3. M. E. Renne Ramp, I. V. Paukstelis, and R. J. Cooks, Tetrahedron, 27, 4407 (1971).
4. H. Ogura, S. Sugimoto, and T. Itoh, Org. Mass Spectrom., 3, 1341 (1970).
5. D. Simov and K. Davidkov, Khim. Geterotsikl. Soedin., No. 2, 173 (1976).
6. D. Simov, B. Galobov, and K. Davidkov, Zh. Prikl. Spektrosk., 15, 339 (1971).

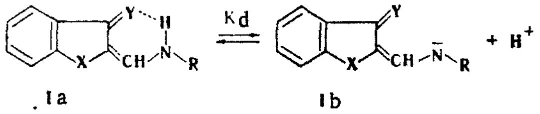
ACIDIC PROPERTIES AND STRUCTURES OF HETEROCYCLIC AMINOVINYL KETONES AND AMINOVINYL THIONES*

L. L. Popova, Zh. V. Bren',
V. A. Bren', and V. I. Minkin

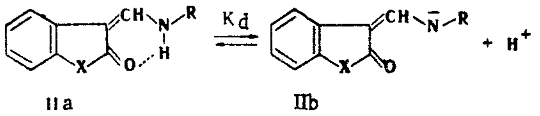
UDC 547.728'735:541.127

The ionization constants of 33 keto and thiono amines of the benzo[b]furan, benzo[b]thiophene, indan, and 1-methylindole series were determined by potentiometric titration in acetonitrile. The effect of various structural factors on the acidities of these compounds was ascertained. The effect of N-aryl substituents on the free energies of the deprotonation reactions was evaluated quantitatively by means of correlation analysis.

Keto and thiono amine structures are characteristic for heterocyclic azomethines Ia and IIa [2-7]. The proton of the NH group participates in the formation of an intramolecular hydrogen bond (IHB), the strength of which depends on the peculiarities of the structures of imines Ia and IIa.



(1)



(2)

I a,b X=O, S, CO, CH_2, SO_2, Y=O, S; R=Ar, Alk; IIa,b X=S, NCH_3; R=Ar, Alk

We have previously investigated the relationship between the basicities of compounds of the Ia and IIa type and the nature of the R grouping attached to the imine nitrogen atom. In the present research we set out to determine the acidities of aminomethylene ketones and aminomethylene thiones Ia and IIa and to investigate the effect of substituents R, heteroatoms X and Y, and other structural factors of Ia and IIa on their ability to undergo acidic ionization via Eqs. (1) and (2).

With this end in mind we measured the acid dissociation constants (K_d) of Ia and IIa and, by means of correlation analysis, evaluated the structure-acidity relationships in these reaction series. For the determination of the K_d values we selected nonaqueous potentiometric titration in acetonitrile [8, 9], which we used in [1] for the study of the basic properties of compounds of the Ia type.

According to the results of previous studies [9-11], equilibria (1) and (2) may be complicated by the formation of homoconjugates of the Ia·Ib and IIa·IIb type, which exist in equilibrium with the unassociated forms. The titration curves of the majority of the Ia and IIa compounds in the buffer region differ little from the theoretically calculated curves,

---

*Communication 19 from the series "Basicities and structures of azomethines and their structural analogs"; see [1] for Communication 18.

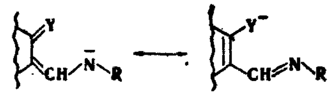
Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don 344006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 309-312, March, 1981. Original article submitted July 9, 1980.

0009-3122/81/1703-0217$07.50

TABLE 1. Thermodynamic Constants for the Ionization of Ia and IIa in Acetonitrile at 25°C

