Russian Journal of Organic Chemistry, Vol. 37, No. 3, 2001, pp. 416–420. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 3, 2001, pp. 441–445.

Basicity of Phenyl-Substituted 1,3-Oxazoles

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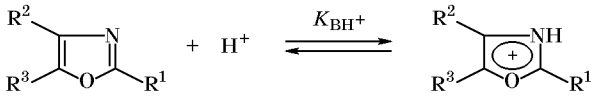
Received March 4, 1999

Abstract—Phenyl substituents in positions *2*, *4*, and *5* of the oxazole ring exert different effects on the electronic structure of the heteroring, which are reflected in the basicity constants of isomeric phenyl-substituted oxazoles and in changes of the spectral patterns on protonation. The calculated (AM1) gas-phase proton affinities and energies of ionization of isomeric methyl-, phenyl-, and methylphenyloxazoles were correlated with the experimental pK_{BH^+} values. In acid medium specific solvation of phenyloxazoles is possible with participation of the heterocyclic fragment.

The basicity of aromatic nitrogen-containing heterocycles is an important problem of modern heterocyclic chemistry, which is far from being solved. There are some published data on protolytic equilibria of 1,3-oxazoles. Haake and Baucher [1] were the first who tried to determine pK_{BH^+} values for compounds of this series by potentiometric titration. With three oxazole derivatives as examples it was found that the oxazole ring is protonated in the pH region of ~1. Later on, Brown and Ghosh [2] determined the basicity of a series of 1,3-oxazoles, including the unsubstituted compound, by spectrophotometry. Shvaika *et al.* [3] studied the basicity of a series of 2,5-diaryl-1,3-oxazoles. Finally, Kenny [4] estimated on a quantitative level the acceptor power (K_β) of oxazole ring with respect to ptoton in hydrogen bonding.

Nevertheless, quantitative data on the basicity of 1,3-oxazoles cannot be regarded as comprehensive for the following reasons. The known publications are fragmentary, in some cases published data are contradictory, and pK_{BH^+} values were calculated with no regard to the modern concept of quantitative comparison of weak organic bases. As applied to some models, inappropriate experimental methods were used. For example, spectrophotometric method was applied to determine basicity constants of compounds with an absorption maximum at $\lambda < 200$ nm or potentiometric titration was used in the pH region below unity. Most publications lack detailed information on spectral measurements and methods of calculation of basicity constants.

In the present work we determined by spectrophotometry the basicity constants of phenyl-substituted 1,3-oxazoles: 4-phenyloxazole (**I**), 2,4-diphenyloxazole (**II**), 2-methyl-5-phenyloxazole (**III**), 2-methyl-4-phenyloxazole (**IV**), and 5-methyl-2-phenyloxazole (**V**). These derivatives contain phenyl groups in different positions of the heteroring and are sufficiently stable to perform necessary spectral measurements in acid solution.



I–XXII

The basic center in 1,3-oxazoles is the pyridine-like nitrogen atom [5]. Protonation of the oxygen atom which also possesses a lone electrone pair is improbable, for the resulting cation is extremely unfavorable from the thermodynamic viewpoint. This was shown previously for furan derivatives which are protonated mainly at carbon atoms [6, 7]. According to calculations, protonation of oxazoles at the oxygen atom is by 50–60 kcal/mol less favorable than protonation at the nitrogen atom [8, 9].

Table 1 contains pK_{BH^+} values calculated by Eq. (1) (for organic bases which are protonated in the pH range from 0 to 14) and Eq. (2) (for weak bases which are protonated in the acidity range described by the acidity function H_0; Yates–McClelland equation) [10–12]. In these equations, I is the ionization ratio determined according to the Stewart–Granger rule

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Table 1. Basicity constants of oxazoles **I**–**V** in aqueous solutions, calculated by Eqs. (1) and (2)

Comp. no.	λ, nm	Parameters of Eqs. (1) and (2)				
		pK_{BH^+}	pK'_{BH^+}	*m*	*r*	*n*
I	230	–0.51 ± 0.09	–0.37	0.72	0.97	6
II	305	–0.04 ± 0.04	–0.04	1.05	0.99	8
III	270	2.13 ± 0.07	1.28	0.60	0.98	6
IV	235	1.10 ± 0.09	0.91	0.83	0.97	8
V	290	1.94 ± 0.07	1.41	0.72	0.98	8

Table 2. UV spectra of free bases and conjugate acids of phenyl-substituted 1,3-oxazoles **I**–**V** in aqueous solution

