A Study on Protonation Equilibria in a Series of Amino-1-(substituted phenyl)pyrazoles

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Received March 3, 1989

The ionization constants (proton gain) of 3-,4-, and 5-amino-1-(substituted phenyl)pyrazoles, have been measured in 10% v/v ethanol-water. p*K*a values show a good linear dependence on Hammett substituent constants. The reaction constants ϱ are in keeping with the respective protonation sites in the three series of monocations. The uv spectra of 1-(*m*-nitrophenyl)pyrazole and 1-(*p*-methoxyphenyl)pyrazole and of their 3-amino, 4-amino, 5-amino analogues recorded in acidic and neutral media, show that in the three series the first protonation site does not change with change in substituent at phenyl ring.

J. Heterocyclic Chem., **26**, 1515 (1989).

Introduction

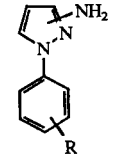
The physico-chemical characterization of the intermediate basic amines is an important step in the structure-activity studies on sulfonamides. In fact it has been shown that it is possible to predict *in vitro* activity of sulfa drugs using molecular descriptors of these precursors [1]. In a previous paper [2] we reported on the protonation sites in the three derivatives 3-amino-1-phenylpyrazole (**1a**), 4-amino-1-phenylpyrazole (**1b**) and 5-amino-1-phenylpyrazole (**1c**). Phenyl-substituted of these compounds were used by Alberti and co-workers to prepare pyrazole sulfonamides [3]. In this work in order to have additional confirms of our findings we discuss on the results of a study of the ionization reaction susceptibility (proton gain) to the influence of the substituents in the series **a, b, c**. The uv spectra of **1a, 1b, 1c**, and of their meta-nitro and para-methoxy analogues, recorded in acidic and neutral media, are also discussed in the light of the problem of the protnation sites.

Results and Discussion

All N-1 substituted aminopyrazoles could potentially exist in equilibrium with the tautomeric imino forms. It has been shown that the amino structures are strongly predominant [4].

The series of compounds studied in the present work were designed in order to have a large spread in the Hammett σ constants of the R substituents on the phenyl ring.

Scheme 1



a, 3-NH_2
b, 4-NH_2
c, 5-NH_2

a,b,c	R
1	H
2	*m*-CH_3
3	*p*-CH_3
4	*m*-OCH_3
5	*p*-OCH_3
6	*m*-Cl
7	*p*-Cl
8	*m*-NO_2
9	*p*-NO_2

The results of the p*K*a measurements are reported in Table 1.

Table 1
p*K*a Values for 3-Amino, 4-Amino and 5-Amino-1-(substituted phenyl) pyrazoles in 10% v/v Ethanol-water

R	σ[a]	p*K*a 3-NH_2	p*K*a 4-NH_2	p*K*a 5-NH_2
p-OCH_3	-0.268	2.82 (±0.01)	4.73 (±0.01)	3.42 (±0.01)
p-CH_3	-0.170	2.76 (±0.01)	4.68 (±0.02)	3.38 (±0.01)
m-CH_3	-0.069	2.69 (±0.01)	4.61 (±0.01)	3.30 (±0.02)
H	0	2.66 (±0.01)	4.60 (±0.01)	3.23 (±0.02)
m-OCH_3	+0.115	2.55 (±0.01)	4.56 (±0.02)	3.09 (±0.02)
p-Cl	+0.227	2.52 (±0.01)	4.49 (±0.02)	2.92 (±0.03)
m-Cl	+0.373	2.44 (±0.02)	4.43 (±0.01)	2.79 (±0.01)
m-NO_2	+0.710	2.17 (±0.01)	4.21 (±0.02)	2.34 (±0.03)
p-NO_2	+0.778	1.93 (±0.02) [b]	4.10 (±0.04) [b]	2.11 (±0.05) [b]

[a] Values selected by McDaniel and Brown [11].
[b] Values obtained by spectrophotometric measurements.

The order of decreasing basicity in the three series, the substituent of the phenyl ring being equal, is **b > > c > a**. This trend is in keeping with previous measurements by Tabak and co-workers [5] of the p*K*a values of **1a, 1b, 1c** in water-alcohol mixtures with diminishing concentrations of alcohol from 50% to 10%. The p*K*a's in water, resulting from extrapolation of these data, are in order **1b > > 1c ≥ 1a**. The p*K*a values of Table 1 show, in the three series of amines, a good linear dependence on Hammett substituent constants. The equations I, II, III, obtained using the method of least squares are reported in Table 2.

