OXIMES OF AZOLECARBALDEHYDES AND Δ^2-AZOLINECARBALDEHYDES AND THEIR DERIVATIVES

IV.* IONIZATION CONSTANTS AND TAUTOMERIC EQUILIBRIA IN AQUEOUS SOLUTIONS

I. N. Somin, N. I. Shapranova,
and S. G. Kuznetsov

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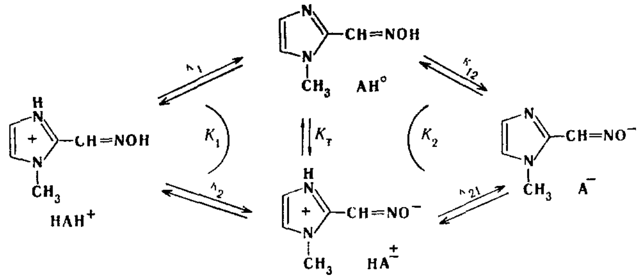
The parameters of the acid–base and tautomeric equilibria of the E (syn) isomers of 1-methyl-substituted benzimidazole-2-carbaldehyde oxime, imidazole-2-carbaldehyde oxime, Δ^2-imidazoline-2-carbaldehyde oxime, and Δ^2-pyrazoline-3-carbaldehyde oxime in aqueous solutions at 25°C have been determined by a potentiometric method using model compounds. The tautomeric ratio (zwitterion)/(uncharged form) rises in parallel with an increase in the basicity of the parent heterocycle. Unlike known heterocyclic aldoximes, 1-methyl-Δ^2-imidazoline-2-carboxaldehyde oxime exists in the zwitterionic form.

The complete scheme for the prototropic equilibrium of nitrogen-containing heterocyclic aldoximes in aqueous solution includes four ionic forms (microforms) of the substance: the cation (HAH^+), the anion (A^-), the uncharged form (AH^0), and the zwitterion ($HA^\pm$). The latter two forms are tautomeric. For example, for 1-methylimidazole-2-carbaldehyde oxime:



The system is described quantitatively by two macroconstants (K_1, K_2), four microconstants (k_1, k_2, k_{12}, k_{21}),† and the constant of the tautomeric equilibrium (K_T). The following relation exists between them:

$$K_1=\kappa_1+\kappa_2;\quad K_2^{-1}=\kappa_{12}^{-1}+\kappa_{21}^{-1};\quad K_1K_2=\kappa_1\kappa_{12}=\kappa_2\kappa_{21};\quad K_T=[HA^\pm]/[AH^0]=\kappa_2/\kappa_1=\kappa_{12}/\kappa_{21}.$$

It is sufficient to determine three parameters – for example, two macroconstants and one microconstant or K_T, or three microconstants, and so on – in order to describe the system completely [2-4].

Considerable interest is presented by aldoximes containing onium centers and existing, even if only partially, in the form of zwitterions in neutral aqueous solutions [4-6]. This property is possessed by many quaternary ammonium derivatives of heteroaromatic aldoximes, in particular by derivatives of pyridine-2- and -4-carbaldehyde oximes. Under these conditions, the nonquaternized pyridinecarbaldehyde oximes exist almost solely in the uncharged form, which is due to the low values of K_T (10^{-4}-10^{-5}) [7]. The

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* For Communication III, see [1].

† The system of numerical indices to denote the microconstants is similar to that adopted by Edsall et al. [2].

