

AMPHOTERIC CHARACTER OF 1-PHENYL-3-METHYLPYRAZOLIN-5-ONES

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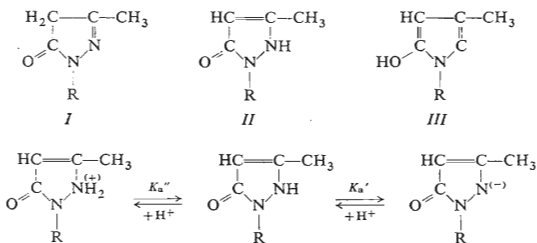
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Twelve 3'- or 4'-substituted 1-phenyl-3-methylpyrazolin-5-ones have been prepared and their ionization properties measured and correlated with substituent constants. The constants of dissociation of the proton from the neutral molecule as well as the equilibrium constants of the proton addition and that of the dissociation of the monoprotonated form have been ascertained in 20% ethanol (by vol.). No influence of prototropic tautomerism has been observed. The influence of substituents in the series studied is practically the same as with aromatic carboxylic acids. From the measurements carried out it follows that, in a definite range of H_2SO_4 concentrations (0.01—1 mol/l), the acidity function value equals the acid concentration.

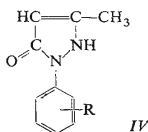
Measuring the IR, UV and NMR spectra and pK_a of protonation of 1-phenyl-3-methylpyrazolin-5-ones, Katritzky and Maine¹ found recently that this compound can be present in three tautomeric forms *I*—*III* ($R = C_6H_5$). In aqueous ethanolic solutions the form *II* predominates, the forms *I* and *III* being present in small quantities only.

Pyrazolin-5-ones, being ampholytes, can both accept the proton in acid medium and split off the proton in more basic medium. The acid-base equilibria can be described by Scheme 1. According to the literature cited we presume the predominant existence of the form *II* in this Scheme. Ionization constants of neutral or protonated forms of several industrially important pyrazolin-5-ones of the type *IV* were measured in aqueous solutions event. in other usual solvents²⁻⁵.



SCHEME 1

From the papers available no general conclusion can, however, be drawn as for the influence of tautomeric equilibria (which are considerably complex in this system) or the influence of substituents of 1-phenyl group of pyrazolone ring on the ionization constants of the both types.



At the present time, the relations between basicity and acidity of amphoteric compounds attract much attention. The both properties are a function of electron densities on the respective reaction centres and a well established relation should exist between them as far as these centres are influenced by substituent according to the same mechanism, and as far as no deforming influence of other factors (*e.g.* tautomerism) makes itself felt. Papers of this kind are seldom found in literature^{6,7}. The aim of the present work was to determine the ionization constants K_a^I and K_a^{II} of pyrazolin-5-ones IV, to find a relation between them, and to judge an eventual influence of tautomerism.

EXPERIMENTAL

Preparation of Pyrazolin-5-ones

All the twelve 1-phenyl-3-methylpyrazolin-5-ones were prepared from the respective substituted hydrazines and ethyl acetoacetate by known methods⁸⁻¹⁹. The compounds were recrystallized from ethanol or water until constant melting point (Table I).

pK_a Determination

The measurements were carried out in 20% (by vol.) ethanol with respect to a poor solubility of some derivatives.

Potentiometric titration. The pyrazolinones well soluble in aqueous ethanolic solution ($R = H, 4'-CN, 4'-OCH_3, 4'-CH_3, 3'-CH_3, 3'-Cl, 4'-NH_2$) were titrated directly with 0.01M aqueous KOH (free of carbonates). In all the cases 97% ethanol was used. The solutions of pyrazolin-5-ones were prepared in such a way that their final concentration was $5 \cdot 10^{-3}$ mol/l, and alcohol concentration in solution was 20% (by vol.). The remaining pyrazolin-5-ones ($R = 4'-CO_2CH_3, 3'-NO_2, 4'-Cl, 4'-Br, 4'-NO_2$) were dissolved in ethanolic (20%) solution 0.01M-KOH, and the solutions were titrated with 0.1M-HCl. As the consumption of the titration reagent was small, the change of alcohol concentration was neglected. pH Values were measured with a Research pH-meter (Beckmann) using a glass G 222 B and a saturated calomel K 401 electrodes (Radiometer). The mean pK_a values were computed from nine measurement results obtained according to Eq. (1).

