Basicity of Azoles. VII [1]. Basicity of *C*-Aminopyrazoles in Relation to Tautomeric and Protonation Studies

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The pK_a values of five aminopyrazoles [3(5)-amino, 1-methyl-3-amino, 1-methyl-5-amino, 4-amino and 1-methyl-4-amino] were determined. The aqueous basicities are discussed in terms of tautomerism (72% of 3-amino tautomer), protonation site (only 4-aminopyrazoles protonate on the amino group) and amino substituent effects. The results of theoretical calculations, carried out at the semiempirical INDO level, indicate that in the gas phase 3- and 5-aminopyrazoles protonate on the pyrazolic nitrogen atom, whereas 4-aminopyrazoles possess similar proton affinities for both nitrogen atoms (pyrazolic and amino).

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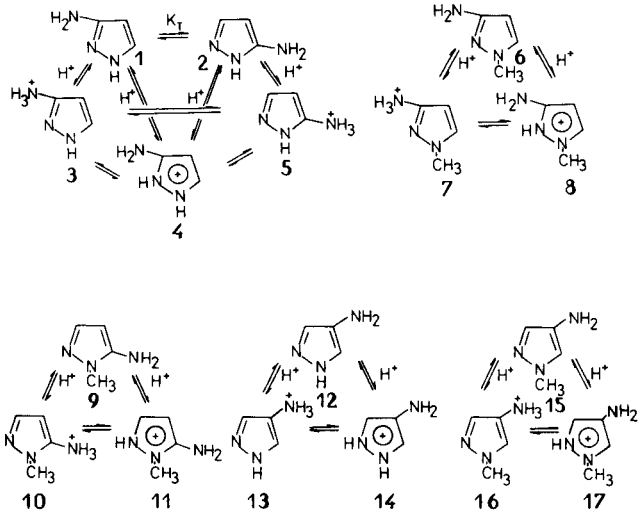
The tautomerism of aminopyrazoles has been the subject of many qualitative studies [3]. In the present work, the pK_a values of five aminopyrazoles have been determined in water at 25° in order to get quantitative information. The following equilibria (Scheme 1) are present in water for the five compounds: 3(5)-aminopyrazole **1(2)**, 1-methyl-3-aminopyrazole **6**, 1-methyl-5-aminopyrazole **9**, 4-aminopyrazole **12** and 1-methyl-4-aminopyrazole **15**.

Scheme 1



For the sake of simplicity, the diprotonated cations (five more structures) have not been included since all our basicity measurements deal with the first protonation equilibria. In the case of 3(5)-aminopyrazole, the literature results [3,4] agree that the 3-amino structure **1** should be more stable than the 5-amino isomer **2**. As far as protonation site is concerned (tautomerism of aminopyrazole cations), recent work carried out by ^{13}C nmr proves that in trifluoroacetic acid or in mixtures of hexadeuteriodimethylsulfoxide-trifluoroacetic acid, the most stable monocations have the structures **4**, **8**, **11**, **13** and **16** [5]. Basicity measurements of *N*-phenyl-substituted derivatives corresponding to structures **6**, **9** and **15** also lead to the same conclusion [6].

Table I contains the experimental pK_a values of five aminopyrazoles.

Table I

Basicity of Aminopyrazoles

Compound	pK_a (25°)
3(5)-Aminopyrazole **1** (**2**)	4.11 ± 0.02
1-Methyl-3-aminopyrazole **6**	3.81 ± 0.02
1-Methyl-5-aminopyrazole **9**	4.23 ± 0.02
4-Aminopyrazole **12**	5.57 ± 0.02
1-Methyl-4-aminopyrazole **15**	5.52 ± 0.02

Discussion.