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TABLE 1. Parameters of the Prototropic Equilibrium of Heterocyclic Aldoximes in Aqueous Solution[a]

Oxime	pK_0[b]	Macro-const.[c]		Microconstants[c]				lg K_T	Difference in constants[d]			pH_i[e]	Proportion of $HA^{\pm}$, %	
		pK_1	pK_2	pk_1	pk_2	pk_{21}	pk_{12}		$\Delta pk'$	$\Delta pk''$	$\Delta pk'''$		pH_i	pH 7,4
I	5,57[14]	3,71	11,17	3,71	7,68	7,20	11,17	−4,0	1,86	−1,63	3,49	7,44	0,01	
II	7,33[14]	5,92	10,96	5,92	8,23	8,65	10,96	−2,3	1,41	−1,32	2,73	8,44	0,5	
III	11,0[15]	7,32	12,10	9,62	7,32	12,10	9,80	2,3	1,3	−1,1	2,48	9,71	99	54
IV	3,90[16]	2,33	9,80	2,33	7,91	4,22	9,80	−5,6	1,57	−0,32	1,89	6,06	0,0002	
V	5,23[14]	3,63	10,14	3,63	8,00	5,77	10,14	−4,4	1,60	−0,54	2,14	6,89	0,004	
VI	5,23[14]	4,10	10,36	4,10	9,22	5,24	10,36	−5,1	1,11	−0,03	1,14	7,23	0,0008	
VII	5,23[14]	4,77	9,99	4,77	8,57	6,19	9,99	−3,8	0,42	−1,00	1,42	7,38	0,015	

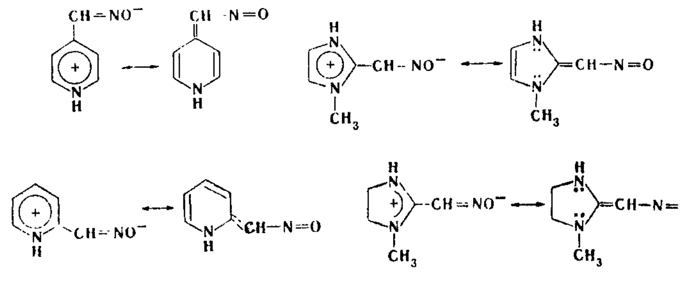
[a] At 25 ± 0.1°C; for (V–VII) the figures obtained at 20°C [7] are given. [b] Ionization constant of the parent [for (I–IV) the 1-methyl-substituted] heterocycle. For 1-methyl-Δ^2-imidazoline the calculated value [15] is given. [c] "Mixed" constants. [d] See text. [e] Isoelectric point: $pH_i = 0.5\ (pK_1 + pK_2)$.

possibility of obtaining aldoximes giving comparable amounts of the tautomeric forms has been demonstrated on aliphatic amino-substituted α-oxo aldoximes [4-6]. Among heterocyclic aldoximes, such compounds have hitherto been unknown.

We assumed that a shift of the tautomeric equilibrium in the required direction can be achieved by using heterocycles more basic than pyridine. A comparison of the ionization constants of pyrimidine, pyridine, and their carbaldehyde oximes [7, 8] showed that an increase in the affinity of the ring nitrogen for a proton is not accompanied by a very considerable increase in the proton affinity of the oxygen of the oxime group. As subjects of investigation we selected 1-methylbenzimidazole-2-carbaldehyde oxime [9], 1-methylimidazole-2-carbaldehyde oxime, 1-methyl-Δ^2-imidazoline-2-carbaldehyde oxime, and 1-methyl-Δ^2-pyrazoline-3-carbaldehyde oxime [10] (I-IV), which are individual E (syn) isomers [11, 12]. The oximes (I-III) contain an amidine system of bonds in the ring, leading to an increase in the basicity of the parent rings as compared with pyridine.

To calculate the parameters of the prototropic equilibrium we used the macroconstants (K_1 and K_2), which were determined by potentiometric titration [13], and also the microconstants k_2 (I, II, IV) and k_1 (III). As the latter we used the ionization constants of model (fixed) compounds [2-4, 7]: the methiodides of the oximes (I, II, and IV) and the O-methyl ether of the oxime (III), respectively. The results obtained, together with those [7] on pyridine-2-, -3-, and -4-carbaldehyde oximes (V-VII), are given in Table 1.