Comp. no.	Base		Conjugate acid	
	λ_{max}, nm (ε, l mol^{-1} cm^{-1})	H_0 (H_2SO_4, wt %)	λ_{max}, nm (ε, l mol^{-1} cm^{-1})	H_0 (H_2SO_4, wt %)
I	241 (9650)	–0.03 (5.24)	238 (10000)	–2.45 (38.39)
II	273 (13700)	pH 1[a]	297 (17650)	–1.50 (25.7)
III	266 (18950)	pH 3.7[b]	261 (17600)	0.0 (4.8)
IV	247 (12200)	pH 2.63[c]	241 (13900)	–0.82 (15.8)
V	274 (14300)	pH 4.43[b]	281 (15700)	–0.82 (15.8)

[a] Standard 1 N solution of sulfuric acid.
[b] Formate buffer.
[c] Phosphate buffer.

[11], and *x* and *m* are solvation coefficients for the linear dependences of log *I* versus acidity (pH, H_0). In order to avoid influence of the solvation coefficient on the basicity constant, pK_{BH^+} was assumed to be equal to the ratio of the free term to the slope of Eqs. (1) and (2) [12].

$$\log I = -x\,\mathrm{pH} + pK'_{BH^+},\ pK_{BH^+} = pK'_{BH^+}/x; \quad (1)$$

$$\log I = -m\,H_0 + pK_{BH^+},\ pK_{BH^+} = pK'_{BH^+}/m. \quad (2)$$

As follows from the data in Table 1, oxazoles are weak bases. The basicity constant of the oxazole ring is by more than 6 order of magnitude lower than the corresponding value for its analog containing only nitrogen atoms, imidazole [13]. The position of the phenyl group strongly affects the basicity constant. In all cases 4-phenyl-1,3-oxazoles **I**, **II**, and **IV** are weaker bases than 2- and 5-phenyl derivatives. This fact may be explained in terms of different modes of π,π-conjugation between the heteroring and phenyl rings in positions *4*, *2*, and *5* [2, 14]. According to our data, the basicity of 4-phenyloxazole (**I**) is considerably higher than that reported in [2] (pK_{BH^+} –1.21). The solvation coefficients for oxazoles **I** and **V** and especially for oxazole **III** are much lower than unity, which suggests specific protonation of the oxazole ring as compared to typical Hammett bases [11]. This may be due to formation of intermediate solvate complexes [15].

Compounds **I**–**V** show different changes in the UV spectra on protonation (Table 2). Protonation of oxazoles **II** and **V** having a phenyl group in position *2* of the heteroring produces a strong red shift of the absorption maximum and a small hyperchromic effect. 4-Phenyl and 5-phenyl derivatives **I**, **III**, and **IV** are characterized by a small blue shift and slight variation of the molar absorption coefficient (Fig. 1). Presumably, proton addition to 2-phenyloxazoles **II** and **V** affects the conjugated electronic system of the oxazole and benzene rings most strongly.

The UV spectral patterns of 2-methyl-5-phenyl-1,3-oxazole (**III**) and 5-methyl-2-phenyl-1,3-oxazole (**V**) in strongly acidic medium (where the protonation is complete) change in a way typical of equilibrium processes (Fig. 1). From the dependence of the molar absorption coefficient on the acidity of the medium we calculated by Eq. (2) the Hammett acidity function

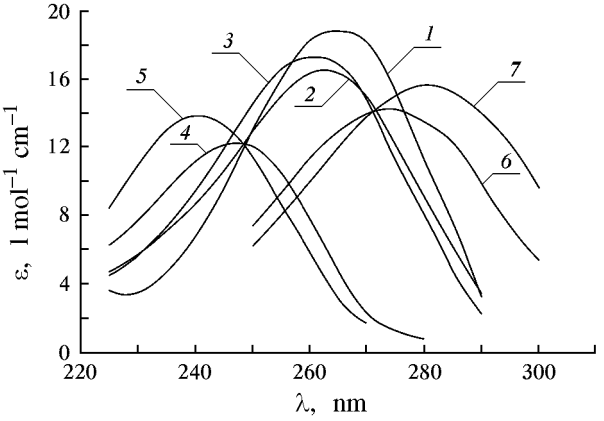

Fig. 1. Electron absorption spectra of free bases and conjugate acids of isomeric phenyloxazoles in aqueous solutions. 2-Methyl-5-phenyl-1,3-oxazole (**III**): (*1*) pH 3.7, (*2*) H_0 0, (*3*) H_0 –4.75; 2-methyl-4-phenyl-1,3-oxazole (**IV**): (*4*) pH 2.63, (*5*) H_0 –0.82; 2-phenyl-5-methyl-1,3-oxazole (**V**): (*6*) pH 4.43, (*7*) H_0 –0.82.

corresponding to equal concentrations of the equilibrium forms of oxazole **III** in solution ($H_0 = pK_X$): $pK_X = -3.17 \pm 0.27$; $m = 0.46$, $r = 0.97$, $n = 8$, $\lambda = 255$ nm. Probably, the observed pattern is the result of decomposition of the oxazole ring [16], but additional investigation by independent methods is necessary to draw a final conclusion.