Compound	X	Y	R	pK_d	Compound	X	Y	R	pK_d
I	O	O	C_6H_5	23,78	I	CO	O	p-ClC_6H_4	22,38
I	O	O	p-$OCH_3C_6H_4$	24,21	I	CO	O	p-BrC_6H_4	22,33
I	O	O	p-$CH_3C_6H_4$	24,00	I	CO	O	p-$COOC_2H_5C_6H_4$	21,89
I	O	O	m-$CH_3C_6H_4$	23,76	I	CO	O	$CH(CH_3)_2$	25,78
I	O	O	p-ClC_6H_4	23,04	I	O	S	C_6H_5	21,39
I	O	O	m-$NO_2C_6H_4$	22,14	I	O	S	p-$OCH_3C_6H_4$	22,00
I	S	O	C_6H_5	23,49	I	O	S	p-$CH_3C_6H_4$	21,82
I	S	O	p-$OCH_3C_6H_4$	24,34	I	O	S	p-ClC_6H_4	20,72
I	S	O	p-$CH_3C_6H_4$	24,04	I	O	S	p-$COOC_2H_5C_6H_4$	20,46
I	S	O	m-$CH_3C_6H_4$	23,73	I	O	S	2,4,6-$(CH_3)_3C_6H_2$	20,70
I	S	O	p-ClC_6H_4	22,78	I	O	S	$CH_2C_6H_5$	23,71
I	S	O	m-ClC_6H_4	22,48	I	CH_2	O	C_6H_5	25,29
I	S	O	p-BrC_6H_4	23,02	I	SO_2	O	C_6H_5	20,60
I	S	O	p-$COOC_2H_5C_6H_4$	22,14	II	S	O	C_6H_5	23,10
I	S	O	CH_3	26,22	II	NCH_3	O	C_6H_5	24,13
I	CO	O	C_6H_5	23,21	II	NCH_3	O	$CH_2C_6H_5$	26,46
I	CO	O	p-$OCH_3C_6H_4$	23,38					

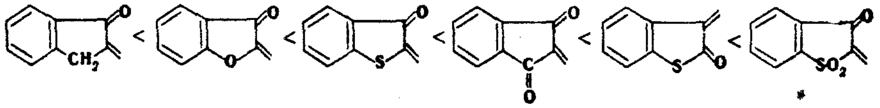
and this indicates the insignificant role played by homoconjugation processes. This result can be explained both by the relatively high stability of the anions by virtue of considerable delocalization of the negative charge (B ↔ C) and by the extremely strong intramolecular hydrogen bond in Ia and IIa, which hinders association.



B C

The pK_d values of Ia and IIa in acetonitrile at 25°C are presented in Table 1. All of the investigated aminomethylene ketone and aminomethylene thione derivatives are weak NH acids. The lowest capacity for dissociation via schemes (1) and (2) is noted for alkylaminomethylene compounds Ia and IIa (R = Alk) (Table 1). With respect to its acidity, II (X = NCH_3, R = $CH_2C_6H_5$), for example, is comparable to phenol, the pK_d of which in acetonitrile is 26.9 [8]. When the alkyl group attached to the nitrogen atom is replaced by an aryl group, the acidity of the NH group increases markedly, and the pK_d constants for acid dissociation increase by 2-2.5 orders of magnitude (Table 1). Monotypically constructed I (X = O) with an exocyclic Y ketone atom are less acidic than their thione analogs I (X = O, Y = S), as a consequence of the stronger intramolecular —NH...S= bond as compared with —NH...O= [4].

In comparing the pK_d values of the compounds that have a common structural fragment — a phenylaminomethylene residue (R = C_6H_5) — and a variable heterocyclic fragment one may note that the character of the latter has a pronounced effect on the acidity of the molecules. The acidity increases in the order presented below (the variable fragment and the corresponding values of the phenylaminomethylene derivative and the chemical shift of the signals of the NH protons in parts per million are given):



pK_d=25,29	23,78	23,49	23,21	23,10	20,60
δ_{NH}=9,43	10,15	10,30	11,12	11,20	11,40

In addition, in summarizing the data on the chemical shifts of the NH protons in the PMR spectra [2-7] one can see that the strength of the intramolecular hydrogen bond increases in this series in the same order. Consequently, the strength of the intramolecular hydrogen bond and the acidity of the investigated Ia and IIa molecules change in the same direction. Compounds Ia (X = O, Y = O; X = S, Y = O; X = CO, Y = O; X = O, Y = S) in Table 1 constitute individual reaction series, the variable fragments in which are aryl ring substituents. Electron-acceptor substituents increase the acidity of Ia and IIa, whereas electron-donor R groups have the opposite effect. The acidity of compound Ia (X = O, Y = S, R = mesityl) with three donor methyl groups in the ring is similar to that of Ia (X = O, Y = S, R = p-ClC_6H_4)

