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PROTOLYTIC PROPERTIES OF CERTAIN ALKYL AND ARYL DERIVATIVES OF IMIDAZOLE

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Acidity constants of certain alkyl and aryl derivatives of imidazole in water and in acetone were determined by an extrapolation method. Certain solvents were evaluated in terms of their leveling or differentiating effect on the acidic properties of the imidazoles.

Imidazoles substituted in position 2 have found extensive applications as catalysts for curing epoxy resins [1-3] and also in the determination of hydroxyl groups in polymers by the phthaloylation method [4, 5].

We can assume that the curing rate of epoxy resins will be determined by the nucleophilicity of the catalyst and that the protonation constants of imidazoles can be regarded as a quantitative characteristic of their nucleophilicity. Since imidazoles are used in reactions that take place in nonaqueous solvents or mixtures, information is needed on their protolytic characteristics in such solvents.

Data on the acidity of imidazoles [6] are limited and somewhat ambiguous. The work reported in the present communication was aimed at investigating the protolytic characteristics of certain imidazole derivatives in water, water/acetone solutions, and nonaqueous solvents.

In this work, we used the following imidazole derivatives: 2-phenyl (I), 2-undecyl (II), 2-heptyl (III), 2-hexyl (IV), 2-ethyl (V), 2-methyl (VI), 2,4-dimethyl (VII), and 2-ethyl-4-methyl (VIII).

Most of the imidazole derivatives are insoluble in water; therefore, we attempted to determine protonation constants by a method based on successive dilution of acetone solutions with water to obtain extrapolation relationships

$$pK_{ai} = aC_a + b,$$

where C_a is the mass fraction of acetone in the water/acetone solution; *a* is the slope of the linear relationship; *b* is the intercept of the extrapolation line on the ordinate axis.

These linear relationships are shown in Fig. 1, and the results of a statistical workup by the least squares method [7] are presented in Table 1. The protonation constants of compounds I, V, and VI for aqueous solutions are in good agreement with values reported in the literature. The refined value of pK_a for the imidazole VII is 7.96 (an approximate value of 8.5 has been reported in the literature).

The acidic properties of the imidazoles in water increase in the following order:

$$\mathrm{VIII < V < VII < IV < III < VI < II < I.}$$

With $C_a = 1$, the values of pK_a obtained from the extrapolation equations are such that this series can be represented as follows:

$$\mathrm{VIII < VI < V < IV < III < VII < II < I.}$$

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TABLE 1. Results of Determinations of Protonation Constants of Imidazoles in Water (n = 5, p = 0.95)

Imidazole	Equation of straight line $pK_i = (a + \Delta a)C_a + (b + \Delta b)$	s_r	pK_a		Literature [6]
			$C_a = 0$	$C_a = 1$	
VI	$(-2{,}07 + 0{,}01)C_a + (7{,}88 + 0{,}05)$	0,015	7,88	5,81	7,85; 8,16
I	$(-2{,}69 + 0{,}08)C_a + (6{,}30 + 0{,}05)$	0,054	6,30	3,61	6,39; 6,48
IV	$(-2{,}37 + 0{,}01)C_a + (7{,}89 + 0{,}07)$	0,20	7,89	5,52	—
III	$(-2{,}73 + 0{,}01)C_a + (7{,}81 + 0{,}01)$	0,005	7,81	5,08	—
II	$(-3{,}00 + 0{,}00)C_a + (7{,}35 + 0{,}00)$	0	7,35	4,35	—
V	$(-2{,}37 + 0{,}02)C_a + (8{,}07 + 0{,}06)$	0,08	8,07	5,70	8,00
VII	$(-2{,}88 + 0{,}02)C_a + (7{,}96 + 0{,}08)$	0,07	7,96	5,08	8,50
VIII	$(-2{,}41 + 0{,}01)C_a + (8{,}50 + 0{,}05)$	0,08	8,50	6,09	—

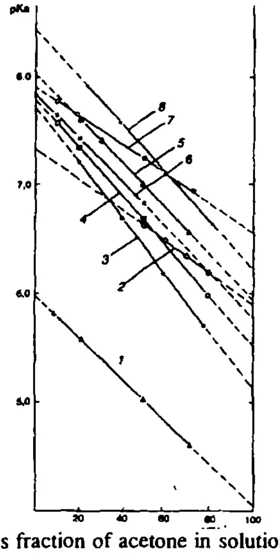

Fig. 1. Value of pK_a of imidazoles as a function of mass fraction of acetone in solution. Identification of imidazoles: *1*) I; *2*) II; *3*) III; *4*) IV; *5*) V; *6*) VI; *7*) VII; *8*) VIII.

