BASICITIES AND TAUTOMERISM OF 4,4,6-TRIMETHYL-2-ARYLAMINO-4H-1,3-THIAZINES

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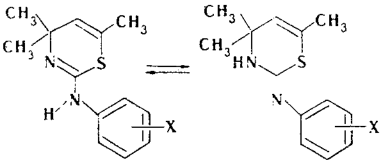
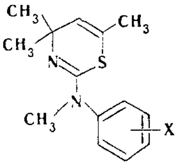
The relative basicities of 4,4,6-trimethyl-2-arylamino-4H-1,3-thiazines, which are capable of amine–imine tautomerism, and of model compounds with fixed amino and imino structures were determined by potentiometric titration in methanol. Good correlation was observed between the pK_a values and the Hammett σ constants in the investigated reaction series. The anomalous pK_a values of the model amines and imines are explained by the different character of the electronic interactions in them, which is due to the change in the three-dimensional orientation of the aromatic ring and the amidine fragment.

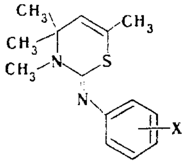
We have previously shown [1] by means of spectral methods that 4,4,6-trimethyl-2-arylamino-4H-1,3-thiazines (I) in the crystalline state exist in amino form IA and that this form is the predominant one in solvents of varying polarity.



IA IB



II



III

In the present research we attempted to determine the constants of the tautomeric equilibrium in the IA $\rightleftarrows$ IB system using a well-known method (for example, see [2]) based on a comparison of the ionization constants of model compounds II and III, which have fixed amino and imino structures: $K_T = K_a^{III}/K_a^{II}$.

Another method for the determination of the tautomeric equilibrium constants is based on the use of correlation analysis as applied to tautomeric systems [3-6]. In conformity with the "method of intersecting lines" [3, 4], one might have expected either a curvilinear dependence in coordinates of $pH_{a\ \mathrm{eff}}$ and σ when comparable amounts of both tautomeric forms are present in the system or a rectilinear dependence in the same coordinates if one of the tautomers predominates in the system.

Both methods can be used if the prototropic amine–imine tautomerism is realized through a common ambident cation and under the condition that the protonation centers of the model compounds and the corresponding tautomeric forms coincide [2]. In this case, it is assumed that the introduction of a methyl group in place of a hydrogen atom changes the pK_a value only slightly and in one direction.

The UV spectra of solutions of model compounds IIe and IIIe in 0.1 N hydrochloric acid are completely analogous (and they do not have absorption maxima at 220-340 nm), and this constitutes evidence for a structure of the same type for the cation formed during protonation. This is possible only if the aminothiazine is protonated at the ring nitrogen atom and the iminothiazine is protonated at the exocyclic nitrogen atom.

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TABLE 1. Relative Basicities of 2-Arylamino-4H-1,3-thiazines (I) and Model Compounds II and III

Compound	X	pK_a		
		I	II	III
a	p-OCH_3	5,84	6,26	5,15
b	p-OC_2H_5	5,89	6,30	5,24
c	p-CH_3	5,50	6,15	—
d	m-CH_3	5,31	6,08	4,60
e	H	5,10	5,88	4,42
f	p-Br	4,56	5,46	3,65
g	m-Cl	4,11	5,26	3,36
h	—	6,97	6,44	7,40
i	—	7,31	7,12	7,84

TABLE 2. Parameters for Correlation of the pK_a Values with the Hammett σ Constants (methanol, 25°C)

Reaction series	ρ	pK_a^0	r	s	s_ρ
I	−2,75	5,14	0,997	0,06	0,11
II	−1,66	5,88	0,993	0,05	0,09
III	−2,98	4,41	0,995	0,08	0,15

The relative pK_a values of Ia-g, IIa-g, and IIIa-g determined by potentiometric titration in methanol are presented in Table 1. As seen from Fig. 1 and Table 2, the pK_a values in all three reaction series correlate satisfactorily with the Hammett σ constants. Within each reaction series one observes the usual (for bases) regularity in the change in the ionization constants of the compounds as a function of the substituent in the aromatic ring, as attested to by the negative reaction constants. The greater absolute value of the ρ^{III} reaction constant as compared with ρ^{II} is explained by the closeness of the substituent in the aromatic ring to the reaction center.

The rectilinear dependence of the $pK_{a\ eff}$ values on the Hammett σ constants in the series of aminothiazines Ia-g constitutes evidence for a pronounced shift of the IA $\rightleftarrows$ IB tautomeric equilibrium to favor one of the forms. Taking into account the spectral data [1] regarding the position of the tautomeric equilibrium of I, it can be asserted that this form is amino form IA, whereas the $pK_{a\ eff}$ values of Ia-g are close to the pK_a values of the corresponding true amino forms Ia.

On the other hand, it is known that a tautomeric equilibrium is always shifted to favor the form that has the lower ionization constant [3]. Inasmuch as amino form IA predominates in the IA $\rightleftarrows$ IB equilibrium, it might have been expected that the basicities of amines II would be lower than the basicities of imines III and the reaction constants ρ_{eff} and ρ^{II} would be close to one another.

An analysis of the data on the basicities of model compounds IIa-g and IIIa-g and of the correlation parameters of reaction series I-III reveals the following principles: the basicities of imines IIIa-g turn out to be lower than the basicities of the corresponding amines IIa-g; the absolute value of the ρ^{II} reaction constant is substantially depressed as compared with the ρ_{eff} value of the series of tautomeric I.

