

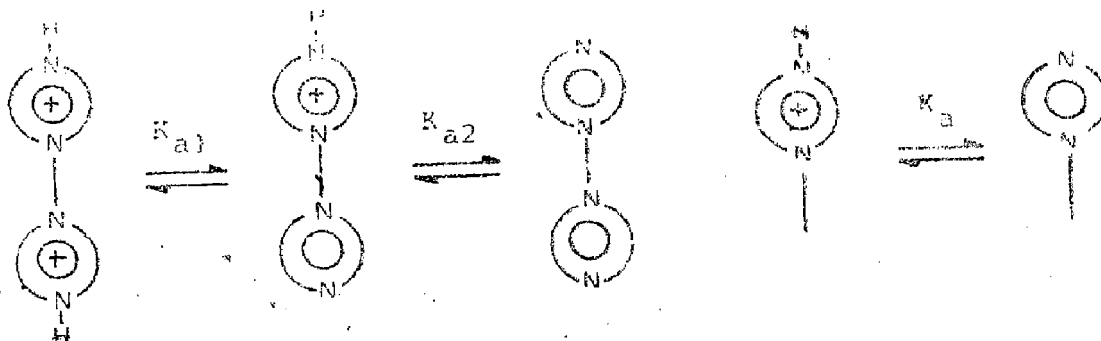
Table 1

Thermodynamic pK_a values of bisazolyalkanes and literature values of related *N*-methyl- and *N*-ethyl-azoles

Compound	pK_{a1}	pK_a	pK_{a2}
(1) pz-CH ₂ -pz	-2.12 ± 0.07		0.12 ± 0.02
(2) dmpz-CH ₂ -dmpz	0.37 ± 0.03		2.14 ± 0.09
(3) pz-CH ₂ -CH ₂ -pz	-0.24 ± 0.09		1.67 ± 0.04
(4) dmpz-CH ₂ -CH ₂ -dmpz	1.30 ± 0.04		3.39 ± 0.08
(5) brpz-CH ₂ -CH ₂ -brpz	-1.9 ± 0.2		0.0 ± 0.2
(6) im-CH ₂ -im	3.76		5.56
(7) mim-CH ₂ -mim	4.97	} b	6.64
(8) im-CH ₂ -CH ₂ -im	4.87		6.41
(9) mim-CH ₂ -CH ₂ -mim	5.83		7.28
(10) bzim-CH ₂ -CH ₂ -bzim	3.71		4.61 ^a
(11) pz-CH ₃		2.06 ¹	
(12) dmpz-CH ₃		3.74 ¹	
(13) brpz-CH ₃		0.17 ¹	
(14) pz-CH ₂ -CH ₃		1.94 ¹	
(15) im-CH ₃		7.12 ¹	
(16) mim-CH ₃		8.00 ¹	
(17) im-CH ₂ -CH ₃		7.19 ¹	
(18) bzim-CH ₂ -CH ₃		5.62 ¹	

^a Lit.³ gives 4.56 for water-alcohol 1:1. ^b for the error in potentiometric measurements, see experimental part (Sigma pH fit).

To discuss the pK_{a2} s of Table 1, some *N*-methyl and *N*-ethylazoles are also necessary. The idea is to consider both successive equilibria as reflecting the perturbation of the pK_a of a *N*-methylazole (-CH₂- series) or a *N*-ethylazole (-CH₂-CH₂- series) by an azole or an azolium protonated azole substituent.



The ΔpK_a values thus obtained are collected in Table 2.

Table 2 values correspond roughly to the following expected observations:

i) Replacement of one hydrogen of the *N*-methyl or the *N*-ethyl substituent by an azolyl (neutral or charged) produces a base-weakening effect.