The absolute values of pK_a in this series are formal in character; however, the change in order of ranking of the imidazoles can be used to evaluate the solvating effect of acetone. Thus, pK_a for the imidazole VI should increase substantially, and pK_a for VII should decrease, in comparison with pK_a of the other imidazoles in water, the positions of which in these series remain practically unchanged as the transition is made from water to acetone. For the imidazoles I and VI, the differences of the extrapolated values $\Delta pK_a = pK_a(VI) - pK_a(I)$ increase as the change is made from water to acetone; this suggests a greater differentiating effect of acetone on the difference in pK_a values. Referral of ΔpK_a to values of the absolute scales of acidity of water ($K_s = 14$) and acetone ($K_s = 21.4$) [8], 0.259 and 0.123 respectively, leads to the conclusion that the differentiating effect of acetone is reinforced as a result of an increase in the length of the acidity scale of acetone, whereas the acid properties of the imidazole are leveled out, in view of the decrease in the relative magnitude $\Delta pK_a/K_s$.

The slope of the extrapolation relationships can be regarded as a quantitative criterion of the solvating effect of acetone on the length of the acidity scale of the mixed solvent and on the magnitude of the protonation constant of the imidazoles. Despite the formal character of the acidity scale of the imidazoles in acetone, it is obviously in good agreement with the parameters of the mesomeric effect of substituents for 2-substituted imidazoles, whereas in water this correlation breaks down.

In evaluating the acid-base properties of substances in nonaqueous solvents and the leveling/differentiating properties of these solvents, the usual practice is to determine ionization constants by the use of a standard, with a subsequent calculation based on the magnitudes of the half-neutralization potentials, using Henderson's equation [9]. In the work reported here, we used a different approach in which the half-neutralization potentials were determined for two imidazoles having pK_a values in

TABLE 2. Conditions of Potentiometric Titration of Imidazoles I and VI in Nonaqueous Solvents

Solvent	Imidazole	$E_{1/2}$, mV	ΔE, mV	$\Delta E_{1/2}$, mV	ΔpK_a, mV	K_s	$\Delta pK_a/K_s$
Acetone	VI	381,9	208,1	38,1	0,65	21,4	0,030
	I	420,0	170,0				
Diacetone alcohol	VI	268,3	181,7	8,6	0,15	—	—
	I	276,9	173,1				
Acetylacetone	VI	378,4	191,6	8,3	0,14	—	—
	I	386,7	184,0				
Butyl acetate	VI	349,6	270,4	13,5	0,23	23,28	0,010
	I	363,1	256,9				
Ethylene glycol	VI	189,7	91,4	8,9	0,15	15,75	0,010
	I	198,6	100,3				
1,3-Propylene glycol	VI	143,3	166,7	38,4	0,65	16,98	0,040
	I	181,7	128,3				
1,4-Butanediol	VI	123,0	127,0	46,3	0,78	—	—
	I	169,3	80,7				
1-Propanol	VI	184,7	125,3	31,5	0,53	19,45	0,027
	I	216,2	93,8				
1-Butanol	VI	187,8	122,2	38,4	0,65	20,1	0,032
	I	226,2	83,8				
1-Octanol	VI	217,5	122,5	28,5	0,48	18,68	0,026
	I	246,0	94,0				
Benzyl alcohol	VI	220,5	109,5	2,7	0,05	—	—
	I	223,2	106,8				
2-Propanol	VI	183,0	137,0	40,6	0,69	20,8	0,033
	I	223,6	76,4				
2-Butanol	VI	150,9	109,1	35,8	0,61	18,8	0,032
	I	186,7	73,3				
Isoamyl alcohol	VI	192,6	67,4	31,4	0,53	—	—
	I	224,0	36,0				
Acetonitrile	VI	277,0	343,0	113,4	1,92	33,3	0,058
	I	390,4	229,6				
DMF	VI	98,9	151,1	53,8	0,91	23,1	0,039
	I	152,7	97,3				
DMSO	VI	30,6	149,4	63,8	1,08	33,3	0,032
	I	94,4	85,6				
THF	VI	266,6	183,4	62,0	1,05	—	—
	I	328,6	121,4				
Chlorobenzene	VI	327,3	272,2	88,5	1,50	—	—
	I	415,8	184,2				
Water	VI	86,9	199,8	86,9	1,55	14,0	0,111
	I	0	156,4				

water that differed substantially - for example, the imidazoles I and VI. Henderson's equation can be written in the form

$$pK_a(I) = pH_{st} + \frac{E_{1/2}(I) - E_{1/2\ st}}{0.059}\ ;\ pK_a(VI) = pH_{st} + \frac{E_{1/2}(VI) - E_{1/2\ st}}{0.059}.$$

Then, $\Delta pK_a = pK_a(VI) - pK_a(I) = E_{1/2} - E_{1/2}\ (I)/0.059$.*

The magnitude of ΔpK_a as determined on the basis of the half-neutralization potential is a quantitative characteristic of the leveling/differentiating effect of a nonaqueous solvent on acid-base properties. Referral of ΔpK_a to the absolute value of K_s for this particular solvent can serve as a characteristic of the leveling/differentiating effect of this solvent in comparison with others.

