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Basicity and Acidity of Azoles: The Annelation Effect in Azoles

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Abstract: The acidity and basicity in the gas phase and in aqueous solution of a representative set of azoles have been determined. From the corresponding thermodynamic data, it is possible to demonstrate the intrinsic effects that annelation has on the acid–base properties of azoles. Thus, whereas the acidity increases between 5.9 and 8.2 kcal/mol, the basicity increases only between 1.5 and 2.4 kcal/mol. Moreover, these intrinsic differences explain why in aqueous solution the benzazoles (benzene annelated azoles) are more acidic and less basic than the corresponding azoles. Another consequence is that the annelation effect in this kind of substances, which are simultaneously acids and bases, shows a linear relationship that covers a wide range of pK_a's. Finally, the effects of aza and *N*-methyl substituents on the basicity of the diazoles (imidazole, benzimidazole, pyrazole, and indazole) are discussed. The prototropic tautomerism of indazole in the gas phase is also examined.

During the past decade, substituted pyridines have been the subject of many thermodynamic studies both in the gas phase and in solution. The results of these studies give a better understanding of the fundamental nature of intrinsic basicity,[1] solvation,[1,2] substituent effects,[3] and nitrogen lone pair properties.[4] It is foreseeable that in the next decade azoles will replace pyridines as substrates in these investigations, since azoles have simultaneously easily ionizable acid and basic heterocyclic centers. This characteristic has allowed us to introduce the "electrostatic proximity effect" as a new and interesting inherent effect.[5] Moreover, a careful study of the acid–base properties of azoles is crucial to an understanding of (i) their exceptional importance as substrates in the generation of laser emission[6a] or to act as photoprotectors[6b] by intramolecular proton transfer, (ii) their role as ligands in coordination chemistry,[7] and (iii) their role as bifunctional catalysis.[8]

Many studies of acid–base equilibria of azoles have been reported, but these almost exclusively relate to aqueous solution.[9] From these studies some intriguing conclusions emerge: (i) annelation (benzene ring fusion) decreases the basicity of an azole by about 1.5 pK_a units,[10] but it increases the corresponding acidity by about 1 pK_a unit[10,11] (ii) the replacement of the pyrrolic hydrogen by a methyl group (N-methylation)[12] of an azole has a negligible effect on the aqueous basicity, (iii) the ionization of a neutral azole in aqueous solution is an isoentropic process,[13] (iv) part of the decrease in basicity caused by annelation (see i) is partly due to steric inhibition of solvation caused by the vicinal benzene ring,[14] and (v) the corresponding $\Delta S°$ values for the imidazole and benzimidazole protonation processes in aqueous solution are nearly identical,[15] suggesting that water acts similarly in both cases.

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Table I. Gas-Phase Acidity and Basicity Results Obtained with Standard Acids and Bases (in kcal/mol)

heterocycle	standard acid	$\Delta G°_{std}$[a,e]	$\delta\Delta G°_{obsd}$[b,f]	$\Delta G°$[c,g]	$\Delta G°_{bv}$[d,h]	PA
	Acidities					
imidazole **1a**	phenol	8.4	−0.9 ± 0.1	7.5		
	p-cyanoaniline	9.1	−1.5 ± 0.1	7.6		
	p-methylphenol	7.3	0.6 ± 0.1	7.9	7.7 ± 0.2	350.6
pyrazole **3a**	*m*-nitroaniline	5.7	−1.1 ± 0.1	4.6		
	i-PrSH	3.7	0.5 ± 0.1	4.2	4.4 ± 0.2	353.9
1,2,3-triazole **8a**	*o*-fluorophenol	11.6	0.0 ± 0.1	11.6		
	(*p*-chlorophenyl)acetonitrile	12.1	−0.1 ± 0.1	12.0	11.8 ± 0.2	346.9
indazole **4a**/**5a**	*o*-fluorophenol	11.6	−1.3 ± 0.2	10.3		
	3,5-bis(trifluoromethyl)aniline	10.0	0.3 ± 0.1	10.3	10.3 ± 0.1	348.4
benzotriazole **10a**	*p*-(trifluoromethyl)phenol	20.3	−0.7 ± 0.1	19.6		
	4-fluoro-bicyclo[2.2.2]octane-1-carboxylic acid	18.8	0.9 ± 0.2	19.7	19.6 ± 0.2	338.7
imidazole **1aH**$^+$	3-methylpyridine	20.6	−0.6 ± 0.1	20.0		
	tert-amylamine	19.2	0.9 ± 0.1	20.1		
	2-methoxypyridine	18.2	1.8 ± 0.1	20.0	20.0 ± 0.1	223.6 (222.1)[i]
1-methylimidazole **1bH**$^+$	dimethylethylamine	24.3	−0.6 ± 0.1	23.7		
	hexamethylenimine	23.1	0.8 ± 0.1	23.9	23.8 ± 0.2	227.0 (228.0)[i]
pyrazole **3aH**$^+$	isopherone	9.4	−0.2 ± 0.1	9.2		
	4-(trifluoromethyl)pyridine	9.4	−0.2 ± 0.1	9.2		
	di-*tert*-butyl sulfide	10.0	−1.0 ± 0.1	9.0	9.1 ± 0.2	212.7 (212.8)[i]
1-methylpyrazole **3bH**$^+$	butylamine	14.6	−1.5 ± 0.1	13.1		
	ethylamine	12.6	0.7 ± 0.2	13.3	13.2 ± 0.2	216.4
indazole **4aH**$^+$	2-chloropyridine	11.0	−0.2 ± 0.2	10.8		
	4-(trifluoromethyl)pyridine	9.4	1.8 ± 0.1	11.2	11.0 ± 0.2	214.2
1-methylindazole **4bH**$^+$	2-methoxypyridine	18.2	−2.5 ± 0.1	15.7		
	4-(trifluoromethyl)piperidine	16.2	−0.3 ± 0.2	15.7		
	butylamine	14.6	0.8 ± 0.2	15.4	15.6 ± 0.2	218.8
2-methylindazole **5bH**$^+$	3-methoxypyridine	20.7	−0.3 ± 0.1	20.4		
	tert-amylamine	19.2	1.0 ± 0.1	20.2		
	tert-butylamine	17.8	2.5 ± 0.1	20.3	20.3 ± 0.1	223.5
1-methylbenzimidazole **2bH**$^+$	diisopropylamine	26.6	−0.7 ± 0.3	25.7		
	dimethylethylamine	24.3	1.3 ± 0.1	25.6	25.6 ± 0.2	228.9
1,2,3-triazole **8aH**$^+$	*N*,*N*-dimethylformamide	8.0	−1.7 ± 0.2	6.3		
	2-fluoropyridine	7.4	−1.6 ± 0.1	5.8		
	3-cyanopyridine	5.7	0.4 ± 0.1	6.1	6.1 ± 0.2	209.3

