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THE REACTIVITY OF SUBSTITUTED 9AMINOACRIDINES

Annotation

The reactivity of substituted 9-aminoacridines has been studied in reversible conditions by the method of potentiometric titration in the binary ethanol-water solvent at 298 K. The influence of the electronic nature and position of substituents in the molecule of 9-aminoacridine on the basicity of these compounds has been analyzed. Within the principle of linearity of free energies the unified correlation equation for all members of homologous series (except 4-OCH_3) describing the relationship of $pK_{BH}+$ with the Hammett σ-constants with convincing statistical characteristics has been determined. This equation is of great importance for the molecular design of active pharmacophores in this homological series.

Keywords: reactivity, design, substituted 9-aminoacridines, synthesis.

Introduction

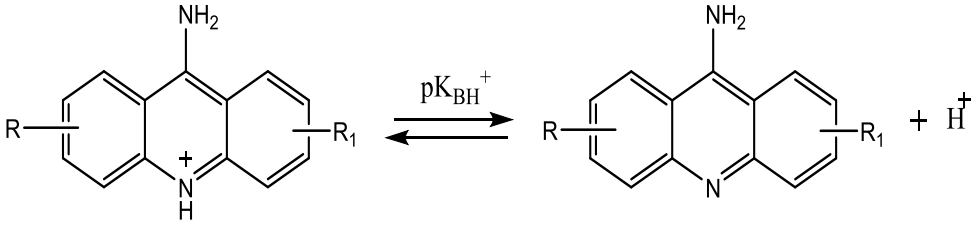
Derivatives of 9-aminoacridine have a wide range of the pharmacological activity [1,2], which depends on their reactivity [3,4]. Therefore, to create drugs with the expected high therapeutic effect the reactivity of this series has been investigated for the first time in reversible conditions by studying the process of ionization of acids conjugated with substituted 9-aminoacridines. At the same time, this study has allowed to quantify the sensitivity of the heterocycle to the effect of substituents with different electronic nature. Therefore, the work is of undoubted scientific and practical interest.

PURPOSE OF THE STUDY

To study the reactivity of 9-aminoacridine derivatives having a wide range of pharmacological activity.

MATERIALS AND METHODS

The acid-base equilibrium has been studied:



where R = H; 6-NO_2; 6-Cl, 7-NO_2

R_1 = H; 2-CH_3; 4-CH_3; 1,3-$(CH_3)_2$; 2,3-$(CH_3)_2$; 2,4-$(CH_3)_2$; 1-OCH_3; 2-OCH_3; 3-OCH_3; 4-OCH_3; 2-Cl

The ionization constants have been determined by the method of potentiometric titration in the binary ethanol-water solvent (50 mole % of ethanol) at 298^0K.

The study of acid-base equilibria was conducted in accordance with the method [5] on an EV-74 ionomer using a glass electrode (ESP-43-074) and a silver-silver chloride electrode (EVL-1M) at the temperature of 25^0C. The titrant was 0.01 M aqueous solution of HCl. The concentration of the solutions to be titrated was 0.001 M. Titration of each substance was performed in triplicates. Assessment of the accuracy of the results obtained was carried out by methods of mathematical microstatistics (the confidence interval was 0.95) [6].

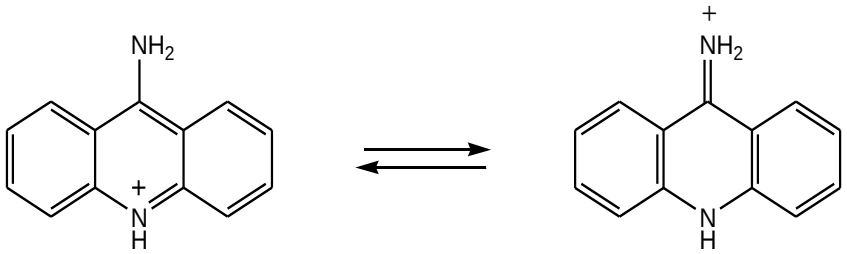
To prepare the binary solvent a bidistillate, which was free of CO_2, and ethanol were used.

The synthesis of 9-aminoacridine derivatives was carried out by the method [7], their physicochemical parameters coincide with the literature data.

RESULTS AND DISCUSSION

Protonization in the study occurs only on the heterocyclic nitrogen [8]. It has been confirmed by our experimental data: mathematical tests of the pH – f(V_{HCl}) experimental curves have not been revealed the second point of inflection.

