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An Experimental and Theoretical Study of the Acid–base Properties of Substituted Indoles.

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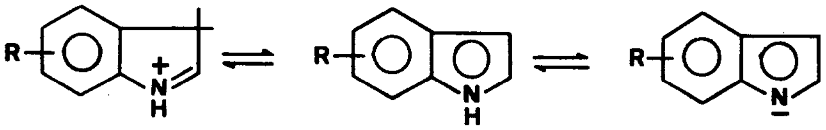
Abstract: Experimental and theoretical studies on the acidity and basicity of a representative set of benzene substituted indoles have been carried out. Aqueous ionization data, obtained spectrophotometrically at 25°C, were comparatively analyzed by the Hammett Acidity function and the Excess Acidity methods. Ionization constants, pKas and solvation m^* parameters are reported. Gas–phase ionization enthalpies have been theoretically calculated using the AM1 semiempirical method. Single and double parameter relationships between the theoretical and experimental ionization data and the Hammett substituent constants are observed.

The acid–base properties represent a fundamental aspect in indole chemistry and, therefore, much experimental and theoretical work on this subject has been already performed.[1] Indoles protonate at ß–carbon atom giving 3H–indolium (or indoleninium) cations and deprotonate at pyrrolic nitrogen atom to give indolate anions (Scheme 1). In aqueous solutions, the acid and basic strengths of indoles are too weak to be measured in the pH–region and, therefore, in pioneering works, the quantitative measurements of the acidities and basicities of indole derivatives were expressed by using different acidity functions.[2-5] In contrast to the widely studied acid–base properties of indoles in aqueous–phase, analogous studies in gas–phase have received very little attention.[6,7]



Scheme 1.– Ionization equilibria of indole ring.

The study of the acid–base properties of benzene substituted indoles should afford information on the transmission mechanisms of electrical effects through the indole ring. However, in spite of their obvious importance, the relationships between these properties and the type and position of the substituents have not been comprehensively analyzed due to the lack of suitable data. The papers of R.L. Hinman and J. Lang[2,3] and G. Yagil[4,5], which constitute the main sources for pKa data of indoles, list a great number of them, but only in some instances, they constitute series in which one parameter has been systematically varied for the purpose of determining substituent effects. Furthermore, since a great number of indole derivatives do not follow any acidity function, the reported pKa values do not represent accurate data concerning the effect of the substituents.

In the framework of our current research program on physicochemical properties and reactivity of indole derivatives of biological and pharmacological significance, we have recently devoted much work to obtain more extensive and accurate data on ionization equilibria of different families of indole derivatives.[8-11] These studies have shown that the Excess Acidity (EA) method[12-14] is more useful than the Hammett Acidity (HA) method. The first method gives reliable pKa values for deviant and non deviant indoles and also interesting information concerning the solvation requirements of the acid–base conjugate pairs.[15] On the other hand, some interesting correlations between pKa values and σ Hammett constants have emerged from some of our studies.

This paper presents a more extensive documentation on these early results and combines them with theoretical gas–phase results obtained by the AM1 semiempirical method. Gas–phase data can provide a more comprehensive insight into the influence of substituents on the intrinsic acid–base properties of indoles in the absence of solvent. We have recently proved that AM1 method gives reliable description of the electronic properties of different substituted and unsubstituted families of indole related compounds and it satisfactorily estimates their gas–phase ionization energies.[16-18]

EXPERIMENTAL AND METHODS.

All indoles used in this study were commercial products of the best available quality (>98%, Aldrich Quimica, Sigma, Lancaster) and were used as received. Stock solutions in the concentration range 1×10^{-3} – 10×10^{-3} M were prepared in methanol and furtherly diluted with appropriate sulphuric acid or potassium hydroxide solutions to finally contain not more than 4% v/v of methanol. Solutions in highly concentrated basic media needed, in some instances, to be warmed, to bring about complete solution. Aqueous potassium hydroxide and sulphuric acid solutions were prepared as described by Yagil[4] and from 96% w/w reagent analysis grade sulphuric acid (Merck), respectively. All these solutions were standardized against appropriate solutions of acids and bases, respectively.

The solutions of indoles were usually stable enough for spectrophotometric measurements and the reversibility of the spectra upon protonation or deprotonation was confirmed. The spectra showed good isosbestic points, thus indicating a very small solvent effect. UV–visible absorption spectra were carried out on a Perkin–Elmer Lambda 5 spectrophotometer whose cell compartment was thermostatted at 25 + 0.1°C. Blanks of the appropriate solvents were always used.