[a] Gas-phase acidities relative to pyrrole, positive values denoting greater acidity. [b] Differential acidity obtained from measured proton-transfer equilibria (2). [c] Acidity of heterocycle relative to pyrrole. [d] Best value of gas-phase acidity relative to pyrrole. For pyrrole, $\Delta G_{acid}° = 350.9$ kcal/mol and $\Delta H_{acid}° = 358.6$ kcal/mol on the basis of the revised gas phase acidity scale of Prof. J. Bartness, July 1987. [e] Gas-phase basicities relative to ammonia, positive values denoting greater basicity. [f] Differential basicity obtained from measured proton-transfer equilibria (1). [g] Basicity of heterocycle relative to ammonia. [h] Best value of gas-phase basicity relative to ammonia (PA = 204.0). [i] Value reported by M. Mautner et al. (ref 17).

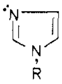
Table II. Aqueous Acidity: Experimental pK_a Values for Proton Ionization of Unsubstituted Azoles at 298.15 K

compound	pK_a	μ
imidazole **1a**	14.4 ± 0.1[a]	0.5
benzimidazole **2a**	12.75 ± 0.1[b]	0.5
pyrazole **3a**	14.18 ± 0.08[c]	0.5
indazole **4a**/**5a**	13.86 ± 0.03[d]	0.5
benzotriazole **10a**/**11a**	8.38 ± 0.03[e]	0.1

[a] Literature values: 14.17 ± 0.02,[10] 14.44,[24] 14.52.[25] [b] Yagil's value[26] is 12.86; other literature values range from 12.3[27] to 13.3.[28] [c] Yagil's value[10] is 14.21 ± 0.08. [d] Yagil's value[26] is 13.80. [e] Literature values: 8.38 ± 0.03,[11] 8.35 ± 0.01,[15] 8.64.[29]

These conclusions involve complex structural and solvent effects that need further study. In particular, to clarify topics such as annelation, aza, and N-methylation effects in azoles, systematic studies of both gas and the condensed phase are necessary.

Data on the acidity (>NH) and basicity (⩾N:) of azoles in the gas phase, although very interesting, are scarce.[1,5,16,17] In this work, we report the acidities of imidazole, pyrazole, indazole, 1,2,3-triazole, and benzotriazole and the basicities of imidazole, pyrazole, 1,2,3-triazole, indazole, 1-methylimidazole, 1-methylpyrazole, 1-methylbenzimidazole, 1-methylindazole, and 2-methylindazole. Estimated values for the benzimidazole acidity and basicity are also given (see later). The aqueous acidities and basicities and the corresponding ionization enthalpies of all the above and also of 2-methylimidazole are also reported. The data for DMSO,[18,19] water,[9] and other solvents (1,2-dimethoxyethane, DME,[19a] and acetone[20]) is used in the discussion.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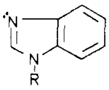
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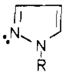
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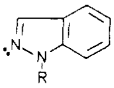
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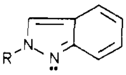
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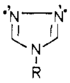
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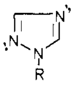
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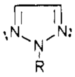
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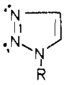
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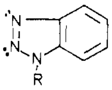
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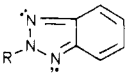
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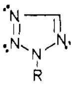
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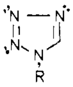
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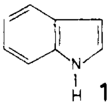
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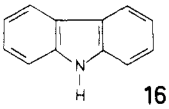
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Experimental Section

Materials. All the compounds were prepared and purified according to the literature.[7] The purity was determined by differential scanning

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calorimetry (Perkin-Elmer, DSC-2): **1a** (99.8%), **2a** (99.8%), **3a** (99.9%), **4a** (99.4%), **10a** (99.9%), **14a** (99.7%), **4b** (99.8%), **5b** (99.3%). GP and HPLC chromatographies were used for the remaining compounds.

Methods. Gas-Phase Acidities and Basicities. The gas-phase acidities and basicities have been obtained as given in ref 5 or as cited therein. The ICR spectrometer has been remodelled to use a 2 in. square trapped cell with turbojet pumping of the manifold and has been accommodated to an FT Ion Spec data system. The proton transfer equilibria results for representative acids and bases have been repeated to confirm that satisfactory agreement is obtained with corresponding earlier results.

Table I presents the results of proton transfer equilibria (1) and (2) obtained in this study with the given standard acids (BH_{ref}) and bases (B_{ref}).

$$BH + B_{ref}^- \rightleftarrows BH_{ref} + B^- \qquad (1)$$

$$BH_2^+ + B_{ref} \rightleftarrows BH_{ref}^+ + BH \qquad (2)$$

In these equilibria, BH is a neutral heterocyclic acid (1) or base (2). The proton affinities of B^- or BH are obtained as $PA = PA_{ref} + 2.303RT \ln K - T\Delta S°$, where $\Delta S°$ for (1) and (2) is estimated satisfactorily by methods previously discussed.[21]

Due to experimental difficulties in the ICR studies dealing with benzimidazole cation and anion, we do not report in Table I the data on the acidity and basicity of this compound. The PA's of benzimidazole used throughout this work are values estimated from the gas phase annelation relationship (25) and the corresponding data of imidazole acidity and basicity (Table I). The values thus obtained, 343.3 and 225.2 kcal/mol, respectively, are consistent with the existing fragmentary experimental data.

pK_a Measurements. Spectrophotometric Determinations. pK_a values for benzimidazole, indazole, indazolium ion (conjugated acid of indazole), 1-methylindazolium ion, and 2-methylindazolium ion were determined spectrophotometrically according to the method described by Ernst and Menashi.[22] A Cary 210 spectrophotometer fitted with a thermostated (25.0 ± 0.1 °C) cell compartment was used. In a first series of measurements the spectrum of each compound was recorded at different hydroxide or proton concentrations in order to determine the best wavelength for pK_a determination and to check that a simple equilibrium takes place. A second series of measurements was then performed at a larger number of hydroxide concentrations or acidic pH's at the wavelength found most suitable. The ionic strength in all experiments was kept constant at $\mu = 0.5$.

