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RESEARCHES ON PYRAZOLES

LV. Dissociation Constant of Isomeric Hydroxy-, Amino-, and Carboxy-1-phenylpyrazoles Substituted in the Pyrazole Ring*

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The dissociation constants (pK_a) of isomeric hydroxy, amino, and carboxy substituted 1-phenylpyrazoles are determined. From the results certain conclusions are drawn regarding the distribution of electron density in the 1-phenylpyrazole ring, and regarding the effect (ortho effect) of substituents at position 5 on the basicities and acidities of these compounds.

As an approach to the problem of different reactivities of substituents at different positions in the pyrazole ring, it was decided to measure the dissociation constants of 1-phenylpyrazoles with hydroxyl, amino, and carboxyl groups at positions 3, 4, and 5 in the pyrazole ring. By comparing these values it should be possible to determine how the effect of the ring on a substituent depends on the position of the latter.

The literature [1] contains data on the relationship of pK_a values in non-aqueous solvents and extrapolated to pK_a in water. So we determined pK_a values in aqueous ethanol for diminishing ethanol concentrations, over the range 50-0% at 10% intervals, whenever possible (compound soluble enough in water). This kind of variation gave many points, and the reliability of extrapolation increased. The experimental gives the titration method and the computing formulas. The pK_a values obtained are given in the table. It should be mentioned straight away that in our case too the inadequacy of the method of extrapolation for determining pK_a in water–ethanol solutions was confirmed. Thus with 1-phenyl-3-aminopyrazole (see table), the value of pK_a decreases when the ethanol concentration is cut from 50 to 20%, and then rapidly increases to the initial value when ethanol is absent. With 1-phenyl-4-aminopyrazole, pK_a steadily increases with decrease in ethanol concentration, while pK_a for the two 5-aminopyrazoles is unaltered with change in ethanol concentration. The table also gives changes in pK_a for some hydroxypyrazoles and pyrazole carboxylic acids.

pK_a Values of 1-Phenyl-X-Substituted Pyrazoles in Water-Ethanol Solutions

Substituent	% ethanol concentration in water-ethanol solution						Reference
	50	40	30	20	10	0	
3—NH_2*	2.97	2.71	2.54	2.50	2.59	2.96±0.04	12
4—NH_2*	4.38	4.44	4.49	4.54	4.60	4.80±0.07	13
5—NH_2*	3.11	3.12	3.14	3.14	3.14	3.14±0.05**	14
3—CH_3; 5—NH_2*	3.91	3.91	3.92	—	3.93	3.95±0.05	15
3—OH	—	—	8.28	3.93	7.79	7.57±0.04	12
4—OH	10.20	9.88	9.50	9.21	9.05	9.05±0.06	17
5—OH	—	—	—	—	—	6.56±0.04	18
3—CH_3; 5—OH	—	—	—	—	—	7.16±0.05	
3—COOH	—	—	—	—	—	3.60±0.08	16
4—COOH	5.60***	—	—	—	—	4.40—4.80****	16
5—COOH	—	—	3.39	—	2.80	2.70±0.06	19
1—C_5H_{11}; 3—CH_3; 5—NH_2	—	—	—	—	—	4.83±0.07	16

* pK_a for conjugated acid.

** Result of graphical extrapolation from 5 previous values, compound insoluble in water.

*** Result of graphical extrapolation, see Fig. 1.

**** Result approximately calculated assuming that pK_a varies regularly with the concentration in the same way as 4-hydroxypyrazole or the 3-carboxylic acid.

With 1-phenylpyrazole-4-carboxylic acid in 50% ethanol, our 8 pH measurements at constant neutralization gave different pK_a values, which fell regularly: 5.32, 5.20, 5.17, 5.07, 5.06, 4.91, 4.80 and 4.71. It is known [1] that

*For Part LIV see [19].

such results obtain when the ionic strength of a solution (steadily increasing) markedly affects the acidity of a compound. In such cases a correction for the ionic strength must be introduced, and the equation for calculation pK_a has the form [1]:

$$pK_aT = pH + \log \frac{[AH]}{[A^-] \cdot f_{\pm}^{1:1}} = pH + \log \frac{[AH]}{[A^-]} - \log f_{\pm}^{1:1},$$

where $f_{\pm}^{1:1}$ = mean activity coefficient of an ion in the electrolyte ($RCOO^-$ Na^+) and pk_a^T = thermodynamic dissociation constant.

The same equation in the form $pK_a^T = pK_a - \log f_{\pm}^{1:1}$ is manifestly linear. For dilute solutions the Debye-Huckel equation gives $\log f_{\pm}^{1:1} = A\sqrt{I}$, where I is the ionic strength, and A a constant depending on solvent and temperature. Extrapolation of the graph equation $pK_a^T = pK_a - A\sqrt{I}$ gives pK_a^T 5.60 (Fig. 1) for I = 0 in 50% ethanol.