TABLE 2. Correlation Parameters of Eq. (3)

Reaction series	Type of σ	ρ	R	S	δ_{pK}	δ_{ρ^0}	pK^0_{calc}
I, X=O, Y=O, R=Ar	σ	2,155	0,994	0,18	0,03	0,103	23,64
	σ^0	2,287	0,993	0,20	0,04	0,122	23,71
	σ^-	2,176	0,994	0,18	0,03	0,104	23,66
I, X=S, Y=O, R=Ar	σ	2,949	0,995	0,21	0,03	0,115	23,54
	σ^0	3,107	0,986	0,36	0,05	0,205	23,63
	σ^-	2,444	0,979	0,42	0,06	0,193	23,57
I, X=CO, Y=O, R=Ar	σ	2,239	0,985	0,33	0,08	0,304	22,92
	σ^0	2,536	0,991	0,17	0,05	0,175	23,07
	σ^-	1,730	0,953	0,38	0,10	0,276	22,95
I, X=O, Y=S, R=Ar	σ	2,274	0,990	0,18	0,04	0,158	21,39
	σ^0	2,435	0,987	0,22	0,05	0,197	21,48
	σ^-	1,717	0,951	0,41	0,10	0,278	21,45

TABLE 3. Correlation Parameters of Yukawa—Tsuno Eq. (4)

Reaction series	ρ^0	$r_{Y\text{-}T}$	R	S	δ_{pK}	δ_{ρ^0}	pK^0_{calc}
I, X=O, Y=O, R=Ar	2,226	0,611	0,995	0,12	0,04	0,118	23,68
I, X=S, Y=O, R=Ar	2,891	0,330	0,990	0,21	0,05	0,236	23,62
I, X=CO, Y=O, R=Ar	2,639	0,106	0,991	0,12	0,06	0,288	23,08
I, X=O, Y=S, R=Ar	2,604	0,185	0,989	0,14	0,06	0,322	21,49

with an electron-acceptor substituent; this can be explained by the steric hindrance created by the o-methyl substituents to the addition of a proton to anion B.

The parameters of correlations of the pK_d constants by means of one-parameter equations of the Hammett equation type (3)

$$\log \frac{K_d}{K_d^0} = \rho\sigma(\sigma^0, \sigma^-). \tag{3}$$

are presented in Table 2. Diverse sets of σ constants [12] were used for the correlations. The best correlation coefficients R (Table 2) were observed in all cases when the constants of substituents that are partially or completely free of the effects of direct polar conjugation — Hammett σ or inductive σ^0 constants — were used.

For the quantitative evaluation of the contribution of the effects of conjugation we made a correlation with respect to an equation of the Yukawa—Tsuno type (4)

$$\log K = \log K^0 + \rho^0(\sigma^0 + r\Delta\sigma_C^-), \tag{4}$$

where $\Delta\sigma_C^- = \sigma^- - \sigma^0$ characterizes the fraction of direct polar conjugation (—C effect) of the substituents with the reaction center.

The results of the correlations are presented in Table 3. The r values, which characterize the degree of conjugation of the substituents with the reaction center, are small in all the I series, and this constitutes evidence for the small contribution of the —C effect of electron-deficient aryl substituents to the change in the free energy of reaction (1). The reason for the small effect of direct polar conjugation of electron-acceptor substituents with the reaction center in the anions is probably associated with the fact that the contribution of resonance structure IC with a negative charge on the Y atom is the most significant one. In fact, the spectral characteristics of metal salts of aminomethylene ketones and aminomethylene thiones of the Ia and IIa type in polar solvents indicate that the electron distribution in the anions corresponds closely to structures of the IC and IIC type [13, 14].

EXPERIMENTAL

The synthesis of I and II was described in [2-7].