Potentiometric determinations were performed with a Radiometer TTA3 pH stat coupled to a Radiometer PHM 28 pH-meter with a thermostated cell (25.0 ± 0.1 °C). All titrations were carried out under nitrogen atmosphere, with 0.1 or 0.5 M HCl as titrating solution. The equipment was calibrated against standard buffer solutions (±0.01 pH unit). All the pK_a values of azolium ions were determined by potentiometric titration, except for indazolium ion and its two *N*-methyl derivatives. Ionic strength was kept constant at 0.1 M KCl except for pyrazolium and *N*-methylpyrazolium ions, which were determined at 0.5 M KCl ionic strength.

In the procedures followed for the pK_a measurements, apparent pK_a values were actually determined, except for the dissociation equilibria of imidazole **1a**, benzimidazole **2a**, pyrazole **3a**, and indazole **4a** (acidic pK_a's). In all the other cases, the true thermodynamic pK_a values were estimated by using the correction[23] $pK_{\mu=0} = pK_{obsd} - 0.5\mu^{1/2}/(1 + \mu^{1/2})$.

Table III. Aqueous Basicity: Experimental pK_a Values of Azolium Ions (Deprotonation in Water at 298.15 K)

compound	pK_a	μ
imidazolium **1aH$^+$**	7.11 ± 0.02[a]	0.1
1-methylimidazolium **1bH$^+$**	7.25 ± 0.01[b]	0.1
benzimidazolium **2aH$^+$**	5.68 ± 0.01[c]	0.1
1-methylbenzimidazolium **2bH$^+$**	5.67 ± 0.02	0.1
pyrazolium **3aH$^+$**	2.64 ± 0.02[d]	0.5
1-methylpyrazolium **3bH$^+$**	2.19 ± 0.02	0.5
indazolium **4aH$^+$** (**5aH$^+$**)	1.25 ± 0.02	0.5
1-methylindazolium **4bH$^+$**	0.51 ± 0.02	0.5
2-methylindazolium **5bH$^+$**	2.13 ± 0.03	0.1

[a] In good agreement with literature results: 6.993 ± 0.002 at μ = 0,[30] 7.22 ± 0.01 at μ = 0.5,[15] 7.14 ± 0.02 at μ = 0.15.[23] [b] Our value is slightly larger than literature values: 7.20 ± 0.01 at μ = 0.15,[23] 7.20 at μ = 1.0,[31] 7.18 at μ = 0.5.[32] [c] Comprised between the best literature values: 5.58 ± 0.02 at μ = 0.16,[33] 5.55 ± 0.04 at μ = 0,[34] 5.77 ± 0.01 at μ = 0.5.[15] [d] In good agreement with the values 2.65 ± 0.03 at μ = 0.2[35] and 2.56 ± 0.01 at μ = 0.5.[15]

Calorimetric Measurements. Calorimetric titrations were performed with a LKB 10700-1 batch microcalorimeter equipped with a LKB titration unit (2107-350).[36] The syringe system was calibrated by weighing the water delivered by the syringes. Control experiments were carried out to determine the small differential compression/mixing and dilution effects, and these results were used to correct the heat quantities recorded in the reaction experiments.[36]

The sensitivity of the instrument was increased 2.5 times by using Melcor thermoelements instead of the Cambion ones used by the manufacturer. The differential calorimetric signal was amplified with a Keithley 150B microvoltmeter. The output voltage-time curve was integrated by a microprocessor and simultaneously monitored by a potentiometric recorder. The calorimeter was calibrated as previously described.[37] Protonation experiments of Tris with HCl gave an average value of −11.3 ± 0.1 kcal/mol at 298.15 K (μ = 0; volume of HCl added in each injection, 5.20 μL) in agreement with literature values.[36,38]

Acidic Ionization Enthalpies. For the determination of these enthalpies for imidazole **1a**, benzimidazole **2a**, pyrazole **3a**, and indazole **4a**, the reaction and the reference vessel were charged with 4.5 mL of NaOH. The reaction syringe was charged with the sample dissolved in 0.5 M KCl and the reference syringe with 0.5 M KCl at the same pH value as the sample solution. The concentration of NaOH in all the experiments carried out with benzimidazole and indazole was 0.5 M. For imidazole and pyrazole, the concentration of NaOH was changed for each series of experiments (0.18–0.5 M). The ionic strength was 0.5.

The dilution of neutral azoles in alkaline solutions can be represented by the reactions:

$$HA_{aq}(v_0) + aq(v) \rightarrow HA_{aq}(v_0 + v),\ \ \Delta H = \Delta H_{d,ln} \qquad (3)$$

$$HA_{aq} + OH_{aq}^- \rightarrow A_{aq}^- + H_2O,\ \ \Delta H = \Delta H_1 \qquad (4)$$

where v_0 and v are the volumes of the azole and the alkaline solutions, respectively. The actual calorimetric experiment can be described by (5), once the dilution heat effect, determined in separated control experiments, has been substracted.