TABLE 1.– Ionization data analysis of the protonation equilibria at 25°C of benzene substituted indoles. The figures between parenthesis are the correlation coefficients.

		HAMMETT			E.A.M.	
	dlogI/d[H_2SO_4]	–dlogI/dH_I	pKa	$(H_I)_{1/2}$[(a)]	m*	pKa
Indole[(b)]	0.46±0.07(0.978)	0.67±0.10(0.978)	–2.38±0.3	–3.55	0.95±0.17(0.967)	–2.43±0.3
4–Me	0.49±0.02(0.999)	0.71±0.03(0.999)	–2.34±0.10	–2.43	1.01±0.07(0.990)	–2.36±0.3
4–OH	0.37±0.04(0.995)	0.54±0.05(0.995)	–2.12±0.05	–2.16	0.72±0.06(0.995)	–2.20±0.2
4–MeO	0.45±0.03(0.998)	0.66±0.05(0.998)	–2.92±0.22	–2.70	0.88±0.09(0.996)	–2.82±0.1
4–Cl	0.48±0.03(0.999)	0.70±0.04(0.999)	–3.66±0.20	–3.15	0.87±0.06(0.998)	–3.48±0.2
4–COOH	0.71±0.06(0.998)	1.02±0.09(0.998)	–5.35±0.44	–5.06	1.37±0.05(0.998)	–4.86±0.1
4–NO_2	0.57±0.04(0.998)	0.82±0.06(0.998)	–5.43±0.43	–5.42	1.06±0.10(0.998)	–5.04±0.2
5–Me	0.39±0.04(0.996)	0.56±0.05(0.996)	–1.98±0.20	–3.54	0.78±0.07(0.997)	–2.09±0.1
5–OH	0.42±0.01(0.999)	0.60±0.02(0.999)	–2.15±0.07	–3.58	0.82±0.04(0.999)	–2.19±0.07
5–MeO	0.40±0.03(0.998)	0.58±0.04(0.998)	–2.11±0.15	–3.64	0.82±0.08(0.996)	–2.26±0.16
5–Cl	0.28±0.01(0.999)	0.41±0.02(0.999)	–2.04±0.10	–5.00	0.48±0.03(0.999)	–2.18±0.08
5–Br	0.33±0.02(0.999)	0.48±0.02(0.999)	–2.26±0.4	–4.70	0.60±0.03(0.999)	–2.33±0.08
5–CN	0.40±0.03(0.998)	0.58±0.04(0.998)	–3.81±0.25	–6.57	0.72±0.05(0.998)	–3.72±0.20
5–COOH	0.35±0.03(0.997)	0.51±0.04(0.997)	–2.89±0.24	–5.67	0.64±0.05(0.987)	–2.90±0.20
5–NO_2	0.39±0.04(0.997)	0.57±0.05(0.997)	–4.38±0.45	–7.80	0.68±0.08(0.996)	–4.18±0.40
6–Me	0.37±0.04(0.995)	0.54±0.06(0.995)	–1.98±0.22	–3.66	0.70±0.08(0.994)	–2.04±0.18
6–MeO	0.45±0.03(0.998)	0.66±0.05(0.998)	–2.92±0.22	–4.42	0.88±0.09(0.996)	–2.87±0.22
6–Cl	0.40±0.05(0.996)	0.57±0.07(0.996)	–2.84±0.33	–4.98	0.74±0.10(0.994)	–2.83±0.27
6–NO_2	0.51±0.04(0.997)	0.73±0.06(0.997)	–5.32±0.43	–7.28	0.93±0.08(0.997)	–4.98±0.35
7–Me	0.34±0.03(0.998)	0.49±0.04(0.998)	–1.70±0.14	–3.47	0.63±0.06(0.997)	–1.82±0.12
7–MeO	0.50±0.02(0.999)	0.72±0.03(0.999)	–2.96±0.12	–4.11	1.00±0.06(0.998)	–2.90±0.12
7–NO_2	0.40±0.02(0.998)	0.59±0.03(0.998)	–4.78±0.25	–8.10	0.71±0.04(0.998)	–4.56±0.21

(a)Acidity function value at half ionization. b)Ionization data taken from ref. 8.

TABLE 2.– Ionization data analysis of the deprotonation equilibria at 25°C of benzene substitued indoles. The figures between parenthesis are the correlation coefficients.

