EFFECT OF meso SUBSTITUENTS ON THE NH ACIDITIES OF BENZIMIDAZOLES

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The NH acidities of a systematic series of 2-substituted benzimidazoles in acetonitrile were studied by potentiometric titration. It was found that the intramolecular interrelationships between the substituent in the 2 position and the acidity center have primarily inductive character and are expressed quantitatively by a dependence of the $pK_a = f(\sigma_m)$ type.

A significant amount of data on the dissociation constants that characterize the acidic ionization of the N–H bonds in 2-substituted benzimidazoles is available in the literature [1-4]. However, because of the different conditions used in the measurement of the acidic properties of these compounds (water [1, 2], 50% ethanol [3], and 1% ethanol [4]) and the lack of standardization in the determination of the pK_a values in [1, 3], the available data cannot be compared on the same basis. For this reason, despite the existence of such copious experimental data (the pK_a values were measured for 17 NH acids of this type), they cannot be examined within the framework of a single reaction series and do not make it possible to reveal structural-functional relationships in series of 2-substituted benzimidazoles.
In this connection, the aim of the present research was to determine the acidic ionization constants of a systematic series of 2-substituted benzimidazoles and to establish the quantitative relationships that link the acidic properties of these compounds with their structures. The correctness of the conclusions regarding the existence of one or another type of structural-functional relationships for the investigated series of compounds depends on the extent to which the selection of the substituents of this reaction series corresponds to the requirements of the "minimal ensemble" [5], which should include substituents of the (–I, –C), (–I, +C), and (+I, +C) type. In the case of the acidic ionization of the N–H bond in 2-substituted benzimidazoles the latter type of substituents (alkyl) for any interrelationships of these substituents with the reaction center (the inductive effect of the substituent or the inductive effect in combination with the conjugation interaction) should have an acid-weakening effect. Moreover, if one takes into account the fact that the acidic ionization of the N–H bond in benzimidazoles does not proceed to a very great extent in aqueous solutions even in the case of those with a phenyl substituent (the pK_a of 2-phenylbenzimidazole has been reported to be 11.91 [2] and 12.50 [1], whereas the pK_a of benzimidazole is 13.2 [6]), it becomes obvious that it is not possible to study the acidic properties of a complete series of 2-substituted benzimidazoles (including all of the types of substituents indicated above) in aqueous solutions by potentiometry (because of the inaccuracy in the readings of the glass electrode at pH > 11 [7]). For this reason, the potentiometric investigation of the acidic properties of 2-substituted benzimidazoles was conducted in acetonitrile. This solvent is characterized by a higher self-protolysis constant ($pK_S = 33.3$ [8]) than water ($pK_S = 14$), which makes it possible to study the acidic properties of slightly dissociated compounds [9], to which class most benzimidazole derivatives belong, in it. In Table 1 one's attention is immediately drawn to the considerable range of change in the acidic properties [on passing from 2-methylbenzimidazole (I) to the corresponding nitro derivative X, the acidity changes by 7.68 pK_a units], which indicates the high sensitivity of the acidity centers of these compounds to the effects of the meso substituent. A study of the acidic properties of heterocyclic compounds in which the acidity center (the N–H bond) is separated from variable substituent R by only one bond (in addition to the bond of the substituent with the ring) shows that the interrelationships of substituent R with the reaction center in these compounds has primarily inductive character. Thus the NH acidities of 2-substituted pyrroles [13] and pyrroloanthrones [14] are satis-

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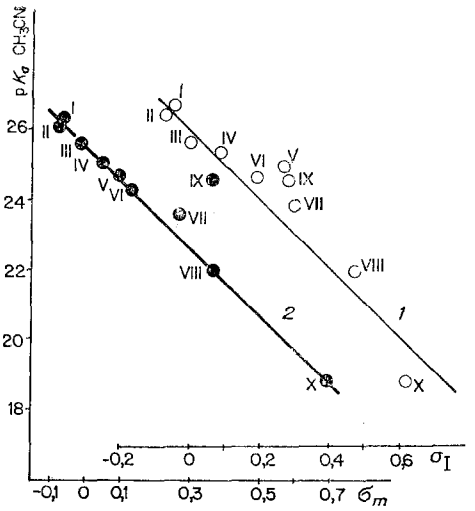
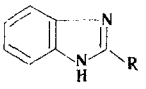


Fig. 1. Correlation of the pK_a values (CH_3CN) of 2-substituted benzimidazoles with the polar substituent constants: 1) $pK_a = f(\sigma_I)$; 2) $pK_a = f(\sigma_m)$ (the numbers of the points correspond to the numbers of the compounds in Table 1).