Table 2

Effect of an 1-azoly and a 1-azolium substituent on the basicity of an azole through one (α effect) or two methylenes (β effect)

Pair of compounds	Substituent	ΔpK_a
(11) - (1)	{pz (α)	-1.94
(12) - (2)	{pz ⁺ (α)	-4.18
(14) - (3)	{dmpz (α)	-1.60
	{dmpz ⁺ (α)	-3.37
1-ethyl-3,5-dimethylpyrazole ^a	{pz (β)	-0.27
(4)	{pz ⁺ (β)	-2.18
1-ethyl-4-bromo-pyrazole ^b	{dmpz (β)	-0.23
(5)	{dmpz ⁺ (β)	-2.32
(15) - (6)	{brpz (β)	-0.05
(16) - (7)	{brpz ⁺ (β)	-1.95
(17) - (8)	{im (α)	-1.56
	{im ⁺ (α)	-3.36
	{mim (α)	-1.36
	{mim ⁺ (α)	-3.03
1-ethyl-2-methylimidazole ^c - (9)	{im (β)	-0.78
(18) - (10)	{im ⁺ (β)	-2.32
	{mim (β)	-0.79
	{mim ⁺ (β)	-2.24
	{bzim (β)	-1.01
	{bzim ⁺ (β)	-1.91

^a Calculated $pK_a = 3.62 [(14) + (12) - (11)]$; ^b Calculated $pK_a = 0.05 [(14) + (13) - (11)]$; ^c Calculated $pK_a = 8.07 [(17) + (16) - (15)]$.

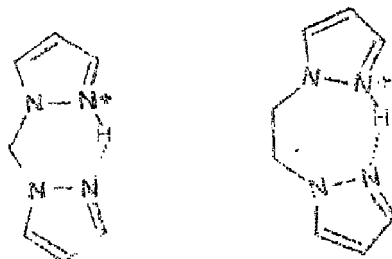
ii) The effect is larger in α than in β , i.e. through a methylene and two methylenes, respectively.

iii) The effect is larger for an azolium cation than for an azole.

A more detailed analysis of Table 2 reveals:

i) Through one methylene (α values), pyrazoles and pyrazolium ions are more base-weakening than imidazoles and imidazolium ions (averaged values: pyrazoles, -1.77, imidazoles, -1.46, pyrazoliums, -3.78, imidazoliums, -3.20) whereas the reverse is true for β values (averaged values: pyrazoles, -0.18, imidazoles, -0.78, pyrazoliums, -2.14, imidazoliums, -2.28). This surprising result is comparable, at least for neutral azoles, to the observation that the α methylene carbon in ¹³C-NMR is more deshielded (35.1 ppm) by a pyrazole than by an imidazole (30.2 ppm)⁴ whereas the β -methylene is more deshielded by imidazole (1.03 ppm) than by pyrazole (0.53 ppm).⁵

ii) There is no clear indication of stabilization of the monocation by chelation. This situation, possible only in the case of pyrazoles, would result in an increase of the difference between pK_{a1} and pK_{a2} . If the phenomenon is present in aqueous solution, the effect is rather insignificant.



iii) The values for compound **5** are less precise. Values near -2.15 and -0.25 for pK_{a1} and pK_{a2} , respectively, would better fit with other compounds of Table 2 ($\Delta pK_a = -0.25$ and -2.20).

EXPERIMENTAL PART

Synthesis

Compounds (**1**),^{6,7} (**2**),⁸ (**3**),^{5,8} (**5**),⁵ (**6**),^{6,9} (**7**),¹⁰ (**8**),^{5,8} and (**10**),⁵ were previously described. Compounds (**4**) and (**9**) were prepared as follows: a suspension of the azole (29 mmoles), anhydrous potassium carbonate (29 mmoles), powdered potassium hydroxide (29 mmoles), tetrabutylammonium bromide (1.4 mmoles), and 1,2-dibromoethane (14.5 mmoles) in 50 mL of toluene or xylene were heated under reflux for 48 h. The hot reaction mixture was filtered and the solid residue was washed twice with 30 mL of anhydrous toluene or xylene. The solutions were dried over anhydrous sodium sulfate and the corresponding compounds purified by column chromatography on silica gel using petroleum ether/ethyl acetate (5 : 2) as eluent. The NMR spectra (δ , Hz) were recorded on a Bruker AC 200.

1,2-Bis(3,5-dimethylpyrazol-1-yl)ethane (4), yield: 75 %, m.p. $126-7^\circ\text{C}$. Rf (Petroleum ether/ethyl acetate 5 : 2): 0.43; $^1\text{H-NMR}$ (CDCl_3): Me_3 : 1.62 (s), H_4 : 5.66 (s), Me_5 : 2.20 (s), CH_2 : 4.30 (s); $^{13}\text{C-NMR}$ (CDCl_3): Me_3 : 13.4 ($^1\text{J} = 126.9$), Me_5 : 9.5 ($^1\text{J} = 128.8$), C_3 : 148.1 ($^2\text{J} = 6.1$), C_4 : 104.8 ($^1\text{J} = 172.3$, $^3\text{J} = 3.8$), C_5 : 140.4 ($^2\text{J} = 6.6$), CH_2 : 48.7 ($^1\text{J} = 141.0$).