		HAMMETT			E.A.M.	
	-dlogI/d[KOH]	-logI/dH_	pKa	$(H_-)_{1/2}$[b]	m^*	$pKa_{(BA)}$
Indole [a]	0.29±0.02(0.999)	1.02±0.06(0.999)	16.90±1	16.57	1.07±0.13(0.996)	16.72±0.16
4-Me	0.31±0.02(0.998)	1.01±0.07(0.990)	17.08±1.1	16.80	1.17±0.11(0.985)	17.08±0.2
4-OH	0.27±0.02(0.999)	0.95±0.05(0.999)	16.30±0.9	17.21	0.89±0.06(0.990)	17.02±0.07
4-MeO	0.28±0.02(0.999)	0.98±0.05(0.999)	16.58±0.98	16.50	0.94±0.07(0.994)	16.58±0.08
4-Cl	0.27±0.02(0.999)	0.93±0.05(0.999)	15.81±0.04	15.77	0.87±0.05(0.990)	15.81±0.04
4-COOH[c]	0.28±0.01(0.999)	0.97±0.05(0.999)	15.82±0.8	16.30	1.02±0.06(0.990)	16.39±0.05
4-NO_2	0.30±0.05(0.993)	1.04±0.16(0.993)	14.55±0.04	14.61	0.85±0.09(0.991)	14.55±0.04
5-Me	0.40±0.02(0.999)	1.38±0.05(0.999)	22.56±0.8	16.35	1.78±0.12(0.999)	17.24±0.14
5-OH[d]	0.40±0.04(0.998)	1.40±0.12(0.998)	24.51±2	17.51	1.74±0.23(0.996)	18.86±0.4
5-MeO	0.37±0.04(0.998)	1.30±0.11(0.998)	21.55±1.2	16.58	1.61±0.23(0.996)	17.33±0.29
5-Cl	0.30±0.03(0.998)	1.06±0.09(0.998)	16.83±1.4	15.87	1.16±0.16(0.996)	16.16±0.16
5-Br	0.28±0.01(0.999)	0.98±0.03(0.999)	15.76±0.4	16.08	1.02±0.06(0.999)	16.20±0.06
5-CN	0.28±0.02(0.999)	0.97±0.10(0.999)	15.05±0.15	15.51	0.95±0.06(0.998)	15.29±0.04
5-COOH[c]	0.33±0.02(0.997)	1.13±0.07(0.997)	18.24±1	16.14	1.31±0.13(0.994)	16.45±0.13
5-NO_2	0.34±0.05(0.991)	1.17±0.17(0.991)	17.47±2	14.93	0.93±0.09(0.996)	14.88±0.03
5-NH_2	0.22±0.01(0.999)	0.77±0.03(0.999)	12.82±0.5	16.65	0.59±0.08(0.997)	16.14±0.10
6-Me	0.42±0.02(0.999)	1.45±0.06(0.999)	22.79±1	15.71	1.89±0.12(0.999)	16.38±0.10
6-MeO						16.9[e]
6-Cl	0.20±0.01(0.999)	0.70±0.04(0.999)	11.32±0.55	16.17	0.48±0.06(0.996)	15.59±0.06
6-NO_2	0.36±0.06(0.992)	1.24±0.20(0.992)	18.35±3	14.80	0.89±0.09(0.997)	14.68±0.02
7-Me	0.68±0.08(0.996)	2.36±0.26(0.996)	38.72±4	16.41	3.63±0.54(0.993)	19.46±0.64
7-MeO	0.41±0.02(0.999)	1.43±0.06(0.999)	22.98±0.9	16.06	1.85±0.10(0.999)	17.03±0.10
7-NO_2	0.34±0.02(0.999)	1.19±0.08(0.999)	18.22±1.15	15.31	1.24±0.09(0.999)	15.52±0.05

a) Ionization data taken from ref. 12 (b) Acidity function value at half ionization(c) Carboxylic group deprotonates in the pH region (ref. 9). d) Phenolic group deprotonation takes place at lower basicities than pyrrolic deprotonation (ref. 9). (e) Estimate value.

Ionization data, at 25°C, were obtained spectrophotometrically as in previous works.[19] For the sake of brevity these data are only reported in mathematical form (Tables 1 and 2). Analysis of the ionization data was performed using eqns. (1)–(3), which derive from the H.A.F. and E.A. methods.

$$\log I = -m\ H + pKa_{(HAF)} \quad (1)$$

$$\log I - \log C_H + = m_p^* X_p + pKa_{p(EA)} \quad (2)$$

$$pK_w + \log C_{OH} - \log a_w + \log I = m_d^* X_d + pKa_{d(EA)} \quad (3)$$

In eqn (1) H represents the acidity functions H_I and H_- established for protonation and deprotonation equilibria of indoles [3,4], respectively. In eqns (2) and (3) C_H and C_{OH} are the acid (C_H = M_{H2SO4})[15] and hydroxide ion concentration, a_w, represents the activity of water and X_p and X_d are the excess acidity functions in acid and basic media, respectively. These parameters were taken from the literature[15] or calculated as in elsewhere.[20]

Semiempirical calculations at the AM1 level were carried out as in previous works.[16–18]

RESULTS AND DISCUSSION

Aqueous phase Acidity and Basicity of Benzene substituted Indoles.