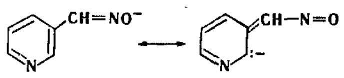
As was to be expected, the values of K_T for the oximes (I-IV) rise in parallel with the basicities of the initial rings (pK_0). This parallelism is connected with the fact that the basicity of the heterocycles of the oximes (pk_1 and pk_{21}) increases in this sequence to approximately the same extent as pK_0, while the values of pk_2 and pk_{12}, which characterize the acidities of the oxime groups, vary within fairly narrow limits. The transfer of a proton from the exocyclic oxygen atom to the ring nitrogen may be favored by the resonance stabilization of the zwitterion (for example, in the hydroxypyridines) [3]. The increase in K_T in the sequence (I) → (II) → (III), and also on passing from (V) and (VII) to (II) and (III) is not, however, accompanied by an improvement in the conditions for such stabilization. The source of growth of K_T is the change in the nature of the conjugation within the heterocycle. The resonance stabilization of the unprotonated ring falls sharply in the sequence (I) → (II) → (III) in connection with which the contribution of the amidine resonance to the stabilization of the protonated form rises.

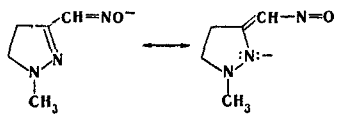


Characteristic for the oximes (II) and (III) is an increase in the acidity of the oxime group with a rise in the basicity of the ring, which also makes a definite contribution to the increase in K_T. Apparently, the main factor determining the values of pk_2 and pk_{12} is the induction effect of the heterocycle. (The low sensitivity of the acidic properties of the oxime group to a change in the π-electron density of the aromatic ring has been shown [17].) This effect is expressed more strongly in the nonaromatic ring due to the localization of the positive charge within the amidinium (amidine) system in the oxime (III) and its "diffusion" over the whole ring in the oxime (II).

The value of $\Delta pk' = pK_0 - pk_1$ characterizes the influence of the non-ionized hydroxyiminoethyl group (CH = NOH) on the basicity of the heterocycle. In all cases, this group lowers the basicity. Judging from the results for pyridinecarbaldehyde oximes, the influence is due mainly to the induction effect – probably its I_σ component [18]. This conclusion is in harmony with the correlation of the ionization constants of the substituted pyridines and 1-methylimidazoles with the σ_m and σ_1 constants [18, 19].

A considerable field effect must be characteristic of the ionized group ($CH = NO^-$), the influence of which is expressed by the magnitude $\Delta pk'' = pK_0 - pk_{21}$. This could explain the increase in the basicity of the ring ($\Delta pk'' < 0$). The low value of $\Delta pk''$ on the introduction of a substituent into the β position of the pyridine ring (where direct conjugation with the reaction center is excluded) shows, however, that the electrostatic effect merely compensates the electron-accepting influence of the hydroxyiminomethyl group. The total I effect of the $CH = NO^-$ group thus differs little from the effect of a hydrogen atom (i.e., from zero on the σ scale). The large effect in the case of the oxime (IV) with conjugation conditions analogous to those of (VI), can be explained by the more favorable delocalization of the negative charge on the neighboring nitrogen in (IV) than on the carbon in (VI) because of the difference in the electronegativities of nitrogen and carbon. The increase in the basicity of the parental ring by 0.5-1.6 pK units [in the oximes (I-III, V, and VII)] is apparently connected with the effect of the direct conjugation of the substituent with the reaction center in the zwitterions. It is characteristic that this effect decreases somewhat in the sequence (I) → (II) → (III), and its value varies within the limits of a single order of magnitude for (I-III) and pyridine-2- and -4-carbaldehyde oximes. This confirms the conclusion drawn above on the second-degree influence of direct conjugation in the increase in the value of K_T on passing from (V), (VII), and (I) to (II) and (III).* In addition to this, the differences in the values of K_T and $\Delta pk''$ within the group of pyridinecarbaldehyde oximes may be connected with the predominance of the resonance stabilization of the para-quinoid structures as compared with ortho-quinoid structures [14].