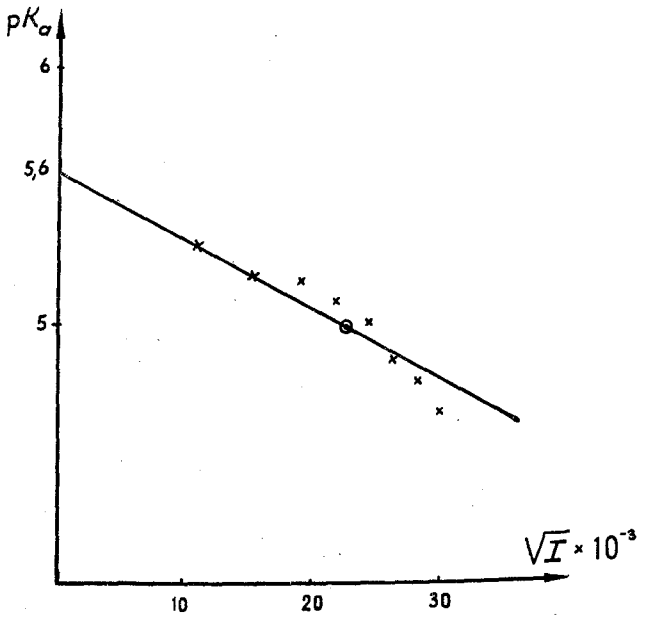
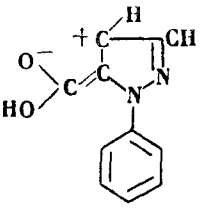


Fig. 1. Effect of ionic strength of the solution on pK_a of 1-phenyl-pyrazole-4-carboxylic acid.

All our further discussions assume that in aqueous medium too all aminopyrazoles, as well as 4- and 3-hydroxypyrazoles, exist as amino and hydroxy forms, and not as imino and oxo ones, as was previously shown [7] for other solvents by means of IR spectroscopy.

Carboxylic acids. It is known that position 4 in the pyrazole ring has a considerably higher electron density than positions 3 and 5 [3]. Since generally the reactivities of the various positions in 1-phenylpyrazole do not differ from the same ones in pyrazole itself, evidently the ratio of electron densities at positions 4 and 3 (or 5) is generally maintained in the former. The considerably greater +I effect of the pyrazole ring in 1-phenyl-4-carboxylic acid must have led to the decrease in its acidic properties in comparison with 3- and 5-carboxylic acids. When comparing acidities of 3- and 5-carboxylic acids it is necessary to take into account the ortho effect of the phenyl substituent at position 1 in 1-phenyl-5-carboxylic acid. In a previous paper we have [4] already considered the converse effect of carboxyl on phenyl, and there the existence of an ortho effect was shown spectroscopically. The presence of an ortho substituent (phenyl) in pyrazole-5-carboxylic acid leads to hindering of resonance in the free acid (+T effect of the aromatic ring decreases the acidity of the carboxyl linked to it), and increases its acidity. This factor (operating in the opposite direction) has a lower value for anions, due to the already existing negative charge on the carboxyl. Hence the 5-carboxylic acid must behave as a stronger acid than the 3 one. Actually, as is evident from the table, the acids from the series 4 < 3 < 5, in order of increasing acidity.



Hydroxypyrazoles. Applying the reasoning used for the pyrazolecarboxylic acids to the phenol-like 1-phenyl-X-hydroxypyrazoles, we arrive at the conclusion that 1-phenyl-4-hydroxypyrazole must have lessened acidic properties (+I effect of the ring) in comparison with the 3 and 5 isomers. Despite Hammond's remark about the insignificance of the spatial requirements of a proton, obviously what determines the comparative acidity of the 3 and 5 isomers is precisely that. The 5-hydroxypyrazole molecule's striving for coplanarity ejects a proton; the somewhat lessened volume of the oxygen anion allows the molecule to partly stabilize itself, and its affinity for proton-acceptance is lessened. Hence the series obtained for the acid, 4 < 3 < 5, is conserved. It is quite interesting that with the assistance of this concept of the ortho effect, it is possible to explain the ability of 5-hydropyrazoles to undergo keto-enol tautomerism (unlike 4- and 3-hydroxypyrazoles), something previously investigated by one of the present authors using IR spectroscopy [7]. On account of the ortho effect (Fig. 2), ketonization of 3-hydroxypyrazole had to be ascribed to partial drawing of the benzene ring from the plane of the pyrazole one, which naturally decreased stabilization of the molecule because of decreased conjugation, and hence has energetic disadvantages.

