constant; $T$ is the absolute temperature.

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

The activation entropy for all compounds is inseparable, and it additionally proves the reaction $B_{\Delta K, 2}$ mechanism. High absolute values of $\Delta S^\circ$ 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 $\Delta S^\circ$ and decrease of $\Delta H^\circ$. The $\Delta H^\circ$ values are small. This fact testifies coincidence of the reaction series. Correla-

### Table 2

| 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 |

### Table 3

| Compound | $\Delta G^\circ$, kJ · mol$^{-1}$ | $\Delta H^\circ$, kJ · mol$^{-1}$ | $\Delta S^\circ$, kJ · mol$^{-1}$ | $r$ | $s$ | $T \Delta S^\circ$, kJ · mol$^{-1}$ |
|----------|----------------------------------|----------------------------------|----------------------------------|-----|-----|----------------------------------|
| 318K     | 108.6                            | 46.6±0.3                         | -194.9±8.9                       | 0.994 | 0.173 | -62.0                            |
| 328K     | 110.5                            | 46.6±0.3                         | -194.9±8.9                       | 0.994 | 0.173 | -62.0                            |
| 338K     | 112.5                            | 46.6±0.3                         | -194.9±8.9                       | 0.994 | 0.173 | -62.0                            |
| 348K     | 114.4                            | 46.6±0.3                         | -194.9±8.9                       | 0.994 | 0.173 | -62.0                            |
| 358K     | 116.4                            | 46.6±0.3                         | -194.9±8.9                       | 0.994 | 0.173 | -62.0                            |
| 2        | 109.7                            | 49.2±0.3                         | -190.3±8.6                       | 0.995 | 0.168 | -60.5                            |
| 3        | 109.5                            | 47.6±0.4                         | -194.8±11.4                      | 0.990 | 0.222 | -61.9                            |
| 4        | 110.1                            | 50.5±0.3                         | -187.5±7.9                       | 0.996 | 0.486 | -59.6                            |
| 5        | 110.4                            | 50.6±0.3                         | -187.9±7.5                       | 0.996 | 0.462 | -59.8                            |
| 6        | 110.5                            | 51.2±0.3                         | -186.4±8.0                       | 0.996 | 0.157 | -59.3                            |
| 7        | 110.7                            | 52.1±0.3                         | -184.3±8.0                       | 0.994 | 0.192 | -58.6                            |
| 8        | 107.2                            | 44.9±0.3                         | -195.8±8.0                       | 0.995 | 0.157 | -62.3                            |
| 9        | 107.1                            | 45.2±0.3                         | -194.7±9.5                       | 0.993 | 0.185 | -61.9                            |
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 \( \beta \).

The synthesis of methyl esters of 4,5-dimethoxy-N-phenylanthranilic acids (1-9) was carried out by Fisher esterification in the medium of absolute methanol in the presence of concentrated sulfuric acid [8].

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 NMR 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.

### Table 4

| \( x \) | \( y \) | \( a \) | \( b \) | \( r \) | \( s \) | \( \beta, K \) |
|--------|--------|--------|--------|--------|--------|--------|
| \( \Delta H^* \) | \( 1.2 \pm 1.2 \times 10^1 \) | \( -9.1 \pm 0.5 \times 10^1 \) | 0.964 | 190 | 615 |
| \( \Delta H^* \) | \( 1.3 \pm 1.4 \times 10^1 \) | \( -9.1 \pm 0.7 \times 10^1 \) | 0.952 | 230 | 625 |
| \( \Delta H^* \) | \( 1.4 \pm 1.6 \times 10^1 \) | \( -10.1 \pm 0.8 \times 10^1 \) | 0.942 | 425 | 608 |
| \( \Delta H^* \) | \( 1.4 \pm 1.7 \times 10^1 \) | \( -10.1 \pm 0.8 \times 10^1 \) | 0.944 | 249 | 629 |
| \( \Delta H^* \) | \( 1.6 \pm 1.8 \times 10^1 \) | \( -9.2 \pm 0.8 \times 10^1 \) | 0.943 | 252 | 610 |
| \( \Delta S^* \) | \( 383 \pm 28 \times 10^2 \) | 585 \pm 31 | 0.963 | 49 | 585 |
| \( 1/T \) | \( -0.890 \pm 0.08 \) | 618 \pm 26 | 0.997 | 1.27 \times 10^{-2} | 618 |

### Table 5

Determination of isokinetic temperature \( \beta \). 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 | \( x \) | \( r \) | \( s \) | \( \beta, K \) |
|---------------|--------|--------|--------|--------|
| \( T_1 \) | \( T_2 \) | | | |
| 318 | 328 | 0.9359 | 0.994 | 6.87 \times 10^{-2} | 607 |
| 318 | 338 | 0.8759 | 0.996 | 5.16 \times 10^{-2} | 608 |
| 318 | 348 | 0.8318 | 0.997 | 4.37 \times 10^{-2} | 575 |
| 318 | 358 | 0.7926 | 0.996 | 4.72 \times 10^{-2} | 622 |
| 328 | 338 | 0.9249 | 0.991 | 7.77 \times 10^{-2} | 575 |
| 328 | 348 | 0.8798 | 0.923 | 6.30 \times 10^{-2} | 541 |
| 328 | 358 | 0.8201 | 0.997 | 3.78 \times 10^{-2} | 628 |
| 338 | 348 | 0.9206 | 0.995 | 5.24 \times 10^{-2} | 613 |
| 338 | 358 | 0.8614 | 0.996 | 4.08 \times 10^{-2} | 566 |
| 348 | 358 | 0.9503 | 0.970 | 4.40 \times 10^{-2} | 610 |
2. The influence of the nature and position of substituents in a non-anthranylic fragment of the molecule upon the numerous kinetic ($\lg k_{318}$, $\lg k_{328}$, $\lg k_{338}$, $\lg k_{348}$, $\lg k_{358}$) and activation ($\Delta H^\ne$, $\Delta S^\ne$, $\Delta G^\ne$, $\ln A$) 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-phenylantranilic acids with the enthalpy type of control, and its $B_{AC}$ mechanism has been confirmed with formation of a high symmetrical intermediate.

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