For the three *para*-nitro derivatives the residuals always have the same sign and are nearly twice the standard error of the estimates. The reason of this deviation - for which also a dependence on the different analytical method used

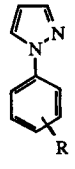
Table 2
p*Ka* *vs* σ Correlations of the Three Series of Amino Derivatives **a**, **b**, **c**

Series a: 3-amino derivatives	n	s	r
Eq. I p*Ka* = -0.76 (±0.06) σ + 2.65 (±0.02)	9	0.06	0.978
Eq. I' p*Ka* = -0.65 (±0.03) σ + 2.65 (±0.01)	8	0.02	0.996 [a]
Series b: 4-amino derivatives			
Eq. II p*Ka* = -0.565 (±0.03) σ + 4.60 (±0.01)	9	0.03	0.989
Eq. II' p*Ka* = -0.51 (±0.02) σ + 4.60 (±0.01)	8	0.02	0.994 [a]
Series c: 5-amino derivatives			
Eq. III p*Ka* = -1.24 (±0.07) σ + 3.19 (±0.03)	9	0.07	0.990
Eq. III' p*Ka* = -1.14 (±0.05) σ + 3.19 (±0.02)	8	0.04	0.993 [a]

n = Number of compounds. s = Standard deviation from regression. r = Correlation coefficient. Standard errors of slope and intercept are reported in brackets. [a] Equation obtained without the nitro derivative.

to measure the ionization constants of these three compounds, cannot be excluded (see Experimental) - needs more insights. Recently [2] we found by uv and ^{15}N nmr integrated study that in water the first protonation site in **1c** is localized at the endocyclic pyridine-like nitrogen, and in **1a** and **1b** principally at the exocyclic nitrogen atoms. We exclude that the deviation shown by the three *para*-nitro derivatives is due to a change of protonation sites with change in substituent at phenyl ring. In fact uv spectra of the monocations of **8c** and **5c** are different from the spectra, measured in neutral medium, of 1-(*m*-nitrophenyl)-pyrazole (**10**) and 1-(*p*-methoxyphenyl)pyrazole (**11**) respectively, while the absorptions of the monocations **8a,b** and **5a,b** resemble them closely (see Figure 1). This picture suggests that the protonation sites in the **a**, **b**, and **c** series do not change with change in substituent at the phenyl ring.

Scheme 2



R = *m*-NO_2 **10**
R = *p*- OCH_3 **11**

The reason for these three outliers could also be ascribed to a mesomeric interaction between the lone electron pair on the N-1 ring nitrogen and the nitro group bound to the *para*-position of the phenyl ring, but additional data are necessary to confirm this hypothesis.

Scheme 3

The ϱ values of the equations reported in Table 2, measure the susceptibility of the ionization reaction to the influence of the substituents. They are similar in the series **a** and **b** and *ca.* twice as high in **c**. These figures are in keeping with the finding that the first protonation site in 5-amino derivatives **c**, is localized at the endocyclic piridine-like nitrogen close to the substituent phenyl ring, while in the 3-amino derivatives **a** and 4-amino derivatives **b**, it is predominantly localized at the more remote exocyclic nitrogen atoms.

EXPERIMENTAL

Most of the derivatives have been prepared following the procedure described in reference [3] and the references there reported. 5-Amino-1-phenylpyrazole (**1c**) [6], 1-(*m*-nitrophenyl)-pyrazole (**10**) [7], 1-(p-methoxyphenyl)pyrazole (**11**) [8] were obtained according to the procedures of the literature cited. 3-Amino-1-(4-nitrophenyl)pyrazole (**9a**) and its *meta*-nitro isomer **8a** have not been yet reported in literature. Details on the synthesis of these compounds will be published in a later paper.

The titration in 10% v/v ethanol-water were performed in a thermostatted bath at 25° ± 0.1, under nitrogen atmosphere on *ca.* $2\text{-}4\cdot10^{-3}$ *M* solutions of the bases (or of the corresponding hydrochlorides) with standardized 0.1 *M* solutions of hydrochloric acid (or 0.1 *M* potassium hydroxide) as titrant. The ionic strength of the solution was adjusted to 0.05 with potassium nitrate. Changes in hydrogen ion concentrations were measured following with the E values with a glass and calomel electrodes of a 605 Metrohm *p*H-meter. After each set of potentiometric measurements, a titration was made with standard solutions of hydrochloric acid to calibrate the glass electrode in the acidic range. The calculations were performed according to Albert and Serjeant [9].