The results obtained show that the presence of the 9-NH_2 – group in the molecule increases its basicity by five orders (pK_{BH}+ of acridine is 4.12) [9] due to the fact that the cation of 9-aminoacridinium is stabilized by conjugation that is absent in the neutral molecule:



However, appearance of the NH_2 – group in positions 1, 2, 4 of the acridine molecule when the resonance stabilization of the corresponding cations is impossible causes only a slight increase in the basicity ($\Delta pK_{BH}+ \approx 0.2$) [9].

It is interesting to note that the relative change of the basicity of 4-aminobenzo(g)quinoline compared to benzo(g)quinoline is the same ($\Delta pK_{BH}+ = 4.1$) as in our study due to resonance stabilization of 4-amino(g)quinolium [9].

Introduction of electron-donor groups increases the basicity of the molecule of 9-aminoacridine (Table 1) due to the increased electron density on the reaction center. Acceptor substituents have the opposite effect.

Within the principle of linearity of free energies (LFE) the quantitative relationships $pK_{BH}+$ with the Hammett σ-constants were determined by the method of correlation analysis.

For substituted 9-aminoacridines (Table 1, series 1):

$pK_{BH}+ = (9.35\pm0.01) – (0.83\pm0.03)\cdot\sigma$ (1)

n = 4 r = 0.997 s = 0.003

For substituted 6-nitro-9-aminoacridines (Table 1, series 2):

$pK_{BH}+ = (8.98\pm0.01) – (0.79\pm0.03)\cdot\sigma$ (2)

n = 7 r = 0.996 s = 0.008

For substituted 6-chloro-7-nitro-9-aminoacridines (Table 1, series 3):

$pK_{BH}+ = (8.83\pm0.08) – (0.15\pm0.11)\cdot\sigma$ (3)

n = 8 r = 0.286 s = 0.082

Equation (3) is statistically insignificant. The $pK_{BH}+$ for 4-OCH_3-substituent is out of the correlation (Fig.); it is possibly due to the presence of the hydrogen bond between the oxygen atom of the methoxy group and the reaction center of the molecule. Similar data are available in the literature [10]. Elimination of $pK_{BH}+$ of this compound from the correlation allows obtaining the equation with statistically significant characteristics:

(Table 1, series 3, without 4-OCH_3-substituent)

$pK_{BH}+ = (8.98\pm0.01) – (0.79\pm0.03)\cdot\sigma$ (4)

n = 7 r = 0.986 s = 0.014

The reaction constant ρ within the error of the experiment (equations 1,2,4) is the same. The correlation for all substituted 9-aminoacridines studied (excluding 4-OCH_3-substituent) was performed, and the unified correlation equation with convincing statistical characteristics was obtained:

$pK_{BH}+ = (9.35\pm0.02) – (0.80\pm0.05)\cdot\sigma$ (5)

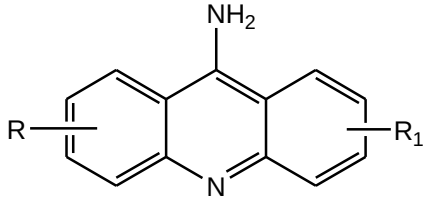
n = 18 r = 0.994 s = 0.027

It follows from equation (5) that the sensitivity of the reaction center of the molecule of 9-aminoacridine to the effect of substituents is insignificant. It is interesting to note that within the error of the experiment the value of the reaction constant ρ for these compounds coincides with ρ for substituted 9-chloroacridine [10].

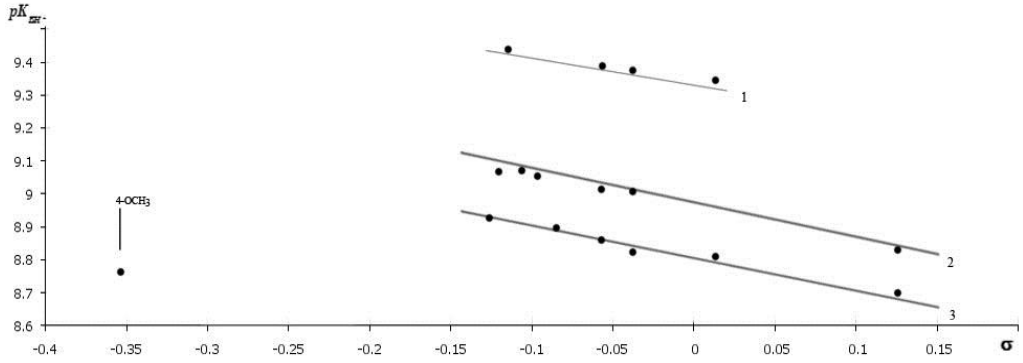
The data obtained allow to analyze the effects of condensation on the sensitivity of the reaction center (heterocyclic nitrogen). The high value ρ = 5.92 for substituted 4-aminopyridine shows a strong interaction between the substituent and the positive nitrogen atom [11]; for substituted 9-aminoquinoline the value ρ decreases to 5.40 [11] despite the fact that the change of substituents occurs in the pyridinium fragment of the molecule. Further annelation to 9-aminoacridine leads to a great decrease in the sensitivity of the reaction center (ρ = 0.80) due to the considerable distance of

This equation (5) allows predict the acid-base properties of various substituted 9-aminoacridines; it is of great importance for the molecular design of active pharmacophores in this homological series.