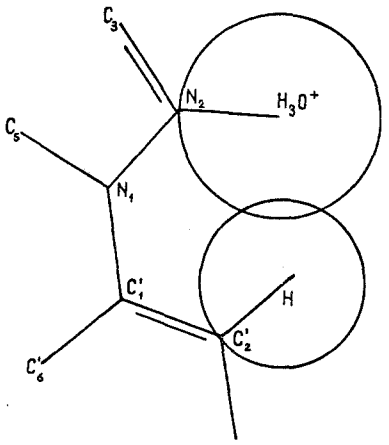
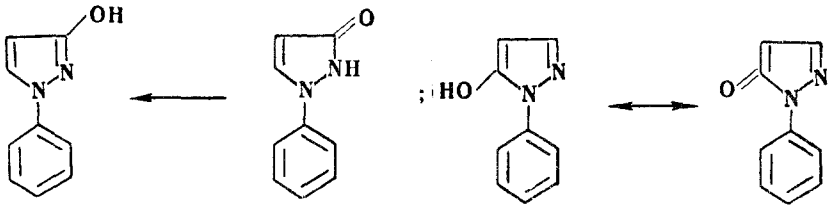


Fig. 2. Geometric model of protonated 1-phenylpyrazole. See paper of [4] for calculation of bond lengths and valence angles. Van der Waal's radius of H_3O^+ 1.40 Å [9].

On the other hand, with 1-phenyl-5-hydroxypyrazole, ketonization leads to disappearance of steric hindrance between the planes of the two rings, stabilization is enhanced, and tautomeric displacement is possible (see the geometric model in [4]).



Aminopyrazoles. Due to the maximum +I effect of the pyrazole ring, 4-aminopyrazole will naturally have maximum basic properties. Comparing the basicities of the 3 and 5 isomers it is seen that for the 5-isomer the ortho effect raises the basicity evidently not only because of the benzene ring's being drawn out of coplanarity (decrease in the conjugation of the system), but also because the amino group is partly drawn out of coplanarity. This can serve as an explanation for the increase in basic properties of the aminopyrazoles: 4 > 5 > 3.

The phenyl substituent lowers the basicity of the amino group in the pyrazole ring because of the conjugation effect. This can be seen from the fact that 1-amyl-3-methyl-5-aminopyrazole has pK_a (in water) 4.83, while the similar compound with a phenyl group at position 1 has pK_a 3.95. Since the steric needs of the alkyl group are close to those of phenyl [6], this increase in basicity is obviously mainly determined by the absence of the conjugation effect of benzene and pyrazole rings. This fact confirms the possibility of increasing basicity by drawing the benzene ring from coplanarity. The ortho effect may also be explained by the known fact [8], that 1-phenylpyrazoles are much less basic than 1-alkylpyrazoles. Actually, protonation at the nitrogen atom in position 2 requires partial drawing of the phenyl group from coplanarity with the pyrazole ring (Fig. 2), and so is hindered.

Experimental

All compounds were purified by repeated recrystallization until they were chromatographically pure [10, 11]. Their constants agreed completely with those given in the literature. The table gives references to the papers followed in synthesizing the compounds.

pH values were determined at 20° under N_2, using a glass electrode and a LP-58 potentiometer. All substances were titrated with 10 portions of titrant until quite neutral [1], at concentration 0.0025 M, with the exception of

1-phenyl-4-carboxylic acid which (because of its low solubility) was titrated at 0.001 M concentration. For amines the titrant was HCl, 0.005 N, for acids and pyrazolones, NaOH, 0.05 N. The following formulas were used to calculate pK_a:

$$pK_a = \mathrm{pH} + \log \frac{[BH^+] - [H^+]}{[B] + [H^+]}$$

for amines (titrated with acid) and

$$pK_a = \mathrm{pH} + \log \frac{[AH] - [H^+]}{[A^-] + [H^+]}$$

for pyrazolones and acids (titrated with alkali).

The following simplified formula was used for 1-phenylpyrazole-4-carboxylic acid, 1-phenyl-3-hydroxy- and 1-phenyl-5-hydroxy-pyrazoles, whose pH values during titration lay in the range 4-10:

$$pK_a = \mathrm{pH} + \log \frac{[AH]}{[A^-]}.$$

For 1-phenyl-4-hydroxypyrazole (pH 8-11), the following formula was used:

$$pK_a = \mathrm{pH} + \log \frac{[AH] + [OH^-]}{[A^-] - [OH^-]}.$$

The $[H^+]$ and $[OH^-]$ values in these formulas were calculated from the measured pH values.

Each value was the average of 8-9 measurements at different degrees of neutralization [1].

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