$$HA_{aq} + OH_{aq}^- \rightarrow (1 - \alpha)HA_{aq} + \alpha A_{aq}^- + \alpha H_2O,\ \ \Delta H = \Delta H_2 \qquad (5)$$

$$\Delta H_2 = \alpha \Delta H_1 \qquad (6)$$

Assuming that the activity coefficient factor $\gamma_{A^-} \cdot a_{H_2O}/\gamma_{OH^-} \cdot \gamma_{HA}$ is equal to 1, the equilibrium constant K for the (4) can be defined as

$$K = \frac{\alpha}{(1 - a)[[OH^-] - \alpha[HA]]} \qquad (7)$$

where [OH$^-$] and [HA] refer to the concentrations of hydroxyl ions and azole before (4) takes place. Combination of (6) and (7) gives

$$\Delta H_1^2 - \Delta H_1 \Delta H_2\left(1 + \frac{[AH]}{[OH^-]} + \frac{1}{K[OH^-]}\right) + \Delta H_2^2 \frac{[AH]}{[OH^-]} = 0 \quad (8)$$

If $[OH^-] \gg \alpha[AH]$, as it is the case in our experimental conditions, it follows that

$$\Delta H_1 = \Delta H_2\left(1 + \frac{K_w}{K_a} \times \frac{1}{[OH^-]}\right),\ K = K_a/K_w \qquad (9)$$

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Table IV. Aqueous Acidity: Thermodynamic Data for Proton Ionization of Unsubstituted Azoles at 298.15 K

compound	$\Delta G°$, kcal mol^{-1a}	$\Delta H°$, kcal mol^{-1}	$\Delta S°$, cal K^{-1} mol^{-1}	μ	ref
imidazole **1a**	19.24 ± 0.14	14.89 ± 0.31^{b,c}	−14.51 ± 1.51	0.5	this work
benzimidazole **2a**	16.98 ± 0.02	12.09 ± 0.17^{b}	−16.39 ± 0.48	0.5	this work
pyrazole **3a**	18.93 ± 0.12	13.91 ± 0.14^{b}	−16.80 ± 0.88	0.5	this work
indazole **4a**/**5a**	18.50 ± 0.05	13.65 ± 0.19^{b}	−16.30 ± 0.79	0.5	this work
1,2,4-triazole **6a**/**7a**	12.97 ± 0.01	9.26 ± 0.02	−12.40 ± 0.09	0.5	15
1,2,3-triazole **8a**/**9a**	11.97 ± 0.02	8.89 ± 0.02	−10.40 ± 0.19	0.05	11
benzotriazole **10a**/**11a**	10.78 ± 0.05	7.46 ± 0.07^{d}	−11.09 ± 0.41	0.1	this work
tetrazole **12a**/**13a**	5.86 ± 0.01	3.08 ± 0.07	−9.30 ± 0.29	0.05	13

[a] A statistical correction has been applied to the data of Table I, taking into account the number of nitrogen atoms in the corresponding conjugate base, **1a**–**4a**, $n = 2$; **6a**–**10a**, $n = 3$; **12a**, $n = 4$ (for more details, see ref 41). [b] $\Delta H°$ are given with regard to the $\Delta H°$ of water ionization at 298.15 K (+13.34 kcal mol^{-1}).[42] [c] A value of $\Delta H° = 16.6 \pm 1.6$ kcal mol^{-1} and $\Delta S° = -8.8 \pm 5.0$ cal K^{-1} mol^{-1} was calculated by the authors[25] from potentiometric titrations at different temperatures (pK_a = 14.44 at 298.15 K). [d] Literature values: 7.47 ± 0.05,[11] 7.12 ± 0.02 kcal mol^{-1}.[15]

Table V. Aqueous Basicity: Thermodynamic Data for Deprotonation of Azolium Ions at 298.15 K

compound	$\Delta G°$, kcal mol^{-1a}	$\Delta H°$, kcal mol^{-1}	$\Delta S°$, cal K^{-1} mol^{-1}	μ
imidazolium **1aH$^+$**	9.96 ± 0.02	8.82 ± 0.05	−3.8 ± 0.2	0.1
1-methylimidazolium **1bH$^+$**	9.72 ± 0.01	8.08 ± 0.07	−5.5 ± 0.2	0.1
benzimidazolium **2aH$^+$**	7.99 ± 0.01	7.24 ± 0.07	−2.5 ± 0.2	0.1
1-methylbenzimidazolium **2bH$^+$**	7.57 ± 0.02	6.57 ± 0.05	−3.4 ± 0.2	0.1
pyrazolium **3aH$^+$**	3.73 ± 0.02	3.75 ± 0.02	0.1 ± 0.2	0.5
1-methylpyrazolium **3bH$^+$**	2.70 ± 0.02	1.91 ± 0.02	−2.6 ± 0.2	0.5
indazolium **4aH$^+$** (**5aH$^+$**)	1.41 ± 0.02	2.22 ± 0.02	2.7 ± 0.2	0.5
1-methylindazolium **4bH**	0.41 ± 0.02	0.78 ± 0.05	1.2 ± 0.2	0.5
2-methylindazolium **5bH$^+$**	2.75 ± 0.02	2.51 ± 0.02	−0.8 ± 0.1	0.5
2-methylimidazolium **14aH$^+$**	11.16 ± 0.02	9.73 ± 0.09	−4.8 ± 0.2	0.1

[a] Corrected as in Table III.

where K_a is the acidity constant of the azole and K_w is the dissociation constant of water. If the equilibrium constant K_a is known, it is possible to determine with (9) the apparent ionization enthalpy, ΔH_1, from the experimental enthalpy change at each hydroxyl ion concentration, ΔH_2, and, accordingly, the ionization enthalpy change, $\Delta H_i = \Delta H_1 + \Delta H_{H_2O}$ (the latter one being the enthalpy of ionization of water).

For those compounds whose ionization parameters, K_a and ΔH_i, were derived simultaneously from calorimetric measurements (imidazole **1a** and pyrazole **3a**), (9) was modified as follows:

$$\frac{1}{\Delta H_2} = \frac{1}{\Delta H_1}\left(1 + \frac{K_w}{K_a} \times \frac{1}{[\mathrm{OH}^-]}\right) \qquad (10)$$

The equilibrium constant and the apparent enthalpy changes were calculated from the ordinate intercept and the slope of the least-squares straight line fitted by following (10).