In the case of the derivatives **9a**, **9b** and **9c**, owing to the low solubility, the p*Ka* values were measured at 25° ± 0.1 by the spectrophotometric method using $5\cdot10^{-5}$ *M* buffered solutions containing 10% v/v ethanol. The ionic strength of Perrin's buffers [10] used in the experiment, was adjusted to 0.05 with potassium nitrate. The hydrogen ion concentration of these solutions were measured according to the above reported procedure. The spectrophotometric measurements were performed on a Perkin Elmer Lamda 5 UV/VIS instrument [analytical wavelength: **9a** and **9b**, 300 nm; **9c**, 255 nm].

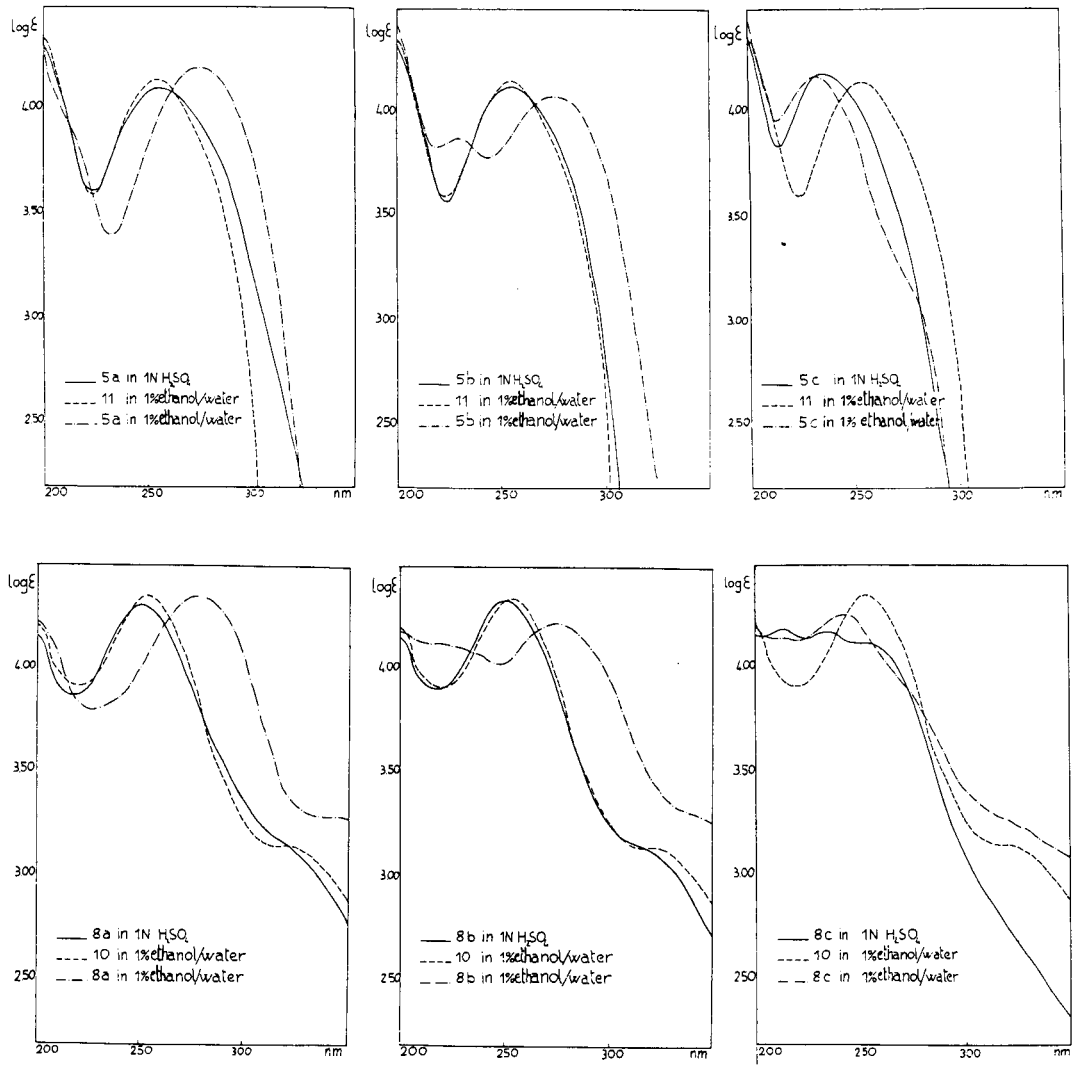


Figure 1. Uv spectra in different media of **5a-c**, **8a-c**, **10** and **11**.

Linear regression analyses were performed by the usual procedure on a Hewlett-Packard 85 desk computer.

REFERENCES AND NOTES

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