The magnitude $\Delta pk''' = \Delta pk' - \Delta pk'' = pk_{12} - pk_2 = pk_{21} - pk_1$ characterizes the influence of the ionization of the ring or of the oxime group on the acid–base properties of the oxime group and the ring, respectively. By virtue of the thermodynamic ratio of the constants (see above), the two effects are of equal size. From the preceding discussion of the values of $\Delta pk'$ and $\Delta pk''$ and from the values of $\Delta pk'''$ for the pyridinecarbaldehyde oximes it is obvious that the changes due to the introduction of charges are caused both by the induction effect and by the resonance stabilization of the zwitterions.

Returning to the question of the existence of oximes in the form of zwitterions in a neutral region (pH ~ 7.4), it must be noted that the proportion of the total concentration of the substance present in this form depends not only on the value of K_T but also on other parameters of the acid–base equilibrium. The

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*The oximes considered are azavinylogs of the corresponding hydroxy-substituted heterocycles. The considerably lower values of K_T for the pyridinecarbaldehyde oximes as compared with the hydroxypyridines (for 2-, 3-, and 4-hydroxypyridines $\log K_T = 2.9, -0.1$, and 3.3, respectively [3]) are explained [7] by the weak conjugation of the lone pair of electrons of the oxygen of the oxime group with the ring. The predominant localization of the negative charge in the zwitterions of pyridine-2- and -4-carbaldehyde oximes on the oxygen is confirmed by literature information [20,21]. The weak p–π interaction is apparently connected with the low transmission capability of the C = N bond [18] and also with the unfavorable electrostatic interactions of the lone pairs of electrons of the nitrogen and oxygen atoms [1], which may prevent the optimum orientation of the p–π system in the C = N–O group.

maximum concentration of the isoelectric form ($AH^0 + HA^{\pm}$) is reached at the isoelectric point (pH_i). Since for the oximes given in Table 1 ($pK_2 - pK_1$) > 4, they all exist completely in the isoelectric forms at pH_i. The values of pH_i for (I), (VI), and (VII) practically coincide, with a value of 7.4, and that for (V) is close to it. However, because of the low value of K_T the proportion of zwitterion in these oximes does not exceed 0.02%. The isoelectric points of (II) and, particularly, (III) are displaced into the alkaline region. Nevertheless, because of the increase in K_T the proportion of zwitterion at pH 7.4 is already appreciable for (II) (0.5%) and is high (54%) for (III). The oxime (III) is apparently the first known heterocyclic aldoxime characterized by an appreciable magnitude of K_T.

EXPERIMENTAL

The oximes (I-IV) have been obtained previously [9, 10].

The O-methyl ether of 1-methyl-Δ^2-imidazoline-2-carboxaldehyde oxime was obtained similarly to (III) using methoxyamine hydrochloride. Yield 39% (oil). Perchlorate: mp 126.5-127.5°C (from isopropanol). Found, %: N 17.6; 17.4. $C_6H_{12}ClN_3O_5$. Calculated, %: N 17.4. PMR spectrum (recorded on an HA-100D-15 spectrometer using a 10% solution in 2 N HCl with tert-butanol as internal standard), ppm: 8.07 (=CH), 3.98 (multiplet, CH_2), 3.85 (OCH_3), 3.20 (NCH_3).

The potentiometric titration of the hydrochlorides (I, II, and IV) of the base (III), of the methiodides of the oximes (I, II, and IV) and of the perchlorate of the O-methyl ether of the oxime (III) was performed with argon stirring in a thermostated cell at 25 ± 0.1°C using a pH-340 instrument. The pH-meter was adjusted with freshly prepared standard buffer solutions. The concentration of the substances being titrated was 0.01 M at the half-neutralization point. The titrants were an 0.1 N solution of KOH purified by a published method [13] and an 0.1 N solution of HCl. The maximum scatter [13] was ± 0.04 pK unit.

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