Basicity: Protonation Enthalpies. The protonation enthalpies of **1a**, **1b**, **2a**, **2b**, and **14a** were determined by successive injections of a few microliters of HCl into the reaction and reference vessels, charged with 4.5 mL of the compound solution (in 0.1 M KCl) and 0.1 M KCl, respectively. In all the experiments, the azole concentration was in excess and the protonation enthalpy change was calculated from the quantity of micromoles of HCl added. The protonation enthalpy of the basic nitrogen for those azoles whose pK_a values were below 3 (pyrazole **3a**, 1-methylpyrazole **3b**, indazole **4a**, 1-methylindazole **4b**, and 2-methylindazole **5b**) was determined by dilution of the neutral form in 0.5 M HCl. The reaction and reference cells were charged with 4.5 mL of the HCl solution, and the syringes leading to them were filled with the sample solution (in 0.5 M KCl) and 0.5 M KCl, respectively.

The dilution of the neutral form of azoles in acidic solutions can be described by the following scheme:

$$\mathrm{HA_{aq}}(v_0) + \mathrm{aq}(v) \rightarrow \mathrm{HA_{aq}}(v_0 + v),\ \Delta H = \Delta H_{\mathrm{diln}} \qquad (11)$$

$$\mathrm{HA_{aq}} + \mathrm{H_{aq}}^+ \rightarrow \mathrm{H_2A_{aq}}^+,\ \Delta H = \Delta H_{\mathrm{p}} \qquad (12)$$

and the calorimetric experiment by (13) when heat quantities measured in the reaction experiments are corrected by substracting the heat of dilution effect. Assuming the activity coefficient γ_{AH} to be unity, the

$$\mathrm{HA_{aq}} + \mathrm{H_{aq}}^+ \rightarrow \alpha\mathrm{H_2A^+} + (1 - \alpha)\mathrm{HA_{aq}},\ \Delta H = \Delta H_2 \qquad (13)$$

$$\Delta H_3 = \alpha \Delta H_{\mathrm{p}} \qquad (14)$$

protonation equilibrium constant can be expressed as

$$K = \frac{\alpha}{(1 - \alpha)\{[\mathrm{H}^+] - \alpha[\mathrm{AH}]\}} \times \frac{\gamma_{\mathrm{H_2A^+}}}{\gamma_{\mathrm{H^+}}} \qquad (15)$$

where [H$^+$] and [AH] are the proton and azole concentrations before protonation takes place. If, as it happens in our experimental conditions, $[\mathrm{H}^+] \gg \alpha[\mathrm{AH}]$, (15) can be simplified to

Table VI. Influence of the Annelation on the Aza Effect

	$\delta\Delta G_{\mathrm{gas}}°$	$\delta\delta\Delta G_{\mathrm{gas}}°$	$\delta\Delta G_{\mathrm{aq}}°$	$\delta\delta\Delta G_{\mathrm{aq}}°$
imidazolium–pyrazolium	10.9		6.2	
		0.0		0.3
benzimidazolium–indazolium	10.9		6.5	
1-methylindazolium–1-methylpyrazolium	10.6		7.0	
		−0.5		0.1
1-methylbenzimidazolium–1-methylindazolium	10.1		7.1	
imidazole–pyrazole	−3.3		0.3	
		−1.8		−1.8
benzimidazole–indazole	−5.1		−1.5	

$$K = \frac{\alpha}{(1 - \alpha)a_{\mathrm{H^+}}} \times \gamma_{\mathrm{H_2A^+}} \qquad (16)$$

and (17) can be easily derived in a way similar to that used for dilution in alkaline solutions, where $K_{\mathrm{app}} = K^{-1}\gamma_{\mathrm{H_2A^+}}$ is the apparent deprotonation constant determined experimentally by spectrophotometry or potentiometry at ionic strength $\mu = 0.5$.

$$\Delta H_{\mathrm{p}} = \Delta H_3\left(1 + K_{\mathrm{app}}\frac{1}{10^{-\mathrm{pH}}}\right) \qquad (17)$$

The relationships between the thermodynamic quantiaties $\Delta G°$, $\Delta H°$, and $\Delta S°$ have been calculated by the method of Exner[39] and Krug, Hunter, and Grieger-Block.[40]

Results and Discussion

The thermodynamic results are in Tables I and IV–VI.

Azole Acidities in Aqueous Solution. The values of Table IV were fitted to (18), by using Exners's method[39] where β is the isoequilibrium temperature. By use of the weighted least-squares

$$\Delta H° = h_{\mathrm{o}} + (\beta/\beta - T)\Delta G° \qquad (18)$$

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Table VII. N-Methylation Effects on the Thermodynamics Data for Deprotonation of Azolium Ion ($\delta\Delta X^\circ = \Delta X_{\mathrm{NMe}}^\circ - \Delta X_{\mathrm{NH}}^\circ$)[a]

	$\delta\Delta G_{\mathrm{gas}}^{\circ b}$	$\delta\Delta G_{\mathrm{aq}}^{b}$	$\delta\Delta H_{\mathrm{gas}}^{b}$	$\delta\Delta H_{\mathrm{aq}}^{b}$	$\delta\Delta G_{\mathrm{ext}}^{\circ b}$	$\delta\Delta H_{\mathrm{ext}}^{b}$	$\delta T\Delta S^{b}$
imidazolium (**1bH$^+$–1aH$^+$**)	3.4	−0.2	3.4	−0.7	−3.6	−4.1	+0.5
benzimidazolium (**2bH$^+$–2aH$^+$**)	~3.7	−0.4	~3.7	−0.7	~−4.1	~−4.4	~+0.3
pyrazolium (**3bH$^+$–3aH$^+$**)	3.7	−1.0	3.7	−1.8	−4.7	−5.5	+0.8
indazolium (**4aH$^+$–4aH$^+$**)	4.6	−1.0	4.6	−1.5	−5.6	−6.1	+0.5

[a] $\Delta X^\circ \equiv \Delta G^\circ$, ΔH°, or ΔS°. [b] Kilocalories/mole.

algorithm describe by Irvin and Quickenden,[43] we obtained (19) and the corresponding β value for $T = 298.15$ K.

$$\Delta H^\circ = -6.32\ (\pm 2.26) + 0.835\ (\pm 0.042)\Delta G^\circ \qquad (19)$$

$$\beta = -2164\ (\pm 659)\ \mathrm{K},\ n = 8,\ r = 0.992$$

These results show that the reaction is neither isoenthalpic nor isoentropic (as assumed);[13] the reaction thus belongs to the *anticompensation* group.[39] Recent work[44] suggest that it is not worth seeking a physical meaning for β, other than the fact that ΔH° and ΔS° are shifted in opposite directions on azole variation.