TABLE 1. Acidic Ionization Constants of 2-Substituted Benzimidazoles



in Acetonitrile at 20°C

Compound	R	σ_I	σ_m	pK_a
I	CH_3	−0,05	−0,069	26,43
II	C_2H_5	−0,05	−0,07	26,36
III	H	0	0	25,60
IV	C_6H_5	0,1	0,06	25,36
V	OC_2H_5	0,27	0,1	24,92
VI	SCH_3	0,19	0,15	24,51
VII	$SCH=CH_2$	0,30*	0,28*	23,70
VIII	Cl	0,47	0,370	21,95
IX	$COCH_3$	0,28	0,376	24,60
X	NO_2	0,63	0,710	18,75

*The σ_I value of the $SCH=CH_2$ group was calculated from the equation $\sigma_I(RS) = 0.45\sigma_I(R) + 0.26$ [10], and the σ_m value was calculated from the dependence $\sigma_I = (3\sigma_m - \sigma_p)/2$ [11], where the σ_p value is the value for $SCH=CH_2$ + 0.25 [12].

factorily described by the σ_I constants. The equilibrium NH acidities of 2-substituted imidazoles and 5-substituted pyrazoles correlate with the σ_m constants [15]. A similar regularity was established in an investigation of the acidic properties of 5-substituted 3-nitro-1,2,4-triazoles [16]. 2-Substituted benzimidazoles are precisely the type of heterocyclic compounds in which, as demonstrated by the investigations, primarily or exclusively an inductive mechanism of interaction of the substituent with the reaction center is realized. On the basis of this, in establishing quantitative relationships that link the acidities of the investigated series of 2-substituted benzimidazoles with their structures we used the σ_I and σ_m constants as the structural parameters that characterize the polar effect of the substituent in the 2 position. Even a qualitative comparison of the pK_a values with the

σ_I inductive constants shows that in the investigated series of compounds ionization of the N–H bond is determined not only by the inductive effect of substituent R and that conjugation interactions of this substituent with the π-electron system of benzimidazole also make a definite contribution to the formation of the acidic properties of these compounds. The character of the change in the acidic properties of V, VII, and IX serves as a confirmation of this. Thus, taking into account the virtually equal σ-electron-acceptor capacities of substituents R in V, VII, and IX (which follows from the equality of the σ_I values) and proceeding from the possible exclusively inductive mechanism of the intramolecular interaction in these molecules, one might have expected that the ionizing capacity of the N–H bond of the examined series of compounds would by characterized by identical pK_a values. However, the experimental pK_a values do not confirm this. The acidity of 2-ethoxybenzimidazole (V) is 1.28 pK_a units lower than the acidity of 2-vinylthiobenzimidazole (VII). In conformity with this, the σ_I inductive constants can hardly describe the change in the acidic properties in the series of 2-substituted benzimidazoles with a high-quality correlation. Judging from the character of the change in the acidic properties already noted above, in the I–X series the best agreement between the experimental data and the structural parameters can be achieved by comparison of these values with the σ_m constants (compare the pK_a values of V and VII with the σ_m constants), which, in addition to the inductive effect, take into account possible conjugation interactions of the substituent with the π-electron system.

In fact, the results of calculations [Eq. (1)] and their graphical representation (Fig. 1, curve 1) show that the linear correlation of the pK_a values of 2-substituted benzimidazoles with the inductive constants is only satisfactory in character.

$$pK_a = (26.19 \pm 0.4) - (10.05 \pm 1.26)\sigma_I \quad (1)$$
$$r = 0.960;\ S_0 = 0.83;\ n = 10$$

At the same time, the interrelationship between the pK_a values and the σ_m constants represented by Eq. (2) (Fig. 1, curve 2) is characterized by high correlation indexes ($r > 0.99$), thereby constituting evidence that the NH ionization of 2-substituted benzimidazoles is very satisfactorily described by the σ_m constants.