1,2-Bis(2-methylimidazol-1-yl)ethane (9), yield: 60 %, m.p. $146-8^\circ\text{C}$, Rf ($\text{CHCl}_3/\text{EtOH}$ 10 : 2): 0.20; $^1\text{H-NMR}$ (CDCl_3): Me_2 : 2.05 (s), H_4 : 6.90 (d), H_5 : 6.58 (d), $J_{45} = 1.4$, CH_2 : 4.12 (s); $^{13}\text{C-NMR}$ (CDCl_3): Me_2 : 11.8 ($^1\text{J} = 128.5$), C_2 : 144.6, C_4 : 127.7 ($^1\text{J} = 189.3$, $^2\text{J} = 9.2$), C_5 : 118.6 ($^1\text{J} = 188.0$, $^2\text{J} = 16.2$), CH_2 : 46.5 ($^1\text{J} = 140.3$).

Basicity measurements

Spectrophotometry. For pyrazole derivatives (**1**)–(**5**), UV spectroscopy was selected as measurement technique, due to the expected low pK_a values. Compounds (**1**), (**2**), (**3**) and (**5**) were measured in concentrated sulfuric acid where the Hammett acidity function H_0 holds.^{11,12} The experiments were carried out between $H_0 = -5.45$ and $H_0 = +3.00$. Compound (**4**), being more basic, was measured in hydrochloric acid solution between $\text{pH} = 1.00$ and $\text{pH} = 5.00$, using potassium chloride to adjust the ionic strength to 0.1.

For each compound, at least three series of measurements were performed using a Hewlett-Packard 841A diode array spectrophotometer. The temperature was maintained constant at $25.0 \pm 0.1^\circ\text{C}$. For each series of measurements, the spectra of 20–25 samples of constant pyrazole concentration ($3 \cdot 10^{-3}$ M) and increasing acidity were recorded between 210 and 260 nm.

To determine the number of species present in solution, the TRIANG program were used.^{13,14} In all cases, three species are present, corresponding to two pK_a s. To calculate these pK_a s, the SPECCK program¹⁵ was used; it yields the values collected in Table 1.

Potentiometry. For much more basic imidazole and benzimidazole derivatives (**6**)–(**10**), potentiometry was chosen to determine their pK_a . Aqueous solutions about 10^{-3} M were prepared and their ionic strength adjusted to 0.1 [$I = 0.5$ for compound (**10**)] with potassium chloride.

The necessary quantity of HCl, plus a slight excess, to protonate both heterocycles were added. These solutions were titrated backwards with 0.1 M solution of KOH [0.5 M for compound (**10**)] at $25.00 \pm 0.05^\circ\text{C}$ under nitrogen atmosphere. A mixture glass-AgCl microelectrode and a Methrom E 536 potentiometer were used.

For each compound, at least three titrations were carried out. The corresponding pK_a values were calculated with the BEST program¹⁶ and afterwards corrected to obtain the thermodynamic values of Table 1.

Compound (**6**): the pK_a values calculated with the program BEST were $pK_{a1} = 4.09$ and $pK_{a2} = 5.67$ (Sigma pH fit = 0.03).

Compound (**7**): the pK_a values calculated with the program BEST were $pK_{a1} = 5.30$ and $pK_{a2} = 6.75$ (Sigma pH fit = 0.02).

Compound (**8**): the pK_a values calculated with the program BEST were $pK_{a1} = 5.20$ and $pK_{a2} = 6.52$ (Sigma pH fit = 0.03).

Compound (9): the pK_a values calculated with the program BEST were $pK_{a1} = 6.16$ and $pK_{a2} = 7.39$ (Sigma pH fit = 0.02).

Compound (10): the pK_a values calculated with the program BEST were $pK_{a1} = 3.88$ and $pK_{a2} = 5.14$ (Sigma pH fit = 0.01).

The applied correction amounts to -0.33 and -0.11 for pK_{a1} and pK_{a2} , respectively, except for compound (10), where the corresponding corrections were -0.17 and -0.53 .

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