It is worthwhile to develop the calculation of the tautomeric equilibrium constant K_T (defined as the ratio between 3- and 5-amino tautomers, K_T = ([1]/[2])[3]. The experimental pK_a value refers to a mixed equilibrium constant K_1 related to the equilibrium constants of each tauromer by the relationship $K_1 = K_A + K_B$, K_A = [4]/[1][H^+] and K_B = [4]/[2][H^+]. K_a and K_B are not amenable to experiment, only K_{MeA} = [8]/[6][H^+] and K_{MeB} = [11]/[9][H^+] can be measured. If we call f a proportionality factor between K_A (or K_B) and K_{MeA} (or K_{MeB}), it is possible to write:

$$K_A = f_A \times K_{MeA}$$
$$K_B = f_B \times K_{MeB}$$
$$K_1 = (f_A \times K_{MeA}) + (f_B \times K_{MeB})$$

If we assume that $f_A = f_B$, then:

$$f_A = f_B = K_1/(K_{MeA} + K_{MeB})$$
$$K_T = K_A / K_B = K_{MeA}/K_{MeB}$$

From the values of Table I, $K_1 = 77.62 = 10^{-6}$, $K_{MeA} = 154.88 \times 10^{-6}$ and $K_{MeB} = 55.88 \times 10^{-6}$, it can be deduced:

$f_A = f_B = 0.363$, $\log f_A = \log f_B = -0.44$
$K_A = 56.24 \times 10^{-6}$, $pK_A = 4.25$
$K_B = 21.38 \times 10^{-6}$, $pK_B = 4.67$
$K_T = 2.63$, $pK_T = 0.42$, 72.5% A (3-amino, **1**)
27.5% B (5-amino, **2**)

The value of log f (- 0.44 pK_a units) is quite normal for the *N*-methylation effect (averaged value, -0.45 [7]); even if f_A is not exactly the same as to f_B, the value of K_T would not be very different from 2.63, a reasonable estimate gives a percentage of 3-amino tautomer between 70 and 75%.

Protonation of 3(5)-Aminopyrazoles.

The above discussion is based on the assumption that 3(5)-aminopyrazoles protonate on the ring nitrogen, giving cations **4**, **8** and **11**. The fact that the *N*-methylation effect is the same in non polybasic pyrazoles (around -0.45 pK_a units), corroborates this assumption. However, no quantitative conclusions can be made concerning the equilibria **3** ⇌ **4** ⇌ **5**, **7** ⇌ **8** and **10** ⇌ **11**.

Protonation of 4-Aminopyrazoles.

These compounds are much stronger bases. In this case, the pK_a is almost insensitive to *N*-methylation (ΔpK_a = -0.05) showing that the protonation site it is no longer the pyrazolic nitrogen, but the exocyclic amino group (formation of cations **13** and **16**).

Effect of the Amino Group on the Basicity of Pyrazoles.

Only compounds that protonate at the same nitrogen atom can be compared. For this reason, the 4-amino derivatives will be excluded. For the tautomeric 3(5)-aminopyrazole we shall use the calculated K_A and K_B values.

Since the pK_a values of pyrazole and 1-methylpyrazole are 2.52 and 2.09, respectively [7], the amino group increases the basicity by 1.72 pK_a units (3-amino: 4.25-2.52; 3.81-2.09) or by 2.14 pK_a units (5-amino: 4.67-2.52; 4.23-2.09).

The pK_a values of 1-methyl 3-, 4- and 5-nitropyrazoles have been determined by Dumanović *et al.* [8]. For the substituents NO_2, H [7] and CH_3 [7] there is a linear relationship between the pK_a's when the substituent is in position 3 and 4.

$$pK_a\,(4) = 0.73 + 0.63\ pK_a\,(3),\ n = 3,\ r^2 = 0.9998$$

This equation allows to calculate the 1-methyl-4-aminopyrazole basicity for protonation on the ring nitrogen (cation **17**, pK_a = 3.14) from the pK_a of 1-methyl-3-aminopyrazole. The experimental value (Table I, 5.52) clearly corresponds to a cation protonated on the amino group, **16**.

Theoretical Considerations.

At the present state of the art it is not possible to calculate theoretically the aqueous basicity (pK_a) of a given compound. A possible way to reach such a value is through a mixture of theoretical calculations and empirical relationships (Scheme 2). To establish these relationships it is necessary to have a set of known derivatives closely related to the compounds whose pK_a we want to predict.