According to published data, in some cases pK_{BH^+} values of aromatic N- and N,O-heterocycles are linearly related to calculated or experimental proton affinities (for the gas phase) or energies of ionization of the corresponding free bases (E_i) [9, 17, 18]. However, the available data refer to only unsubstituted representatives of one or another series, while the substituent effect on the basicity remained beyond the scope of these studies. Theoretical estimation of the substituent effect on the calculated PAs of some 1,3-oxazoles was performed only in [19].

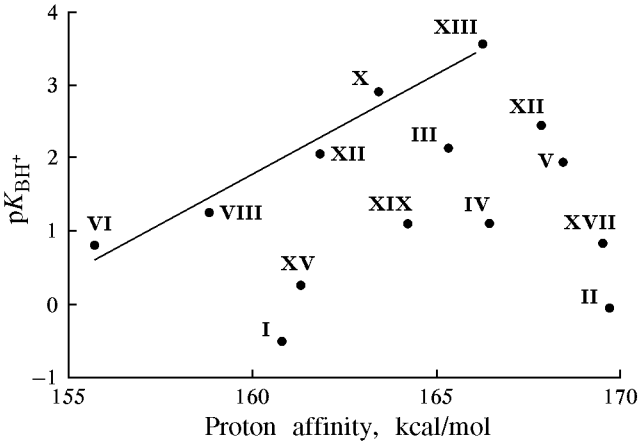

Fig. 2. Correlation between the calculated proton affinities PA (AM1) and experimental pK_{BH^+} values of 1,3-oxazoles (see Table 3).

We calculated by the AM1 method the enthalpies of formation and ionization potentials of the free bases and conjugate acids of possible methylphenyloxazole isomers (Table 3). The proton affinities of free bases were calculated by Eq. (3):

$$PA = \Delta H(H^+) + \Delta H_B - \Delta H_{BH^+}. \quad (3)$$

Here, $\Delta H(H^+)$, ΔH_B, and ΔH_{BH^+} are the enthalpies of formation of proton, free base, and conjugate acid, respectively [20]. The calculated proton affinity of unsubstituted oxazole (Table 3) is appreciably smaller than the experimental value determined by high-pressure mass spectrometry (207.8 [9], 213.3 kcal/mol [21]) and that calculated *ab initio* {212.0 kcal/mol, MP2/6-31G*(*d*,*p*)//STO-3G [8]; 219.6 kcal/mol, MP2/6-31G(*d*,*p*)//STO-3G [9]}. It was previously noted that the results of *ab initio* calculations are better consistent with the experimental data than those obtained by semiempirical methods. However, in both cases general trends in variation of basicity for a given series of heterocycles are similar [22].

As follows from the data in Table 3, both phenyl and methyl group exert the greatest electron-donor effect in position *2* of the heteroring, whereas the donor effect of the same groups in position *4* is the weakest. This finding is generally consistent with the above noted tendency for variation of pK_{BH^+}. However, the effect of the phenyl group on PA is stronger than that of the methyl group. The most basic is 2,4,5-triphenyl-1,3-oxazole; its gas-phase basicity is greater by 7 kcal/mol than the basicity of 2,4,5-trimethyl derivative. Presumably, phenyl substituent provides additional stabilization of the protonated form via delocalization of the positive charge over conjugated π-electron system. In going to solution, the reverse pattern is observed: Replacement of methyl group by phenyl slightly reduces the basicity.