The results of the ionization data analysis for the protonation and deprotonation equilibria of several families of benzene substituted indoles are shown in Tables 1 and 2, respectively. As can be seen from data in Table 1, plots of logI vs. H_I are linear in all the cases. However, excluding the 4–COOH derivative, none of the slopes of these plots are the unity and, therefore, the H_I acidity function does not correlate the protonation equilibria of these bases. On the other hand, the pKa_p values obtained from H.A.F. and E.A. methods show, within the experimental uncertainty, a satisfactory correspondence. The differences between both pKa values are around ±0.10 pKa units for bases having pKas above −4, but the differences are greater for weaker bases. The poor correspondence between H.A.F. and E.A. methods for very weak bases has been frequently observed. It is, at present, one of the most severe criticism to the universality of the E.A. approach.[21–24]

Data in Table 2 for the deprotonation equilibria also show the linearity of logI vs H_- plots, but at variance with protonation equilibria, the slopes of these plots are closer to unity. It must be noticed that, as we have previously demonstrated, H_- is also a good acidity function for describing monoanionic–dianionic ionization equilibria.[9] Despite the closer adherence of indoles to H_-, the $pKas_{d(HAF)}$ and $pKas_{d(EA)}$ usually differ about an unity. A better agreement between H.A.F. and E.A. methods can be observed when $(H_-)_{1/2}$ and $pKas_{d(EA)}$ parameters are compared. This fact can be imputed to the anomalous anchoring procedure used by Yagil to establish the H_- acidity function.[4] Thus, the ionization ratio plots of the Yagil overlapping indicators do not run parallel, changing their slopes in the pH/H_- 13–15 region, from 1.0 to 0.3. Therefore above H_- = 15 the values of $(H_-)_{1/2}$ provide the better estimates of the strength of the acids.

The above results show that E.A. method performs as well as H.A.F. method for protonation equilibria and it provides consistently better results than HAF method for deprotonation equilibria of indoles. On the other hand, apart from its greater generality, E.A. method also affords a more rational insight into the structural and solvent factors influencing the acid-base behaviour. Thus, $pKa_{(BA)}$ values are related with the internal stabilization of the acid-base conjugate pair due to the molecular structure, whereas m^* parameter accounts for the external stabilization by solvation.[15] For all these reasons, we will assume this method as the more suitable to study the influence of the substituents on the ionization equilibria of benzene substituted indoles.

In a previous paper,[10] we have shown the existence of the linear correlations, eqns (4) and (5) among the $pKas_p$ and $pKas_d$ and the Hammett σ^o_m constants for a set of 4-substituted indoles;

$$pKa_{p(EA)} = -0.69\ \sigma^o_m - 2.48\ (r^2 = 0.96) \quad (4)$$

$$pKa_{d(EA)} = -3.18\ \sigma^o_m + 16.48\ (r^2 = 0.98) \quad (5)$$

These results were rationalized by assuming that the pyrrolic nitrogen atom was the reaction center mainly involved in both prototropic equilibria and that the same mechanism for the transmission of the electronic effects operated in the protonation and the deprotonation equilibria of 4-substituted indoles.

However, these conclusions are somewhat surprising in view of the different nature of the prototropic processes and the complex structure of the fused indole ring. In fact, this particular behaviour of 4-substituted indoles does not hold, as we will see below, for other families of benzene substituted indoles.

For the 5-position the pKa_d values correlate satisfactorily with σ_p constants[25] as in eqn (5) ($r^2 = 0.99$). However, for some substituents it is necessary to use σ_p^- values to fit the data. This fact indicates enhanced resonance effects at this site. The slope of this correlation ($\rho = 2.44$) is close to the corresponding value for 4-substituted indoles. It suggests the possibility of including all the pKa values for 4- and 5-substituted indoles into a single correlation with σ values. As fig. 1 shows, this correlation is roughly linear, although substantial scatter for the 5 NH_2 derivative was observed. By excluding this compound the pKa data can be fitted by eqn (6);

$$pKa = -2.51\ \sigma + 16.74\ \ (r^2 = 0.966) \quad (6)$$

where σ represents σ_m values for 4-substituted derivatives and σ_p values for 5-substituted indoles respectively. The value of 2.51 in this correlation is greater than the previously reported by Yagil[5] for a more reduced set of indoles, (1.75) and very close to that of phenols (2.23).[26]

Conversely, substituents at 6-position, i.e. meta position with respect to the acidic center, do not fit eqn (6) with σ_m constants well, but with σ_p constants. However, they yield a different and almost parallel line ($\rho = 2.18$; $r^2 = 0.97$)to that obtained for 4 and 5 derivatives, which does not include the parent compound. It is noteworthy the great acid strengthening effects of the substituents at this position.