$$pK_a^I = pH \pm \log ((N - A)/A). \quad (1)$$

N and A are the volumes of the titration reagent added at the equivalence point and at definite pH value, respectively. In the case of retitration the first equivalence point was taken as the beginning (strong base). Due to low solubilities, the concentration of 4'-bromo and 4'-nitro derivatives was lowered to $2.5 \cdot 10^{-3}$ and $1 \cdot 10^{-3}$ mol/l, respectively.

Spectrophotometric determination. The spectral measurements were carried out first with the use of a Unicam SP 800 apparatus (the choice of analytical wavelength and calculation of approximate pK_a^{II} value), precise values of constants were obtained with the use of a Zeiss VSU-1 spectrophotometer at $20 \pm 0.1^\circ\text{C}$ from seven values in such a way that $\log \left(\frac{[BH^+]}{[B]} \right)$ equaled ± 1 . Analytical concentration of the pyrazolin-5-ones was 10^{-4} mol/l in the solutions studied, the solvent mixtures (20% (by vol.) ethanol - H_2SO_4 - H_2O) having definite H_2SO_4 concentrations. Spectra of neutral molecules and of protonated form of pyrazolin-5-ones were determined in the abovementioned mixtures too: 35% and 40% (by wt.) sulphuric acid concentrations were used for the protonated molecule, and 10^{-4}M solution was used for neutral molecule. In both the cases it was ascertained that the spectra did not further change. The following experiment was carried out to prove the stability of pyrazolin-5-ones in acid medium: The stock solution prepared from 20.8 ml ethanolic pyrazolin-5-one solution and 29.2 ml 96–98% H_2SO_4 had the total pyrazolin-5-one concentration doubled as compared to the samples measured before. 25 ml of the stock solution was diluted with distilled water, the final volume and sulphuric acid concentration being 50 ml and about 40%, respectively. The second sample was prepared from 25 ml of the original stock solution left to stand at the room temperature 24 hours, and then adjusted at 50 ml with redistilled water. The spectra obtained were completely identical with those of freshly prepared solutions in 40, 45 and 50% H_2SO_4 . In all the spectrophotometric measurements the reference solutions were prepared in the same way and had the same composition, pyrazolin-5-ones being absent only. The measurements and calculations were carried out on the basis of Eq. (2) where

TABLE I

pK_a^I and pK_a^{II} Values of Substituted 1-Phenyl-3-methylpyrazolin-5-ones of the Type IV
20% (by vol.) ethanol at 20°C , 3-nitroaniline pK_a^{II} 2.29 (s 0.05, λ_{anna} 230 nm).

Compound	R	M.p., $^\circ\text{C}$	pK_a^I	s^a	pK_a^{II}	s^a	λ_{anna}^b , nm
1	4'-NH ₂	162.5–163	7.89	0.05	0.98	0.03	270
2	4'-OCH ₃	138	7.63	0.03	0.02	0.09	270
3	4'-CH ₃	137	7.45	0.04	1.80	0.01	270
4	3'-CH ₃	113	7.39	0.02	1.70	0.01	270
5	H	128–129	7.39	0.02	1.37	0.04	275
6	4'-Br	175	6.94	0.02	1.34	0.03	275
7	4'-Cl	168	7.03	0.02	1.37	0.04	275
8	3'-Cl	131	6.95	0.06	1.27	0.02	270
9	4'-COOCH ₃	162–163	6.81	0.01	1.02	0.01	290
10	4'-CN	172	6.94	0.01	0.80	0.04	290
11	3'-NO ₂	184–185	6.74	0.03	0.82	0.03	270
12	4'-NO ₂	222–223	6.65	0.02	0.68	0.06	335

^a Standard deviation. ^b For pK_a^{II} determination.