The AM1 energy of ionization (E_i) of unsubstituted 1,3-oxazole (Table 3) is appreciably lower than the experimental value (11.19 eV, photoelectron spectroscopy [18]). On the other hand, the dipole moment of unsubstituted oxazole, calculated by the AM1 method (μ 1.46 D), agrees well with the experimental value and that calculated *ab initio* (μ = 1.50, 1.60 D [8, 23]). No definite relation was observed between the basicity constants in solution and proton affinities of isomeric methylphenyloxazoles (Fig. 2). A good

Table 3. Enthalpies of formation (ΔH_B, kcal/mol) and energies of ionization (E_i, eV) of free bases and enthalpies of formation of conjugate acids (ΔH_{BH^+}, kcal/mol) of isomeric methylphenyloxazoles, calculated by the AM1 method

Compound no.	R^1	R^2	R^3	ΔH_B	E_i	ΔH_{BH^+}	PA[a]	pK_{BH^+}
I	H	Ph	H	37.5	8.96	191.6	160.8	–1.21 [2], –0.51[b]
II	Ph	Ph	H	64.6	8.73	209.8	169.7	–0.04[b]
III	CH_3	H	Ph	31.3	8.77	180.9	165.3	2.13[b]
IV	CH_3	Ph	H	31.6	9.23	180.1	166.4	1.10[b]
V	Ph	H	CH_3	32.2	8.87	178.7	168.4	1.94[b]
VI	H	H	H	12.4	9.89	171.6	155.7	0.8 [2]
VII	CH_3	H	H	5.2	9.58	159.5	160.6	–
VIII	H	CH_3	H	4.4	9.60	160.5	158.8	1.24 [2], 1.07 [1]
IX	H	H	CH_3	5.2	9.53	161.1	159.0	–
X	CH_3	CH_3	H	–2.8	9.34	148.7	163.4	2.91 [2]
XI	CH_3	H	CH_3	–2.0	9.26	149.3	163.6	–
XII	H	CH_3	CH_3	–2.6	9.27	150.5	161.8	2.05 [2]
XIII	CH_3	CH_3	CH_3	–9.7	9.04	139.0	166.2	3.56 [2]
XIV	Ph	H	H	39.3	9.07	188.3	165.9	–
XV	H	H	Ph	38.5	8.94	192.1	161.3	0.26 [2]
XVI	Ph	H	Ph	65.5	8.58	210.9	169.5	0.84 [3]
XVII	H	Ph	Ph	65.8	8.68	214.6	166.1	–
XVIII	Ph	Ph	Ph	92.9	8.44	234.6	173.2	–
XIX	H	CH_3	Ph	31.8	8.91	182.5	164.2	1.09 [2]
XX	Ph	CH_3	H	31.4	8.96	177.9	168.4	–
XXI	H	Ph	CH_3	30.8	8.85	182.0	163.7	–
XXII	CH_3	CH_3	Ph	24.2	8.66	171.3	167.8	2.45 [2]

[a] Gas-phase proton affinities PA (kcal/mol) were calculated by Eq. (3). The AM1 value of $\Delta H(H^+)$ was 314.9 kcal/mol.
[b] Data of this work (see Table 1).

correlation was observed only for isomeric methyl-1,3-oxazoles [Eq. (4)], phenyl-substituted derivatives being excluded.

$$pK_{BH^+} = -(42 \pm 5) + (0.28 \pm 0.03)\,PA; \qquad (4)$$
$$r = 0.983,\ s = 0.24,\ n = 5.$$

An analogous tendency is observed when comparing pK_{BH^+} values with calculated ionization energies E_i [Eq (5)], but the correlation is not satisfactory:

$$pK_{BH^+} = (33 \pm 7) - (3.2 \pm 0.8)\,E_i; \qquad (5)$$
$$r = 0.924,\ s = 0.50,\ n = 5.$$

The observed differences in the behavior of phenyloxazoles and their methyl-substituted analogs may be interpreted in terms of specific solvation of free bases and/or conjugate acids of phenyl derivatives in acid medium, which could involve formation of molecular π-complexes with solvated protons. A number of the above noted specific features of protonation of compounds **I**–**V** can also be explained on the same basis. However, detailed explanation of the effects revealed by the present study requires further experimental and theoretical investigations by independent methods.

EXPERIMENTAL

The electron absorption spectra of compounds **I**–**V** were measured on a Perkin–Elmer Lambda 40 spectrophotometer. The ^1H NMR spectra were recorded in DMSO-d_6 on a Bruker DPX-300 spectrometer. The concentrations of aqueous sulfuric acid solutions were determined by potentiometric titration with an accuracy of ±0.2 wt %. The acidity functions were taken from [24]. Buffer solutions with a ionic strength μ of 0.01 were used for spectrophotometric measurements [25]. Compounds **I**–**V** were synthesized by known methods: 4-phenyloxazole (**I**) [26], 2,4-diphenyloxazole (**II**) [27], 2-methyl-5-phenyloxazole (**III**) and 2-methyl-4-phenyloxazole (**IV**) [28], 5-methyl-2-phenyloxazole (**V**) [29]. Their physical

constants and ^{1}H NMR spectral parameters coincided with those reported in [29]. The AM1 calculations were performed using MOPAC program [30].

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