These results contradict the conclusion drawn on the basis of spectral methods [1] that the equilibrium is shifted to favor amino form IA. In fact, using only data on the basicities of the models, one may arrive at the erroneous conclusion that imino form IB predominates in the tautomeric equilibrium.

The anomalous ratios in the basicities of model compounds IIa-g and IIIa-g are, in our opinion, a consequence of a change in the character of the electronic interactions, which is associated with steric hindrance arising in the molecules of II and III when a methyl group is attached the endo- or exocyclic nitrogen atom. An examination of Stuart models of I and II shows that replacement of the hydrogen atom attached to the exocyclic nitrogen atom of IA

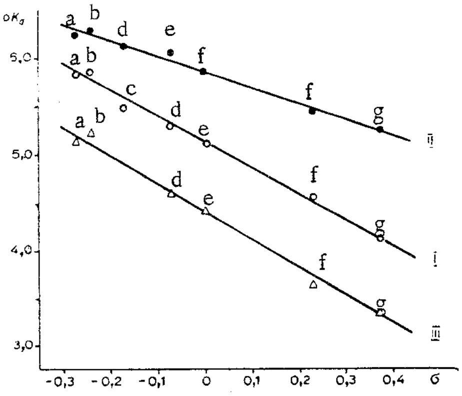

Fig. 1. Dependence of the pK_a values of Ia-g, IIa-g, and IIIa-g on the Hammett σ constants.

by a methyl group, because of the steric effect of the latter, leads to restriction of free rotation of the aromatic ring about the C—N bond, and this is accompanied by partial removal of the p electrons of the exocyclic nitrogen atom from conjugation with the π electrons of the aromatic ring. A consequence of this is a large contribution of the electron pair of the exocyclic nitrogen atom to the electron density on the reaction center, and this leads to an increase in the basicities of amines II. The increase in the basicities of N,N-dialkylanilines as compared with N-alkylanilines, which is greater than corresponds to the +I effect of alkyl groups (for example, see [7]), is explained by similar reasons.

On the other hand, the change in the character of the conjugation of the conducting systems in amines II is accompanied by a decrease in the transmission of the effects of substituents in the aromatic ring to the reaction center (the decrease in the ρ constant in series II as compared with ρ in series I is greater than unity).

The anomalies in the UV spectra of Ia-g and IIa-g, which consist in a decrease in the intensities of the maxima of the absorption bands of amines IIa-g as compared with Ia-g, that we have previously noted [1] are also satisfactorily explained by steric hindrance associated with the introduction of a methyl group.

Competition between the π—π interaction of the electrons of the exocyclic C=N bond and the electrons of the aromatic ring and the p—π interaction of the unshared electrons of the exocyclic nitrogen atom with the electrons of the aromatic ring exists in imino form IB and model imines III, as has been shown, for example, for benzalanilines [8, 9]. The introduction of a CH_3 group in place of a hydrogen atom on passing from IB to III leads to rotation of the aromatic ring about the C—N bond, and this brings about a decrease in the fraction of $\pi_{(C=N)}-\pi_{(Ar)}$ conjugation. The large contribution of the p—π interaction of the nonbonding electrons of nitrogen and the π system of the aromatic ring proves to be an energic compensation for this effect. As a consequence of this, the electron density of the exocyclic nitrogen atom, which is the protonation center, is reduced, and this leads to a decrease in the basicities of model imines III as compared with the basicities of the corresponding imino forms IB.

It is natural to assume that the value of reaction constant ρ in series III is also distorted as compared with ρ in the series of true imino forms IB.

The validity of our ideas regarding the substantial contribution of the character of the electronic interactions to the ionization constants of I-III is confirmed by data obtained by comparison of the basicities of 4,4,6-trimethyl-2-benzylamino-4H-1,3-thiazines (Ih) and its models (IIh and IIIh), and also of 4,4,6-trimethyl-2-methylamino-4H-1,3-thiazine (Ii) and its models (IIi and IIIi). Interaction of the p electrons of the exocyclic nitrogen atom with the substituent electrons is excluded in these compounds; as expected, the pK_a values of model amines IIh, i proved to be lower than the pK_a values of the corresponding imines (IIIh, i) (Table 1), and this is in complete agreement with the spectral data regarding the predominance of amino forms IA in the tautomeric system.

Thus an examination of the character of the electron interactions in molecules of the investigated compounds in conjuction with an analysis of the correlation parameters and data on the basicities makes it possible to conclude that the well-known methods for the determination of K_T, which are based on the use of the ionization constants of model compounds and ρ—σ analysis, cannot be used for the investigated class of compounds.

EXPERIMENTAL METHOD

Compounds I-III were previously synthesized [10, 11]; their purities were confirmed by the results of thin-layer chromatography (TLC) and also by the results of potentiometric titration, the error in which did not exceed 2%. The ionization constants were determined by potentiometric titration with 0.1 N perchloric acid of $(5-7)\cdot 10^{-3}$ M solutions of the compounds in anhydrous methanol at 20° by means of an LPU-01 pH-meter, an ESL-41G-04 glass electrode, and a small calomel electrode filled with a saturated solution of potassium chloride in methanol. The electrodes were calibrated with respect to 0.05 M potassium biphthalate (pH 4.00), a phosphate buffer (pH 6.88), and 0.01 M sodium tetraborate (pH 9.22). The potentiometer was tuned by the method in [12]. The error in the determination of the pK_a values did not exceed 0.04 pK_a unit. The correlation parameters were obtained by statistical treatment of the results by the method of least squares with a Mir computer.

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