Azole Basicities in Aqueous Solution. Equation 18 and the aqueous basicity data of Table V give (20) in which the isoequilibrium temperature $\beta = -1638$ K, is a little smaller than the previous one but still of the same *anticompensation* class.[39]

$$\Delta H^\circ = 1.155\ (\pm 0.086) + 0.846\ (\pm 0.038)\Delta G^\circ \qquad (20)$$

$$\beta = -1638\ (\pm 400)\ \mathrm{K},\ n = 10,\ r = 0.992$$

Since azoles are heteroaromatic bases, it is interesting to compare them with pyridines, to find out whether there are differences due to the ring size, hybridation, or aromaticity. From the literature values[45] of 3- and 4-substituted pyridines, (21) is obtained.

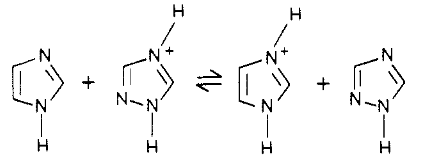
$$\Delta H^\circ = -2.79\ (\pm 0.75) + 0.839\ (\pm 0.03)\Delta G^\circ \qquad (21)$$

$$\beta = -1558\ (\pm 346)\ \mathrm{K},^{46}\ n = 11,\ r = 0.995$$

The slopes of (20) and (21) and the corresponding β values are very similar; the azoles behave as pyridinic bases. Another more surprising conclusion is that azolate anions (19) are also pyridinic bases. *Thus, pyridines, azoles, and azolate anions are bases of very similar nature.* Their strengths are independent of variations in size and charge.

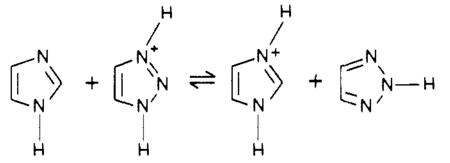
At the same time, it is of little value to use Hepler's theory[23,48] to calculate $\delta\Delta H_{\mathrm{int}}$ for the effects that interest us in these systems because the values thus calculated cannot describe conveniently the corresponding $\delta\Delta H_{(\mathrm{gas})}$, since some of the electronic effects that contribute significantly to that term, e.g., the polarizability, are almost completely lost when going to aqueous solution.[49]

Aza Effects. Recently, Mautner et al.[17] using HPMS measurements at 600 K found that the basicity difference between imidazole and 1,2,4-triazole is 9.7 kcal/mol [see (22)].

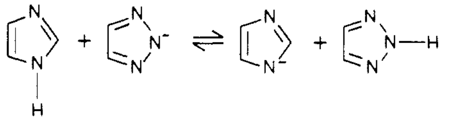

(22)

$\Delta G^\circ = -9.7$ kcal/mol

From Table I data, the ΔG° values for equilibria 23 and 24 are respectively:


(23)

$\Delta G^\circ = -13.9$ kcal/mol


(24)

$\Delta G^\circ = 4.1$ kcal/mol

It is possible to analyze the information existing at this moment concerning triazoles within the framework of the electrostatic model we proposed recently[5] for diazoles and diazines. With this model, the calculated ΔG° values for the above equilibria (eq 22–24) are −8.5, −11.5, and 1.5 kcal/mol, respectively. It is worth noting that the calculations involving 1,2,3-triazole (eq 23 and 24) show a discrepancy of about 2.5 kcal/mol, the 1,2,3-triazole being more acidic and less basic than our model predicts, very probably because of the presence of three adjacent nitrogens.

For the compounds studied we must ask whether the aza effect is modified by annelation. The answer is in Table VI, where the free energy differences of azoles and benzazoles pairs are collected, both for the gas phase and the aqueous solution. The $\delta\delta\Delta G^\circ$ values, also reported in Table VI, stand for $\delta\Delta G^\circ$ differences in basicity and in acidity.

Clearly the additional benzene ring plays a different role in 1,2 and 1,3 situations only for the acidity process, i.e., when anions are involved, but does not significantly intervene when cations are involved.

N-Methylation Effect on the Basicity. In discussing the effect of the substitution on the nitrogen atom (**b** series vs **a** series) it is useful to calculate the $\delta\Delta X^\circ$ values of Table VII from the corresponding ΔX° values of Table V and from the gas-phase data Table I (X refers to G°, H°, or S°).

As can be seen, $\delta\Delta H_{\mathrm{aq}}^\circ$ and $\delta\Delta S_{\mathrm{aq}}^\circ$ are always negative: the N-methylation causes an enthalpy decrease and an entropy increase of the basicity. The enthalpy changes are larger for 1,2-diazoles, pyrazolium, and indazolium, than for 1,3-diazoles, imidazolium, and benzimidazolium.

To obtain information about the changes for the N-methylation effect going from the gas phase to the aqueous solution we need to estimate the external (solvent) contributions to $\delta\Delta X_{\mathrm{aq}}^\circ$. We use the expression $\delta\Delta X_{\mathrm{ext}}^\circ = \delta\Delta X_{\mathrm{aq}}^\circ - \delta\Delta X_{\mathrm{gas}}^\circ$ (Table VII).

We can now draw the following conclusions from the information gathered in that table.

(i) The N-methylation increases the intrinsic basicity by 3.4–4.6 kcal/mol.

(ii) The N-methylation decreases the basicity in aqueous solution, and this is an enthalpy effect mainly due to the loss of an "active solvation center".[12] This effect is appreciably greater in 1,2-diazoles (pyrazole, indazole) than in 1,3-diazoles (imidazole, benzimidazole), which is to be expected because of the difference in the polarizability effects of a methyl group in ortho and meta positions in the pyridine series (1.2 kcal mol^{-1}).[49] However, it must be remembered that the difference between both classes of

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(46) Exner[47] reported $\beta = +3670$ K (i.e., isoentropic); an examination of his sources reveals that the data arise from the van't Hoff equation, which is, according to Exner, very unreliable for entropic calculations.