Scheme 2

Theoretical calculation of protonation energies, ΔE_p [12]
(optimized geometries)
↓
Experimental gas-phase proton affinities, PA [13]
↓
Empirical linear relationship between PA and ($-\Delta E_p$) [12]
$PA = a_0 + a_1 (-\Delta E_p)$
↓
Experimental aqueous basicity, pK_a
↓
Empirical linear relationship between PA and pK_a
$pK_a = b_0 + b_1 PA$
↓
Empirical linear relationship between ($-\Delta E_p$) and pK_a
$pK_a = c_0 + c_1 (-\Delta E_p)$

Since ΔE_p for different basic centers of a given molecule can be calculated, it will be possible to know the pK_a (first protonation) for every cation, for instance **16** and **17**. By comparing these data with the experimental pK_a value, the site of protonation can be determined.

In order to apply the above procedure to aminopyrazoles, two models are necessary: one for the amino group and another one for the cyclic nitrogen N_2. For the first one, anilines of known experimental gas-phase proton affinities, PA [10,14] (*m*-CF_3, *m*-F, *p*-F, H, *m*-OH, *p*-CH_3,

m-NH_2 and *p*-NH_2) were selected. The comparison with INDO calculated ΔE_p's yields [12]:

$$PA = 8.0 + 0.605(-\Delta E_p) (n = 8, r^2 = 0.93) \quad (1)$$

Concerning the protonation on N_2, the widely studied pyridines cannot be used [15]. This leaves only azoles to calculate the relationship between ΔE_p and PA. Actually, the literature PA's of azoles are practically nonexistent and we have had to use Mautner's unpublished results [16]:

$$PA = -90.9 + 0.848 (-\Delta E_p) (n = 3, r^2 = 0.993) \quad (2)$$

Using eqs. (1) and (2) and the INDO ΔE_p values, the PA's of aminopyrazoles were calculated (Table II).

Table II

PA Values (kcal.mol^{-1}) of Aminopyrazoles [a]

Protonation on	3-Amino **1**	5-Amino **2**	4-Amino **12**
$-NH_2$	215.6 **3**	207.0 **5**	214.9 **13**
$\gtrless N_2$	225.2 **4**	224.4 **4**	213.1 **14**

[a] PA = experimental gas-phase proton affinity.

These results show that amination in position 3 (**1**) or 5 (**2**) increases the pyrazole basicity considerably (210.8 [16]), whereas a 4-amino group (**12**) produces a small effect [17]. As far as the basicity of the amino group is concerned, it is interesting to compare aminopyrazoles with aniline (PA = 211.5 [18]). Table II shows that two of them, **1** and **12**, are more basic and another one, **2**, is less basic than aniline. Thus, only in the case of the 3- and 4-amino-substituted isomers, the pyrazole group appears as a π-excessive heterocycle. The results in Table II also show that in the gas phase, 3- and 5-aminopyrazoles are heterocyclic bases (protonation on N_2) whereas the situation is almost balanced for **12**, with a slight preference for the amino group. As eq. (2) is strongly dependent on the PA's of azoles, it must be noted that there is a different value of the PA available for imidazole (224.0 [19]), but the only possible consequence of this minor increase of basicity of the azoles would be to blur the differences between both basic centers in **12**. As a consequence, substituents (on N_1, C_3, C_5 or on the amino group) will shift the balance towards the amino or the N_2 nitrogen in 4-aminopyrazoles. The effect of *N*-methylation is represented in Table III, whose PA's were calculated from eqs (1) and (2) and the theoretical ΔE_p values.

Table III

PA values (kcal.mol^{-1}) of *N*-methylaminopyrazoles

Protonation on	3-amino **6**	5-amino **9**	4-amino **15**
$-NH_2$	216.2 **7**	208.4 **10**	215.5 **16**
$\gtrless N_2$	227.7 **8**	226.5 **11**	216.6 **17**

The *N*-methylation increases the basicity of N_2 (- 2.7 kcal.mol^{-1}) more than the amine basicity (+ 0.9 kcal.mol^{-1}). As a consequence, now N_2 is more basic than the amino group in **15**.

Tautomeric equilibrium constant in the gas phase for 3(5)-aminopyrazole, **1** ⇌ **2**, can be calculated from the values in Table II, since **4** is still the common cation. There is a preference for the 5-amino tautomer **2** (0.8 kcal.mol^{-1}, *i.e.* 79% at 25°). This inversion with regard to the result in water (27.5% **2**), even if it is in agreement with Dewar calculations [20], must be taken with care, since 2-aminopyridines, the six-membered counterpart of 3-aminopyrazoles, deviate from the PA vs. ΔE_p regression line [21]. Thus, we prefer not to continue with the Scheme 2 cascade in the case of 3-aminopyrazoles **1** and **6**.