The above results for 4- and 5-substituted indoles are consistent with the currently accepted mechanisms for the transmission of the electronic effects of the substituents in simple benzenoid rings. However, for the substituents at 6-position a different mechanism seems to be operative in the heteroaromatic indole ring. We will try to rationalize these mechanisms later. We turn now to protonation equilibria looking for similar correlations.

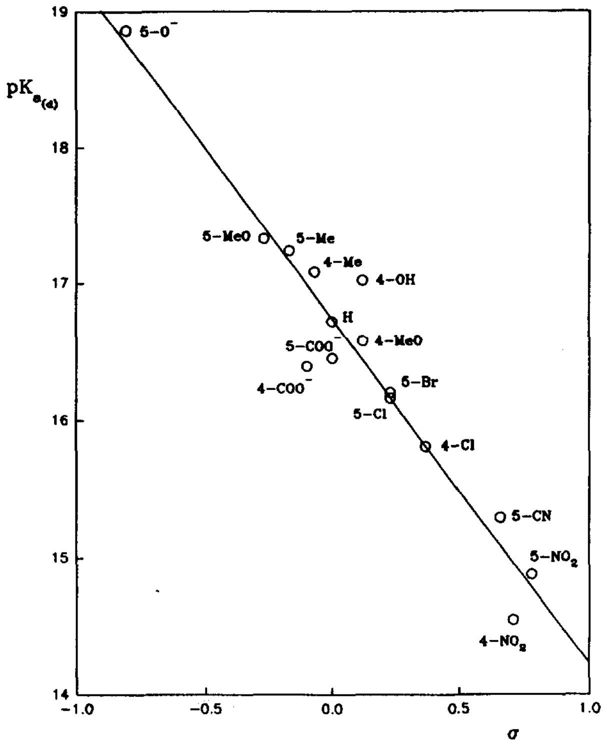


Fig.1: Plot of pka$_d$ of 4- and 5-substituted indoles against Hammett σ constants

Although we have used different sets of σ constants, simple relationships similar to eqn (4) could not be obtained for pKa$_p$ of 5- or 6-substituted indoles. Neither dual parameter correlations using σ_I and σ_R constants gave better results. Therefore, bearing in mind that the protonation process mainly involves two centers in the molecules, the ß-carbon atom and the pyrrolic NH group, we attempted dual parameter correlations as that of eqn (7).

$$\Delta pKa = \sigma_1 \rho_c + \sigma_2 \rho_{NH} \qquad (7)$$

where ΔpKa = pKa (substituted indole) − pKa (parent indole) and σ_1 and σ_2 are the σ_m or σ_p constants of the substituent with respect to these centers. Indoles substituted at the 5-position fit very satisfactorily this correlation with $\rho_c = 0.79$ and $\rho_{NH} = 1.43$. The goodness of the fit can be graphically tested in Fig 2. This figure also shows the scattering of some 6-substituted indoles from this correlation.