$C_{\text{H}_2\text{SO}_4}$ is the known sulphuric acid concentration in mol/l, and C_{B} and C_{BH^+} are the concentrations of unprotonated and protonated forms of pyrazolin-5-one (mol/l) in the equilibrium mixture, respectively.

$$K_{\text{a}}^{\text{II}} = C_{\text{H}_2\text{SO}_4} C_{\text{B}} / C_{\text{BH}^+} \quad (2)$$

For spectrophotometric measurements, the Eq. (2) was transformed into logarithmic form (3), where E_{B} and E_{BH^+} are the extinctions of the respective forms of pyrazolin-5-ones, and E is the extinction of the equilibrium mixture.

$$pK_{\text{a}}^{\text{II}} = -\log C_{\text{H}_2\text{SO}_4} + \log [(E_{\text{B}} - E)/(E - E_{\text{BH}^+})] \quad (3)$$

This procedure of measurement necessitates that the pyrazolin-5-ones studied are simple Hammett indicators which means that the ratios of activity coefficients in the solutions mentioned are the same for all the compounds. This condition is fulfilled, as the angular coefficients of the dependences of indicator ratios of the compounds studied are identical with each other and with the angular coefficient of this dependence of *m*-nitroaniline (Table II). From the results of measurements it follows that $\log C_{\text{H}_2\text{SO}_4}$ can be considered equal $-H_0$ in the sulphuric acid concentration range used in 20% (by vol.) ethanol. This could be expected with respect to dissociation of sulphuric acid being complete at low concentrations. The results of measurements are summarized in Table I. In H_2SO_4 concentration data no correction was introduced for the acid decrease caused by protonation of pyrazolinones, because the concentration of pyrazolines (10^{-4} mol/l) was low as compared to acid concentration (10^{-2} — 1 mol/l).

TABLE II
Numerical Values of Hammett Indicator Diagrams^a

Compound	Angular coefficient	<i>s</i>	<i>r</i>	Compound	Angular coefficient	<i>s</i>	<i>r</i>
1	0.926	0.012	0.999	7	0.986	0.029	0.998
2	1.079	0.116	0.982	8	0.894	0.022	0.998
3	0.854	0.043	0.991	9	0.944	0.024	0.998
4	0.928	0.025	0.998	10	0.872	0.063	0.987
5	0.876	0.024	0.998	11	0.973	0.043	0.995
6	0.965	0.026	0.998	12	0.893	0.058	0.990

^a For 3-nitroaniline the angular coefficient is 0.915, *s* = 0.033 and *r* = 0.997.

RESULTS AND DISCUSSION

The compound series studied have electronic spectra different from the usual shape of spectra of benzene derivatives. In the spectra, only two absorption bands are developed, *viz.* at 200–250 nm and at 240–250 nm. The third absorption band usually found with aromatic compounds is superposed by the second band here and

results in a not very marked inflex in the range about 270 nm. This band shifts by the influence of substituents to higher wavelengths so that it is better developed. During measurements in alkaline medium where the anion is present only (Scheme 1), the picture of spectrum is only slightly different from the spectrum of neutral form. A sufficiently accurate determination of pK values⁹ by spectrophotometric method was thus impossible. More substantial changes occur on transition from neutral to acid region due to the proton addition. The long-wave band gradually disappears, and, at the same time, the intensity of the second absorption maximum increases which suggests a decrease of the conjugation extent in the molecule.

With respect to the different spectral behaviour of the compounds studied in the region of acid and basic dissociation, the measurements of pK_a^I and pK_a^{II} were carried out by potentiometric titration and spectrophotometrically, respectively. As for the differentiation between the individual types of constants, *i.e.* solution of the question whether the identical mixed or concentration constants are operating in the both cases, we incline to believe (as many authors do, *e.g.*²⁰) that their values are identical at concentrations lower than 0.01 mol/l. If we also take into account that the species studied are monoacid acids or bases in ethanolic solutions, we can consider the results of measurements to be comparable and the results obtained to be ionization constants of mixed type (non-aqueous medium). The index a of the constants given only denotes the fact that the ionization of the respective acid or conjugate acid is meant. Table II presents the values of angular coefficients of the dependence of $\log ([BH^+]/[B])$ on sulphuric acid concentration calculated by the least squares method. Most of the compounds studied can be considered to be indicators fulfilling the Hammett conditions within experimental error. The lower value of angular coefficient of the reference indicator (*m*-nitroaniline) as well as of the compounds studied is caused by the presence of ethanol.