It is known [22] that an aqueous medium produces an attenuation effect on the acid-base properties. For a given family of compounds, the attenuation corresponds to the slope of the regression line between aqueous and gas phase properties. The slope strongly depends on the compounds, ranging from 1.15 for hydrocarbon bases giving highly charge-delocalized carbocations [23] to 10.6 for the acidity of benzoic acids [24]. Moreover, when the substituent presents relatively important interactions with the solvent, as it is the case of the amino group [10,22,25], the data of the corresponding compound deviate noticeably from the correlation found for the other compounds of the same family.

Assuming that the amino group is an "inert" substituent, is is possible to continue with the calculations of Scheme 2. For protonation on N_2, the model compounds were *C*-methyl substituted 1-methylpyrazoles [26].

$$pK_a = -41.2 + 0.12(-\Delta E_p) (n = 5, r^2 = 0.92) \quad (3)$$

Equation (3) allows one to predict a pK_a value of 3.9 for 1-methyl-5-aminopyrazole **9** (Table IV). The difference between this and the experimental value, -0.33 pK_a units, is considerably smaller than those found for 3-amino (-1.5) and 4-aminopyridine (-0.9) [27]. For 1-methyl-4-aminopyrazole, the calculated pK_a value is 2.5 (for the cation **17**, we had estimated previously an empirical value of 3.14).

Turning now to the amino group, the hypothesis, already made, that aminopyrazoles behave like anilines, allows us to obtain eq. (4) from the gas [13,14,18] and aqueous data [14] for the following anilines: *p*-CH_3O, *p*-CH_3, H, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *m*-CH_3, *m*-I, *m*-Br, *m*-CF_3 and *m*-CN.

$$pK_a = -35.7 + 0.19\ PA\ (n = 12, r^2 = 0.81) \quad (4)$$

From this equation and data in Tables II and III, the pK_a's (amino protonation) of Table IV were calculated.

Conclusion.

From this study it can be concluded that 4-aminopyraz-

Table IV

Calculated pK_a Values of 4- and 5-Aminopyrazoles According to Scheme 2

Protonation on	5-NH_2 **2**	1-Me-5-NH_2 **9**	4-NH_2 **12**	1-Me-4-NH_2 **15**
-NH_2	3.5 **5**	3.7 **10**	5.0 **13**	5.1 **16**
N_2	4.6 [a] **4**	3.9 **11**	3.0 [a] **14**	2.5 **17**
Experimental	4.67	4.23	5.57	5.52

[a] Calculated using *N*-unsubstituted *C*-methylpyrazoles [26] as model compounds.

oles protonate on the amino group in solution and that in the gas phase both basic centers are of similar strength. On the other hand, 3- and 5-aminopyrazoles always protonate on the ring nitrogen, being typical heterocyclic bases. Theoretically calculated pK_a's are in fair agreement with the experiment, but the difference is too small to be used as a protonation criterion in the case of 1-methyl-5-aminopyrazole **9**.

EXPERIMENTAL

The aminopyrazoles **1**, **6**, **9**, and **12**, studied in this work were prepared according to the literature [28]. 1-Methyl-4-aminopyrazole **15** was obtained by catalytic reduction (Pd-C, room temperature, atmospheric pressure) of 1-methyl-4-nitropyrazole. The yield was 53% after distillation at 150° (0.6 torr). For the ^{13}C nmr spectra, see [5].

Anal. Calcd. for $C_4H_7N_3$: C, 49.48; H, 7.22; N, 43.30. Found: C, 49.52; H, 7.21; N, 43.05.

The potentiometric titrations for the determination of the pK_a values were performed on freshly purified samples with a Radiometer TTA3 pH-stat coupled with a Radiometer PHM 28 pH-meter and using a thermostated cell. All titrations were carried out under nitrogen atmosphere, using 0.1 M HCl as titrating solution and constant ionic strength, $\mu = 0.1$. The equipment and the HCl solutions were standardized with NBS standard samples. During the measurements the solutions were thermostated at 25.0 ± 0.1°C. The uncertainties of the pK_a values correspond to the standard deviations of the average of three titrations.

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