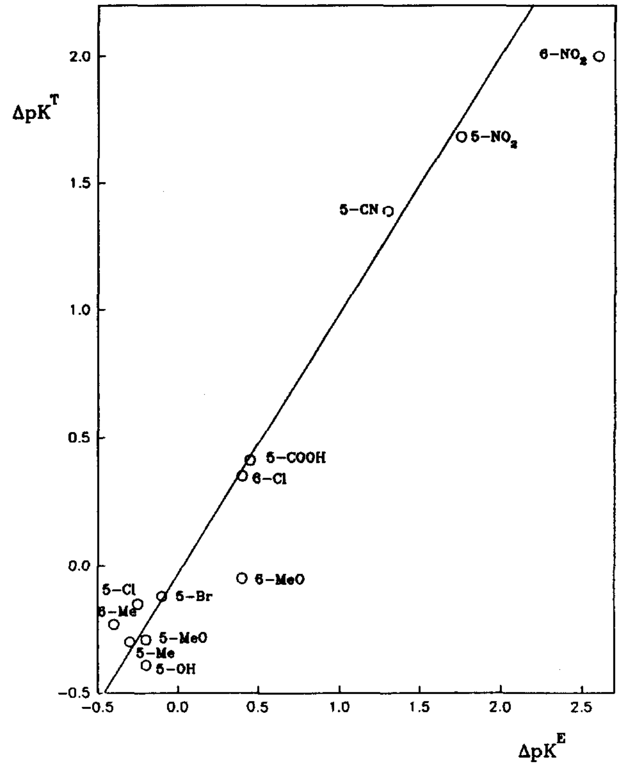


Fig.2: Scatter diagram comparing the experimental ΔpK_p^E with the calculated ΔpK_p^T obtained from eqn.(7)

Unfortunately, only a limited number of 7–substituted indoles has been at our disposal, and therefore we can not say much about the influence of the substituents at this position. Moreover, since the 7–position is ortho with respect to the pyrrolic nitrogen atom, in all likelihood steric interactions will exist and good correlations will not be expected.

Finally, the data listed in Tables 1 and 2 show that substitution on benzene moiety of the indole ring also influences the solvation m^* parameter for protonation and deprotonation equilibria. Since solvation is a very complex phenomenon and substituents can simultaneously modify diverse structural factors influencing solvation, it is not our purpose to quantitatively discuss the influence of substituents on m^*. The interpretation of m^* values is a formidable task, and it has only been achieved for more relevant structural modifications. Notwithstanding, a perusal of the data in Tables 1 and 2 indicates some significant trends of m^* values.

a) The m^* values for protonation equilibria of benzene substituted indoles are usually smaller than the value of the parent indole. This effect is more noticeable in the case of electron–withdrawing substituents at the

5–position, probably due to the greater localization of the positive charge of the cations and therefore their increasing interaction with the solvent.

b) Data on m^* for the deprotonation equilibria of a variety of substituted indoles span only a very limited range, so that these acids meet the suggested requirements for constructing an acidity function.[14] This fact is in agreement with the previously indicated good adherence of these compounds to the H_- acidity function. On the other hand, it is surprising the high m^* values of several electron–releasing groups at the 5–position. It seems as these substituents favour the delocalization of the negative charge of the anions into the ring.

c) The sequence of m^* values 7–NO_2 < 7MeO < 7–Me for deprotonation equilibria is consistent with the expected steric hindrance to solvation exerted by those groups on the deprotonation site.

Theoretical Gas–phase Acidities and Basicities of Benzene substituted Indoles.

In recent years, considerable interest has been focussed on the ionization of compounds in the gas–phase since it allows the analysis of intrinsic acid–base properties without the interference of the solvent. Therefore, as a complement to the experimental work, we have carried out theoretical calculations, at the AM1 level, on the electronic properties and ionization enthalpies of a series of benzene substituted indoles. For this study we have selected a set of 4–,5– and 6–substituted indoles. We have deliberately excluded OH, COOH and NH_2 derivatives and 7–substituted indoles, because the possibility of different ionization patterns or steric interactions might obscure the calculations and the discussion of the results. We have also excluded the 5–CN derivative, because it is known the failure of the AM1 method to describe this substituent.[27] The results of the AM1 calculations are summarized in Tables 3 and 4.

The electronic redistribution induced by the substituents on the neutral (N), anionic (A) and cationic (C) molecules has been examined by means of the Mulliken population analysis of the wavefunctions. The net charges, q^x_t, and the donated or accepted π (Δq^x_π) and σ (Δq^x_σ) charges on the substituents are listed in Table 3.

As can be seen from these data, the electronic influence of the substituents on the neutral molecules are expected on the basis of their electron accepting or donating character. Moreover, the σ–effects predominate over the π–effects and the transmission of the electronic effects is almost independent of the substituent position in the benzene ring. On the other hand, a comparison of the electronic effects induced by the substituents in the neutral molecules with those induced in the charged species, shows that, as expected, the net charge transferred from the ring to the substituent is reinforced in the anions and reduced in the cations. As a consequence, MeO and Cl groups, behave as electron–donating substituents in the cations, whereas they have the opposite character in neutral and anionic molecules. Another significant result is the π–donor character of methyl groups in the anions.

TABLE 3.- Mulliken population analysis of the neutral (N), anionic (A) and cationic (C) substituted indoles; net (q_t) and donated (+) or accepted (−) σ (Δq_σ) and π (Δq_π) charges on the substituent group.