$$pK_a = (25.78 \pm 0.07) - (9.90 \pm 0.24)\sigma_m \quad (2)$$
$$r = 0.998;\ S_0 = 0.16;\ n = 8$$

To ascertain the degree of participation of the inductive and conjugation components in the overall effect of the meso substituent we made a thorough analysis of a two-parameter correlation of a dependence of the $pK_a = f(\sigma_I, \sigma_C)$ type, where $\sigma_C = \sigma_m - \sigma_I$, which is represented by Eq. (3).

$$pK_a = (25.58 \pm 0.09) - (9.83 \pm 0.26)\sigma_I - (3.86 \pm 0.33)\sigma_C \quad (3)$$
$$r = 0.998;\ S_0 = 0.17;\ n = 8$$

It follows from the absolute values of the coefficients (ρ_I and ρ_C) of the regression presented above that the acidic ionization of the N–H bond in 2-substituted benzimidazoles is determined both by the inductive effect and the conjugation effect of the substituent, although the inductive effect plays the predominant role.

The data on the pK_a values of 2-acetyl- (IX) and 2-vinylthiobenzimidazole (VII) were not used in the calculation of the parameters of correlations (2) and (3), inasmuch as in the first cycle of the calculations it was established that the points that correspond to these compounds experience significant deviations from the regression line [$\Delta pK_a = pK_{a(exp)} - pK_{a(calc)} = 2.54$ for IX; $\Delta pK_a = 0.69$ for VII], which substantially exceed the probable values for correlations (2) and (3) (according to the Student distribution). On the basis of this, the observed noncompliance of the acidic properties of VII and IX with the overall quantitative dependence established for 2-substituted benzimidazoles (Fig. 1, curve 2) constitutes evidence for the presence of special structural effects in the molecules of these compounds. Thus, in the case of 2-acetylbenzimidazole (IX) the markedly decreased capacity for ionization of the N–H bond is associated with the presence of a strong intramolecular hydrogen bond between the hydrogen (in the NH group) and oxygen (in the acetyl fragment) atoms in this compound. If the deviation of the pK_a value of 2-acetylbenzimidazole ($\Delta pK_a = 2.54$) is related only to the effect of H bonding, the upper limit of the strength of this bond can be estimated as $2.303RT\Delta pK_a = \Delta\Delta G$, and $\Delta\Delta G = \Delta\Delta H - T\Delta\Delta S$; if one disregards the change in the entropy term, $\Delta\Delta H = 3.45$ kcal/mole.

Despite the identical character of the deviations of the acidic properties of VII and IX on the established dependence $pK_a = f(\sigma_m)$, the reasons for weakening of the acidic properties of these compounds evidently differ. Whereas in the first case, viz., for IX, the realization of an intramolecular hydrogen bond is the reason, in the case of VII the most acceptable version that explains its decreased acidity is steric shielding of the acidity center by the β-hydrogen atoms of the S—CH=CH_2 group when it is solvated.

EXPERIMENTAL

The acidic ionization constants of 2-substituted benzimidazoles in acetonitrile were determined by potentiometric titration at 20°C with a 340 pH meter with the aid of glass (ÉSL 43-07) and silver chloride (ÉVL-1MZ) electrodes. The silver chloride electrode was filled with a saturated solution of LiCl and AgCl in acetonitrile. The titrant was a 0.1 N solution of tetrabutylammonium hydroxide, which was prepared in benzene—methanol (9:1). The measurements were made at acid concentrations of 0.005 mole/liter.

The equivalence points on the titration curves and the half-neutralization potentials [E] were found graphically. The half-neutralization potential was taken as the average to four to five parallel determinations that differed by no more than 3-4 mV.

The acidic ionization constants (pK_a) were calculated from the formula $pK_a = pK_o + (E_o - E_x)/59$, where E_o and E_x, respectively, are the half-neutralization potentials of the standard and investigated compounds in millivolts. Benzoic acid, the acidic ionization constant (pK_a°) of which in acetonitrile is 20.7 [17], was used as the standard. The reproducibility of the pK_a values was ±0.1 logarithmic units.

Compounds I-V and VIII-X were obtained by methods, reviews of which were presented in [18-20]; VI and VII were obtained by the methods in [21, 22].

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