Ionization Constants. The K_d values of acids I and II were determined at 25 ± 0.1°C by potentiometric titration in anhydrous acetonitrile containing 0.002 mole/liter of $(C_2H_5)_4NClO_4$ as the buffer. Following the recommendations in [15, 16], the K_d values were determined under experimental conditions that maximally guarantee obtaining real and reproducible results. The titrant was a 0.1 N benzene–methanol solution (5:1) of $(C_2H_5)_4NOH$ prepared by ion exchange [17]. The measurements were made with a pH-340 potentiometer rebuilt to the millivolt scale. The glass–silver (auxiliary) electrode couple had the characteristic pH = (376–E)/59.1, where E is the millivoltmeter reading. The electrodes were calibrated with respect to the following standard substances: picric acid, pK_d = 11.0 [9]; 2,4-dinitrophenol, 16.0 [8]; benzoic acid, 20.7 [9]; p-nitrophenol, 20.8 [8]; o-nitrophenol, 22.0 [8]; phenol, 26.9 [8].

The acid concentration at the beginning of the titration was $2 \cdot 10^{-3}$ mole/liter. The vessels containing the titrant and acetonitrile and the cell for the titration were maintained in an atmosphere of pure dry argon. The accuracy in the measurements was ±2 mV.

The thermodynamic pK_d values were obtained by averaging two to three measurements at the half-neutralization point by means of the equation

$$pK_d = p_{aH}{}^{1/2} - \log f,$$

where $p_{aH^{1/2}}$ is the hydrogen index of the solution at the half-neutralization point, which is equal to $-1.5\sqrt{\mu}$, where μ is the ionic strength of the solution [8].

LITERATURE CITED

1. Zh. V. Bren', V. I. Usacheva, G. D. Palui, V. A. Bren', and V. I. Minkin, Khim. Geterotsikl. Soedin., No. 5, 619 (1977).
2. V. A. Bren', V. I. Usacheva, and V. I. Minkin, Khim. Geterotsikl. Soedin., No. 7, 920 (1972).
3. V. A. Bren', Zh. V. Bren', and V. I. Minkin, Khim. Geterotsikl. Soedin., No. 2, 154 (1973).
4. V. A. Bren', V. I. Usacheva, Zh. V. Bren', B. Ya. Simkin, and V. I. Minkin, Khim. Geterotsikl. Soedin., No. 5, 631 (1974).
5. V. A. Bren', V. I. Usacheva, V. I. Minkin, and M. V. Nekhoroshev, Khim. Geterotsikl. Soedin., No. 5, 635 (1975).
6. L. M. Sitkina, V. A. Bren', and V. I. Minkin, Khim. Geterotsikl. Soedin., No. 4, 499 (1975).
7. Zh. V. Bren', V. A. Bren', B. Ya. Simkin, and V. I. Minkin, Zh. Org. Khim., 13, 1723 (1977).
8. I. F. Coetzee and G. R. Padmanabhan, J. Phys. Chem., 69, 3163 (1965); 70, 856 (1966).
9. I. M. Kolthoff and M. K. Chantooni, J. Am. Chem. Soc., 87, 4428 (1965); 90, 23 (1968).
10. I. F. Coetzee, G. R. Padmanabhan, and G. P. Cunningham, Talanta, 11, 93 (1964).
11. I. M. Kolthoff and M. K. Chantooni, Anal. Chem., 39, 1626 (1967).
12. Yu. A. Zhdanov and V. I. Minkin, Correlation Analysis in Organic Chemistry [in Russian], RGU, Rostov-on-Don (1966).
13. M. B. Stryukov, M. I. Knyazhanskii, V. A. Bren', V. I. Minkin, and Zh. V. Bren', Opt. Spektrosk., No. 6, 1051 (1973).
14. M. B. Stryukov, M. I. Knyazhanskii, V. A. Bren', V. I. Minkin, B. Ya. Simkin, and V. I. Usacheva, Teor. Éksp. Khim., 10, 520 (1974).
15. I. M. Kolthoff, M. K. Chantooni, and S. Bhowmik, Anal. Chem., 39, 1627 (1967).
16. L. N. Bykova and S. I. Petrov, Usp. Khim., 41, 2065 (1972).
17. A. P. Kreshkov, L. N. Bykova, and N. A. Kazaryan, Acid-Base Titration in Nonaqueous Solutions [in Russian], Khimiya, Moscow (1967).