Table 1 - The ionization constants (pK_{BH}^+) of acids conjugated with substituted 9-aminoacridines



Series No.	R	R_1	pK_{BH}^+
1	H	H	9,35±0,03
	H	2-CH_3	9,40±0,02
	H	4-CH_3	9,38±0,04
	H	2-OCH_3	9,44±0,03
2	6-NO_2	2-Cl	8,84±0,04
	6-NO_2	2-CH_3	9,03±0,04
	6-NO_2	4-CH_3	9,01±0,02
	6-NO_2	1-OCH_3	9,08±0,03
	6-NO_2	3-OCH_3	9,07±0,03
	6-NO_2	1,3-$(CH_3)_2$	9,06±0,02
	6-NO_2	2,3-$(CH_3)_2$	9,06±0,04
3	6-Cl,7-NO_2	H	8,82±0,03
	6-Cl,7-NO_2	2-CH_3	8,87±0,04
	6-Cl,7-NO_2	4-CH_3	8,83±0,04
	6-Cl,7-NO_2	2-OCH_3	8,91±0,04
	6-Cl,7-NO_2	4-OCH_3	8,78±0,02
	6-Cl,7-NO_2	2,3-$(CH_3)_2$	8,91±0,03
	6-Cl,7-NO_2	2,4-$(CH_3)_2$	8,94±0,05
	6-Cl,7-NO_2	2-Cl	8,70±0,02



Picture 1 - The dependence of $pK_{BH}+$ for substituted 9-aminoacridines (1 – series 1, 2 – series 2, 3 – series 3).

CONCLUSIONS

1. The reactivity of substituted 9-aminoacridines has been studied in reversible conditions.

2. The ionization constants of the corresponding conjugate acids ($pK_{BH}+$) have been determined for 19 compounds by the method of potentiometric titration in the binary ethanol-water solvent at 298 K.

3. The influence of the electronic nature and position of substituents in the molecule of 9-aminoacridine on the basicity of these compounds has been analyzed. The electron donating substituents have been shown to increase their basicity, and the acceptor ones weaken it.

4. Within the principle of linearity of free energies the unified correlation equation for all members of homologous series (except 4-OCH_3) describing the relationship of $pK_{BH}+$ with the Hammett σ-constants with convincing statistical characteristics has been determined.

5. This equation allows to predict the acid-base properties of various substituted 9-aminoacridines; it is of great importance for the molecular design of active pharmacophores in this homological series.

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РЕЗЮМЕ

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РЕАКЦИОННАЯ СПОСОБНОСТЬ ЗАМЕЩЕННЫХ 9-АМИНОАКРИДИНОВ

Исследована реакционная способность замещенных 9-аминоакридина в обратимых условиях методом потенциометрического титрования в бинарном растворителе этанол-вода, при 298 К. Проанализировано влияние электронной природы и положения заместителей в молекуле 9-аминоакридина на основность этих соединений. В рамках принципа линейности свободных энергий получено единое корреляционное уравнение для всех членов гомологического ряда (за исключением 4-OCH_3), описывающее связь $pK_{BH}+$ с σ-константами Гаммета, с убедительными статистическими характеристиками. Это уравнение имеет большое значение для молекулярного дизайна активных фармакофоров в этом гомологическом ряду.

ТҮЙІН

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9-АМИНОАКРИДИННІҢ ОРЫН БАСУ РЕАКЦИЯСЫНА ТҮСУ ҚАБІЛЕТТІЛІГІ

9-аминоакридиннің 298 К этанол-су бинарлы еріткіштерінде потенциометриялық титрлеу әдісімен орын басу реакциясына түсу қабілеттілігі зерттелді. 9-аминоакридиннің молекуласындағы негізгі қосылыстарғы электронды табиғи және орын басу орнынының әсер ету талдамасы жасалынды. $pK_{BH}+$ σ-Гаммета константалырмен қарым-қатынасын бейнелейтін айқын статистикалық сипаттамаларымен Еркін сызықтық энергияның принципі аясында гомологиялық қатар мүшелерінің барлығына (4-OCH_3 қоспағанда) біріңғай корреляциялық теңдеу алынды. Осы гомологиялық қатар белсенді фармакофор молекуласынның дизайны үшін маңызы зор болып табылады.