	N			A			C		
Substituent	q_t	Δq_π	Δq_σ	q_t	Δq_π	Δq_σ	q_t	Δq_π	Δq_σ
4-Me	+0.074	−0.018	+0.092	+0.012	+0.022	−0.010	+0.127	−0.055	+0.182
5-Me	+0.066	−0.016	+0.082	+0.004	+0.018	−0.014	+0.131	−0.050	+0.181
6-Me	+0.068	−0.020	+0.088	+0.004	+0.017	−0.013	+0.129	−0.050	+0.179
4-MeO	−0.034	+0.105	−0.139	−0.112	+0.080	−0.192	+0.034	+0.135	−0.101
5-MeO	−0.046	+0.099	−0.145	−0.124	+0.089	−0.213	+0.055	+0.140	−0.085
6-MeO	−0.044	+0.102	−0.146	−0.126	+0.093	−0.219	+0.041	+0.120	−0.079
4-Cl	−0.016	+0.039	−0.055	−0.119	+0.026	−0.145	+0.068	+0.052	+0.016
5-Cl	−0.028	+0.033	−0.061	−0.128	+0.021	−0.149	+0.078	+0.062	+0.016
6-Cl	−0.025	+0.036	−0.061	−0.127	+0.021	−0.148	+0.072	+0.053	+0.019
4-NO_2	−0.157	−0.037	−0.120	−0.278	−0.093	−0.185	−0.065	−0.020	−0.045
5-NO_2	−0.162	−0.041	−0.121	−0.284	−0.103	−0.181	−0.052	−0.015	−0.037
6-NO_2	−0.159	−0.037	−0.122	−0.282	−0.101	−0.181	−0.052	−0.017	−0.035

The theoretical AM1 enthalpies for the protonation (ΔH°_p) and deprotonation (ΔH°_d) processes, are listed in Table 4. This Table also includes the enthalpic differences for the isodesmic processes $XIndH^+_2$ + IndH → XInd H + Ind H^+_2 , ($\delta\Delta H^\circ_p$) and XIndH + Ind^- → $XInd^-$ + IndH ($\delta\Delta H^\circ_p$). It should be noted the good agreement between the computed (1448.5KJ/mol) and experimental[7] (1471KJ/mol) deprotonation enthalpies for the parent compound. Unfortunately, the lack of information on experimental gas-phase acidities and basicities of benzene substituted indoles precludes a more extensive comparison of the theoretical results.

The influence of the substituents on the theoretical gas-phase ionization enthalpies has been examined by means of linear relationships with σ_m and σ_p gas-phase Hammett constants.[25] The plot of $\delta\Delta H^\circ_d$ vs. σ constants gives a reasonable linear correlation (r^2 = 0.98) although, as in aqueous-phase, the correlation improves when σ_p instead of σ_m constants are used for the 6-substituted derivatives (r^2 = 0.99). The plot of $\delta\Delta H^\circ_p$ vs. σ constants shows a dispersion of points, with the exception of 4-substituted derivatives which are linearly correlated with σ_m constants (ρ = 61.8, r^2 = 0.986). Again, as in aqueous-phase, $\delta\Delta H^\circ_p$ values for 5- and 6-substituted derivatives fit better an equation similar to the dual parameter correlation in eqn (7), with ρ_c = 31.4 and ρ_{NH} = 104.4).

TABLE 4.– Ionization enthalpies for the protonation, ΔH°_p, and deprotonation, ΔH°_d, processes of benzene substituted indoles at 25°C in kJ. mol^{-1}.

Compound	ΔH°_p	ΔH°_d	$\delta\Delta H^\circ_p$(a)	$\delta\Delta H^\circ_d$(a)
Indole	902.1	1448.5	0	0
4–Me	906.7	1449.6	−4.6	+1.1
5–Me	908.1	1448.7	−6.0	+0.2
6–Me	906.2	1449.2	−4.1	+0.7
4–MeO	898.3	1439.0	+3.8	−9.5
5–MeO	910.9	1442.5	−8.8	−6.0
6–MeO	905.6	1446.5	−3.5	−2.0
4–Cl	889.2	1427.4	+12.9	−21.1
5–Cl	888.3	1425.8	+13.8	−22.7
6–Cl	886.5	1426.2	+13.8	−22.3
4–NO_2	856.4	1379.3	+45.7	−69.2
5–NO_2	841.9	1374.2	+60.2	−74.3
6–NO_2	847.1	1372.4	+55.0	−76.1

a) Ionization enthalpies for the isodesmic processes;

$$XIndH_2^+ + IndH \rightarrow XIndH + IndH_2^+ \;,\; (\delta\Delta H_p^\circ) \text{ and } XIndH + Ind^- \rightarrow XInd^- + IndH \quad (\delta\Delta H_d^\circ)$$