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Table VIII. Comparative Annelation Effects in Benzene and Imidazole[a]

$$\Delta H_{g\rightarrow aq}{}^{\circ} = \Delta H_{aq}{}^{sol} - \Delta H^{sub(vap)}$$

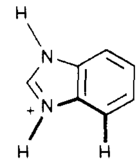
	benzene	imidazole	naphthalene	benzimidazole
$\Delta H_{aq}{}^{sol}$	0.5^{51}	$3.1^{52,53}$	$7.1^{54,55}$	4.8^{56}
$\Delta H^{sub(vap)}$	8.1^{57b}	19.3^{58}	17.4^{59}	23.6^{50}
$\Delta H_{g\rightarrow aq}{}^{\circ}$	−7.6	−16.2	−10.3	−18.8
specific reactions	−8.6		−8.5	

[a] Values in kilocalories/mole. [b] ΔH^{vap}.

diazoles is already implicit in the corresponding $\delta\Delta H_{aq}$ values.

(iii) The entropy contribution accounts for the relative increase in the basicity (~0.5 kcal/mol) of the N-methylated derivative in aqueous solution.

Annelation Effects on Acid-Base Properties. It is interesting to examine possible steric hindrance in the solvation of the benzimidazole protonated form (peri effect). As we have suggested elsewhere and confirmed here, benzimidazole is more basic than imidazole in the gas phase but less basic in aqueous solution.[16] This inversion may be due to a peri steric effect in the **2aH⁺** cation.



2aH⁺

A recent determination of the heat of sublimation of benzimidazole[50] has made possible an estimation of the specific interaction of the aqueous solvent with benzimidazole **2a** (Table VIII).

The solvent effects on the neutral molecules **1a** and **2a** are identical with and insensitive to the peri effect, probably because the specific interactions of benzimidazole **2a** with respect to naphthalene are nearly identical, with those of imidazole **1a** with respect to benzene. As water specific solvation effects of benzimidazole **2a** and benzimidazolium ion **2aH⁺** should have similar steric contributions, the values in Table VIII indicate that the decrease of the basicity of benzimidazole in water is not due to a peri steric effect.

Table IX shows the annelation effects in the gas phase and in aqueous solution, as well as the calculated external contributions.

From these values the following conclusions can be drawn.

(i) The intrinsic annelation effect increases the basicity of the reported imidazoles and pyrazoles from 1.5 to 2.4 kcal/mol. It is worth noting that these values are much lower than those, about 6 kcal/mol, founded by Mautner[14] for the azines protonation.

(ii) Annelation affects the acidity much more than the basicity varying from 5.9 to 8.2 kcal/mol in the studied compounds.

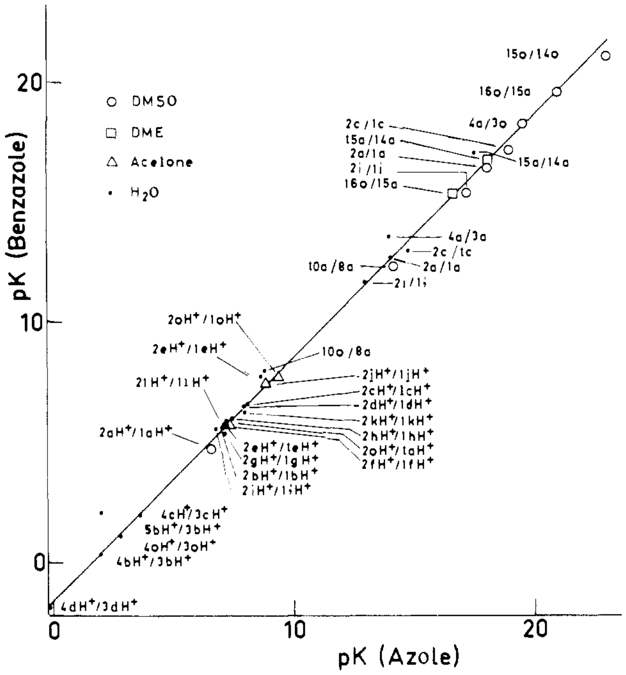


Figure 1. Plot of benzazole pK_a's vs azole pK_a's in water (●), DMSO (○), acetone (△), and DME (□) solutions. **1a**, imidazole; **1b**, 1-methylimidazole; **1c**, 2-methylimidazole; **1d**, 2-ethylimidazole; **1e**, 1-ethylimidazole; **1f**, 1-*n*-propylimidazole; **1g**, 1-*n*-butylimidazole; **1h**, 2-benzylimidazole; **1i**, 2-phenylimidazole; **1j**, 2-aminoimidazole; **1k**, 1,2-dimethylimidazole; **1l**, 1-vinylimidazole; **2a**, benzimidazole; **2b**, 1-methylbenzimidazole; **2c**, 2-methylbenzimidazole; **2d**, 2-ethylbenzimidazole; **2e**, 1-ethylbenzimidazole; **2f**, 1-*n*-propylbenzimidazole; **2g**, 1-*n*-butylimidazole; **2h**, 2-benzylbenzimidazole; **2i**, 2-phenylbenzimidazole; **2j**, 2-aminobenzimidazole; **2k**, 1,2-dimethylbenzimidazole; **2l**, 1-vinylbenzimidazole; **3a**, pyrazole; **3b**, 1-methylpyrazole; **3c**, 3(5)-methylpyrazole; **3d**, 3(5)-chloropyrazole; **4a**, indazole; **4b**, 1-methylindazole; **4c**, 3-methylindazole; **4d**, 3-chloroindazole; **5b**, 2-methylindazole; **8a**, 1,2,3-triazole; **10a**, benzotriazole; **14a**, pyrrole; **15a**, indole; **16a**, carbazole.

(iii) The inversion of basicity observed in aqueous solution (where the benzologues are always less basic than the corresponding azoles) is due to the annelation enthalpy, which lowers the basicity between 3.6 and 4.7 kcal/mol.