In the both series of ionization constants linear dependences on the Hammett σ constants²¹ can be seen (Figs 1 and 2), and the straight lines obtained correspond to Eq. (4) and (5), the correlation coefficients being -0.977 and -0.993 for $n = 12$ and 11, respectively.

$$pK_a^I = (-0.953 \pm 0.066)\sigma + (7.296 \pm 0.097), \quad (4)$$

$$pK_a^{II} = (-1.216 \pm 0.049)\sigma + (1.648 \pm 0.022). \quad (5)$$

The pK_a^{II} value of 4'-amino derivative was not included in the correlation of pK_a^{II} with σ constants, because this value deviates from the whole series markedly (Fig. 2) which can be explained by the fact that, in the acid region, the system is once protonated at the amino group already, and the $\sigma_p(NH_3^+)$ values should be used for the regression.

Fig. 3 presents the mutual dependence of ionization constants. The straight line corresponds to Eq. (6)

$$pK_a^{II} = (0.804 \pm 0.061) pK_a^I + (5.980 \pm 0.085). \quad (6)$$

(correlation coefficient 0.969 for $n = 11$) which was obtained by the least squares method excluding the pK_a of 4'-amino derivative again. This relation only confirms the linearity of the relations (4) and (5), and as the latter differ in their slopes, the slope of the former cannot be unity either. The both series of ionization constants show thus roughly the same dependence on the influence of substitution which is comparatively small. This stands in accord with the fact that the influence of substi-

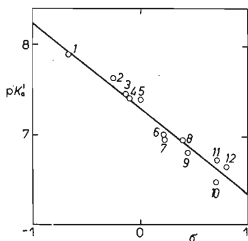


FIG. 1

Dependence of pK_a^I of Dissociation of Substituted 1-Phenyl-3-methylpyrazolin-5-ones on σ Constants in 20% (by Vol.) Ethanol
For numbers see Table I.

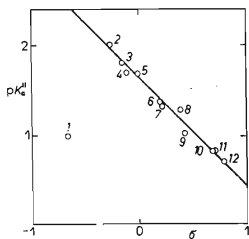
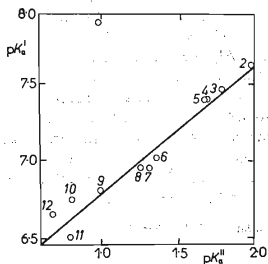


FIG. 2

Dependence of pK_a^{II} of Dissociation of Substituted 1-Phenyl-3-methylpyrazolin-5-ones on σ Constants in 20% (by Vol.) Ethanol
For numbers see Table I.

FIG. 3
Mutual Dependence of Ionization Constants of Substituted 1-Phenyl-3-methylpyrazolin-5-ones in 20% (by Vol.) Ethanol
For numbers see Table I.



tents is transferred through aromatic nucleus into pyrazolone ring, *i.e.* at a greater distance than if the reaction centre were located in the nucleus itself.

The small changes in spectra during dissociation according to Scheme 1 and the low value of reaction constant (-0.953) prove that the ionization process really follows the abovementioned Scheme in the medium used, and that the compounds studied behave practically in the same way as the corresponding carboxylic acids.

The reaction constant (-1.216) of the protonation equilibrium according to Scheme 1 and simultaneous changes in spectra (the hypsochromic shift of the main absorption band), too, suggest that the proton addition takes place at the same centre as the splitting off of the proton (see Scheme 1). With respect to the good linearity of relations between ionization and substituent constants, it can be assumed that tautomerism of the neutral molecule does not make itself felt to a substantial extent during ionization of pyrazolin-5-ones in the medium used. *I.e.* either the substituents affect the position of the tautomeric equilibrium in the same way as they affect the dissociation, or there is only one of the two possible tautomeric forms present predominantly. The results obtained do not, however, allow us to decide which of those cases takes place. We are going to deal with this problem of tautomerism later on.

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