The observed correlations with σ constants reflect the effects of the substituents on the stability of the anion or the cation relative to the neutral molecule. We will try to qualitatively rationalize these effects by considering the electronic properties of the centers mainly involved in the prototropic processes. Indole ring properties are familiarly explained by assuming that there is a significant delocalization of electron density from nitrogen to the carbon atoms of the ring, particularly to C–3.[1-3] In terms of the resonance model, canonical forms such as 1a↔1b can greatly contribute to the resonance hybrid. Theoretical calculations also support this description for the neutral indole, (q^N_t = 0.028 and q^{C-3}_t = −0.201).

Once the molecule has been deprotonated, the increase of the electronic density at nitrogen is much greater than at C–3 atom (q^N_t = −0.256 and q^{C-3}_t = −0.336 for the anion of the parent compound). Therefore, the influence of the substituents will be expected to be more pronounced on the former than on the second center. The fact that a single equation is valid for the deprotonation processes might have its origin on the preponderance of the substituent interactions with the nitrogen atom in these equilibria. Only in the case of the substituents at 6–position, could the interactions with C–3 be important since at this position the substituents are in direct conjugation with this center. This fact might be the cause of the improvement of

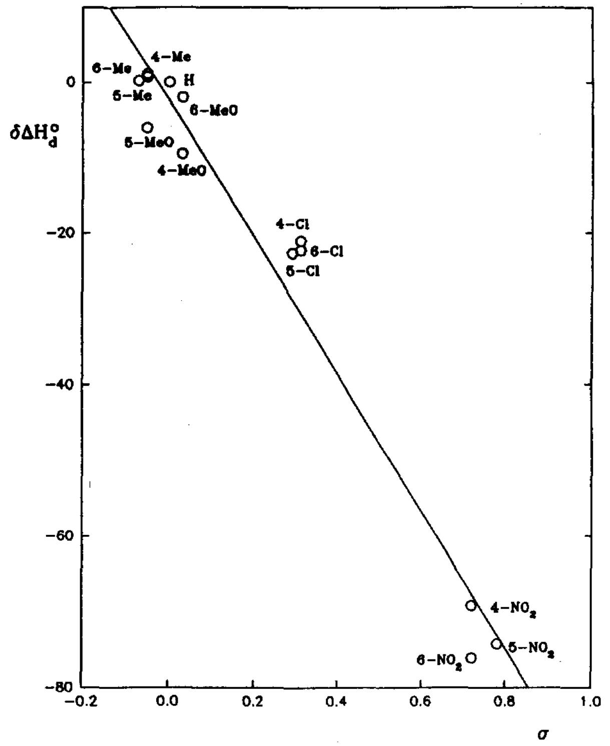


Fig.3: Plot of $\delta\Delta H^\circ_d$ of 4-, 5- and 6-substituted indoles against Hammett σ constants.

the correlation in gas-phase when σ_p is used for the 6-substituents, and the origin of the particular correlation between pKa_d and σ_p constants observed for the 6-substituted derivatives in aqueous-phase.

1a 1b

In the case of the protonation processes, it must be remembered that although indole ring protonates on C-3,[1-3] the charge of the conjugated acid is strongly localized on the pyrrolic nitrogen atom. (For the cation of the parent compound $q^{N}_{t} = +0.249$ and $q^{C-3}_{t} = -0.150$). Therefore, C–3 and pyrrolic nitrogen groups are the centers more closely involved in this prototropic equilibria and the influence of the substituents would be related with the modifications induced by them on both centers. Therefore, the effect of the substitutents might be described by dual parameters correlations better than by single ones.

Finally, in previous papers[16–18] we have found that gas–phase entropic terms remain almost constant along a series of substituted rings structurally related to indole. A similar conclusion has been reached for substituted benzoic acids and phenols.[28–30] On the basis of the validity of this assumption for the present compounds, we have plotted $\delta\Delta H^{\circ}$ values vs pKa constants. These plots reveal that the order of gas–phase basicities and acidities is roughly maintained in solution although a greater dispersion of points is observed for the second case. Thus, while the interaction between anionic species and the solvent could be considered practically constant along the series, in the case of the cations, the solvation seems to be more sensitive to the structural modifications induced by the substituents. We know that this and similar conclusions should be taken with caution, and the modelling of substituent effects in the indole ring undoubtedly requires a more extensive experimental and theoretical effort in this direction. This will be the subject of future work.

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