(iv) The external enthalpy effect of annelation ($\delta\Delta H_{ext}$) is significantly greater on the acidity than on the basicity. Compare, for instance, the respective data for the pyrazole/indazole pair, 5.6 and 3.6 kcal/mol. However it is not large enough to make the benzazoles less acidic than the corresponding azoles. It should be noted that $\delta\Delta G_{ext}$ mainly reflect the $\delta\Delta H_{ext}$ variation.

The fact that, with respect to the corresponding azole, the protonation and, especially, the deprotonation of a benzazole is thermodynamically favored in solution can be explained as a result of larger charge dispersion in the latter. This effect is additional to that arising from the larger dimension of benzazole, which results in less solvation of the charged species. However, differences in polarizability can also play a significant role.

That this effect is greater on the acidity than on the basicity may be because azoles are electron-rich systems, which more readily accommodate positive rather than the negative charge.

In 1979, Therekova et al.[19a] found that in DMSO there is a linear relationship between the pK_a of benzazoles (carbazole, indole, benzimidazole, indazole, and 2-phenylbenzimidazole) and those of the corresponding azoles (indole, pyrrole, imidazole, pyrazole, and 2-phenylimidazole). As shown in Figure 1, we find that the scope of this relationship is even broader, as it applies to both acidities and basicities in water, in DMSO, and, in some other solvents as DME and acetone (few data, see Figure 1).

It is noteworthy that this linear relationship spans a range of some 23 pK_a units, with essentially unity slope (1.009). The intercept is ca. −1.6 pK_a units. Thus annelation increases the acidity of the neutral and the protonated forms in solution by the

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Table IX. Annelation Effect on Basicity and Acidity of Azoles[a]

	$\delta\Delta G_{gas}°$	$\delta\Delta G_{aq}°$	$\delta\Delta H_{gas}$	$\delta\Delta H_{aq}$	$\delta\Delta G_{ext}°$	$\delta\Delta H_{ext}°$	$T\delta\Delta S°$
$2aH^+$-$1aH^+$	~1.6	-2.0	~-1.6	-1.6	~-3.6	~-3.2	~+0.4
$2bH^+$-$1bH^+$	1.9	-2.1	1.9	-1.5	-4.0	-3.4	+0.6
$4aH^+$-$3aH^+$	1.5	-2.3	1.5	-1.5	-3.8	-3.0	+0.8
$4bH^+$-$3bH^+$	2.4	-2.3	2.4	-1.2	-4.7	-3.6	+1.1
4a-3a	-5.9	-0.4	-5.9	-0.3	5.5	5.6	+0.1
2a-1a	~-7.3	-2.3	~-7.3	-2.8	~5.0	~4.5	~-0.5
10a-8a	-8.2	-1.2	-8.2	-1.4	7.0	6.8	-0.2

[a] Values in kilocalories/mole.

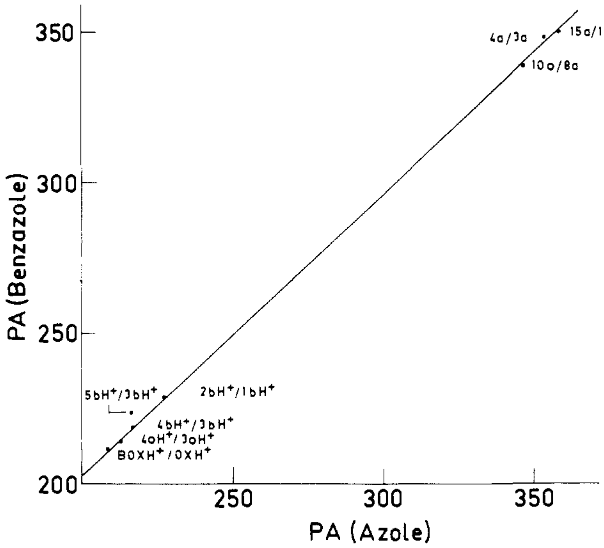

Figure 2. Benzazole PA's vs azole PA's. The PA values are from Table 1 except the benzoxazole/oxazole pair ($BOXH^+/OXH^+$). For these last compounds the value for oxazole is that of ref 17 and the value for benzoxazole has been calculated from the experimental evidente[60] indicating that benzoxazole is 1.0 kcal/mol more basic than 2-fluoropyridine ($\Delta G_{std}°$, see Table I).

same constant amount, 1.6 pK_a units.

As can be seen in Figure 2, there is a linear relationship between the corresponding data in the gas phase:

$$PA_{benz} = 17.7 + 0.93PA_{azole} \tag{25}$$

$$n = 7,\ r^2 = 0.999$$

A detailed comparison of the effect of solvent on acidities where annelation is involved shows that there is a reduction of this effect in dimethyl sulfoxide compared to the gas phase by a factor of $^1/_3$ and for dimethyl sulfoxide compared to water by another factor of about $^1/_3$. These solvent attenuation factors are very different from those observed for the effects on acidity of 1,2- and 1,3-aza substitution. These last solvent effects will be discussed in depth in a future paper.

It is worth noting that in Figures 1 and 2 the point corresponding to 2-methylindazole/1-methylpyrazole clearly deviates from the straight line. This is probably because 2-methylindazole is the only benzazole in this study with a "quinoid" structure **5b**, which lowers its stability relative to "benzenoid" systems like 1-methylindazole, **4b**.

The proton affinities of 1-methylindazole (PA = 218.8 kcal/mol) and 2-methylindazole (PA = 223.4 kcal/mol) point to the greater stability of the 1*H*-indazole tautomer in the gas phase. This conclusion supports the results obtained in gas phase from a UV study of the absorption and emission of indazoles.[61] From gas-phase measurements and from STO-3G/INDO calculations it is possible to estimate that the stability difference between both indazole tautomers, **4a** ⇄ **5a**, is slightly less than 4.7 kcal/mol in favor of the 1*H* tautomer **4a**. In water,[62] K_T = **4a**/**5a** = 40, which corresponds to $\Delta G°$ = 2.2 kcal/mol. Thus, water more effectively stabilizes the tautomer **5a** because of the high dipole moment.

The results obtained in this work justify the importance assigned in the introduction to azoles as substrates for fundamental structural studies. With careful measurements of thermodynamic quantities both in the gas phase and in solution it is possible to disentangle the complex situation of acid-base equilibria of azoles in solution.

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