We carried out potentiometric titrations of the imidazoles I and VI in various solvents (Table 2). Half-neutralization potentials were determined, as well as values of the potential interval (ΔE), representing the difference between the system

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*As in Russian original; it appears that the numerator should be $E_{1/2}(VI) - E_{1/2}(I)$ — Translator.

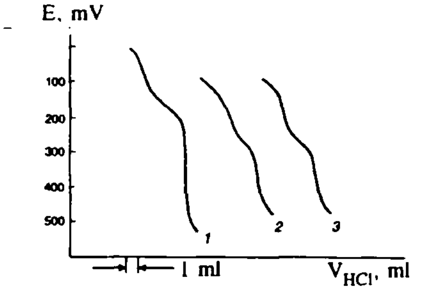

Fig. 2

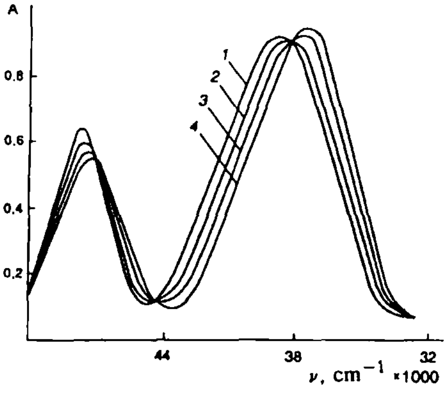

Fig. 3

Fig. 2. Potentiometric titration curves for imidazole pairs: 1) I + VI in acetonitrile; *2*) I + VI in THF; *3*) I + VIII in THF.

Fig. 3. Spectrophotometric titration of imidazole I in acetonitrile (C = 0.0008 g in 60 ml); pH: *1*) 1.32; *2*) 1.92; *3*) 2.87; *4*) 3.96.

potential with 100% excess of the titrant and the half-neutralization potential. In comparing the differentiating capabilities of the various solvents, we used calculated values of $\Delta pK_a/K_s$.

From an analysis of the data of Table 2, we can conclude that water has the maximum differentiating effect with respect to the imidazoles, even though acetonitrile gives the greatest difference of half-neutralization potentials. In any event, acetonitrile is the most suitable solvent for differential titration of the imidazoles, since they are all more soluble in acetonitrile than in water, and the potential jump is sufficiently large to fix the point of equivalence with rather high accuracy.

When using ketones for the titration, solvents that are susceptible to keto–enol tautomerism should be avoided, as this levels out the acidity of the imidazoles. Of the glycol solvents, 1,4-butanediol gives the greatest differentiating effect. Titration in straight-chain alcohols shows that the differentiating capability is not clearly related to the molecular weight of the alcohol, while for secondary alcohols, in contrast, the differentiating effect decreases with increasing molecular weight.

Since the values of pK_a and hence also $\Delta E_{1/2}$ must be constants for a given pair of imidazoles, these values can be used to identify substances by means of potentiometric titrations. In Fig. 2 we show potentiometric titration curves for certain imidazole pairs (alkyl- and aryl-substituted); the imidazole pairs with aliphatic substituents are not titrated separately.

In order to evaluate the feasibility of determining the acidity constants of imidazoles, we carried out spectrophotometric titrations of the imidazoles in water. It was established that the greatest hypsochromic shift of the absorption bands as a result of protonation is observed for the imidazole I. The spectra are reversible as the pH is changed. The values obtained, $pK_a(I) = 6.36$ and $pK_a(VI) = 7.81$, are in good agreement with the results from the potentiometric determinations.

In Fig. 3 we show the spectrophotometric titration curve for the imidazole I, which was selected as a standard for determination of the acidity constants of compound VI in acetonitrile. From the data of the spectrophotometric and potentiometric titrations, we determined $pK_a(I) = 2.89$, calculated by the Henderson equation $pK_a(VI) = 4.81$.

EXPERIMENTAL

The imidazoles I-VIII used in this work were synthesized at the Institute of Organic Chemistry of the Russian Academy of Sciences, using the method described in [10, 11]. The solvents were chemically pure or analytically pure grade. The titrant was a 0.1 M solution of HCl in water (from Fixanal). The pH measurements and the potentiometric titrations were performed in a Mettler DL 40 RC apparatus with glass and calomel electrodes. For titrations of water and water–acetone solutions, the calomel electrode was filled with an aqueous saturated KCl solution; for titrations in nonaqueous solutions, the salt solution was prepared in methanol. The acidity constants in the water and water–acetone solutions were determined by a procedure given in [12]. The imidazole sample (about 0.05 μmole) was dissolved in 60 ml of solvent and titrated with a 0.1 M solution of acid, with a maximum titrant consumption of 2 ml (increment 0.05 ml). The spectrophotometric titrations were performed on a Specord UV-Vis instrument in a 1-cm cuvette on a background of pure solvent, with simultaneous recording of the solution pH. The imidazole concentrations were 0.1-0.12 μmole/liter. The 0.1 M titrant solutions were introduced by means of a microsyringe.

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