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Acid–Base Properties of Substituted 9-Chloroacridines

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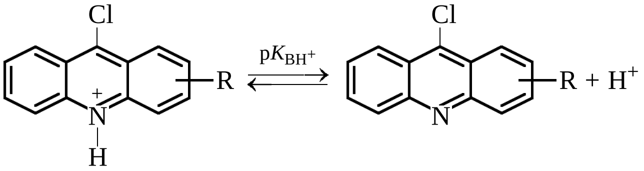
Abstract—Ionization constants (pK_{BH^+}) of eleven substituted 9-chloroacridines in water–ethanol mixtures were measured by potentiometric titration at 25°C. The correlation between pK_{BH^+} and the Hammett σ constants was established, and the reaction parameter ρ was evaluated. The sensitivity of the reaction center to the effect of substituents is low. Annelation of the heterocycle decreases the sensitivity of the reaction center to the structural changes in the molecule.

Substituted 9-chloroacridines are used as starting substances for preparing a variety of biologically active compounds such as 9-amino-, 9-hydrazinoacridines, 9-thioacridones, etc. [1, 2], markers in gene engineering [3], and luminescent indicators in analytical chemistry [4].

Although the UV, IR, and ^{1}H NMR spectra of 9-chloroacridines are published [5–7], the effect of substituents in the 9-chloroacridine molecule on its reactivity was not studied yet.

The reactivity of this group of compounds was evaluated by the studying the acid–base equilibria:



R = H (**I**), 2-CH$_3$ (**II**), 4-CH$_3$ (**III**), 1,3-(CH$_3$)$_2$ (**IV**), 2,3-(CH$_3$)$_2$ (**V**), 2-OCH$_3$ (**VI**), 4-OCH$_3$ (**VII**), 2-Cl (**VIII**), 4-Cl (**IX**), 2-NO$_2$ (**X**), and 3-NO$_2$ (**XI**).

The ionization constants (pK_{BH^+}) of the acids conjugated with the substituted 9-chloroacridines were determined by potentiometric titration in water–ethanol mixture (50 mol % ethanol) at 25°C.

Data in the table show that the basicity of substituted acridines depends on the nature and position of substituents in the molecule. Introduction of chlorine in position 9 of the acridine molecule causes a considerable decrease in the basicity (ΔpK_{BH^+} = 0.82) [8] due to the decrease of the electron density on the reaction center. Introduction of electron-withdrawing substituents into the 9-chloroacridine molecule causes the same effect, though in this case it is not so expressed. On the contrary, electron-donating substituents increase the basicity.

The effect of substituents on the acid–base properties of substituted 9-chloroacridines was quantitatively evaluated by correlation analysis using the Hammett equation. It was shown that the correlation between pK_{BH^+} and σ constants is not statistically reliable (r < 0.5), because pK_{BH^+} for 4-methoxy-substituted compound **VII** lies below the straight line pK_{BH^+} = $a + b/\sigma$. The same effect was observed when studying the acid–base properties of substituted 9-thioacridones [9, 10] and 9-hydrazinoacridines [11]. Probably the value of σ for 4-OCH$_3$ does not adequately describe the experimental facts and needs further refinement.

Exclusion of 4-methoxy-substituted derivative **VII** from the correlation considerably improves the statistic characteristic and makes this correlation statistically reliable.

Properties of substituted 9-chloroacridines

Comp. no.	Yield, %	mp, °C	R_f^a	pK_{BH^+}
I	94	120–121	0.79	3.97 ± 0.03
II	95	152–154	0.82	4.03 ± 0.05
III	86	167–169	0.80	4.01 ± 0.02
IV	92	154–156	0.76	4.07 ± 0.04
V	90	153–155	0.74	4.09 ± 0.02
VI	97	154–155	0.78	4.08 ± 0.04
VII	95	127–128	0.77	4.17 ± 0.02
VIII	95	146–147	0.81	3.85 ± 0.04
X	96	100–101	0.83	3.83 ± 0.03
X	93	124–126	0.81	3.57 ± 0.04
XI	91	121–123	0.76	3.60 ± 0.03

[a] R_f values in the system chloroform–acetone, 4 : 1.

$$pK_{BH^+} = (3.98 \pm 0.01) - (0.85 \pm 004)\sigma;$$
$$n\ 11,\ r\ 0.998,\ s\ 0.01.$$

Using this equation, we have calculated the new value of σ for 4-OCH_3 group, equal to –0.22. Using this value of σ instead of the previously accepted $\sigma = -0.38$ [12], we obtained statistically reliable correlations $pK_{BH^+} = f(\sigma)$ for substituted 9-thioacridones and 9-hydrazinoacridines.

The small value of the reaction constant ρ shows that the sensitivity of heterocyclic nitrogen to the effect of substituents in the molecule of 9-chloroacridine is low. Note that the value of ρ for substituted 9-chloroacridines practically coincides with that for protonation of substituted 9-hydrazinoacridines [10].

Comparison of the reaction constants of protonation of pyridine ($\rho = 5.90$ [13]), quinoline ($\rho = 5.42$ for the substituents in the pyridinium ring [13]), and acridine ($\rho = 0.88$) shows that introduction of the benzo substituent into the pyridinium ring slightly decreases the sensitivity of the reaction center. Appearance of one more benzo substituent in the ring decreases ρ by a factor of about 5 owing to the considerable decrease in the polarizability of the molecule.

EXPERIMENTAL

Study of the acid–base equilibria was carried out by the procedure similar to that described in [14]. Titration was performed with 0.01 M HCl. The concentration of the titrated solution was 0.005 M in the half-neutralization point. Potentiometric titration was performed with an EV-74 pH meter using an ESP-43-074 glass electrode and an EVL-1M silver chloride electrode at 25°C. Each compound was titrated thrice. The accuracy of the obtained results was evaluated by the methods of mathematical statistics (confidence probability 0.95) [15].

The mixed solvent was prepared from double-distilled CO_2-free water and ethanol.

Substituted 9-chloroacridines **I**–**XI** were prepared according to [16], and their physicochemical parameters agreed with the published data [16].

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