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A THEORETICAL STUDY OF THE PROTONATION OF METHYLINDOLE DERIVATIVES

J. CATALÁN, P. PÉREZ and M. YÁÑEZ

Departamento de Química Física y Química Cuántica, Centro Coordinado CSIC-UAM, Facultad de Ciencias C-XIV, Cantoblanco (Madrid, 34), Spain

Abstract—*Ab initio* calculations on indole and all its mono-substituted methyl derivatives, using an STO-3G minimal basis set, show that the most basic site is C3. Protonation at the nitrogen atom cannot compete with protonation at C3; and C2 is the less basic site in all cases. The basicity increases with methyl substitution, with the only exception of 3-methyl indole. A good linear correlation exists between calculated and corresponding thermodynamics pK values. 2-Aminoindole is a much stronger base than methylindoles and its high pK value can be explained by the strong interactions with the solvent through tautomeric forms which accumulate positive charge at the NH_2 group. Intramolecular quenching of the fluorescence of some indole derivatives involves intramolecular proton transfer to C4 rather than C2. Reasons why ring nitrogens can behave as either π-acceptors or π-donors in this series are discussed.

Indole and its derivatives have been the subject of intensive research since many alkaloids contain the indole nucleus[1] as a basic structural unit; some melanins were found[2,3] to be indole derivatives; they also play an important role in the biochemical processes involved in the activity of the central nervous system,[4,5] etc.

It also seems to be well established[6-8] that a considerable number of typical reactions within this family of compounds (dimerization, trimerization, attack by molecular oxygen, hydrogenation, etc.) are either initiated or greatly influenced (as electrophilic substitutions) by protonation of the indole nucleus. This has made this particular process the subject of considerable attention, both from the experimental[9] and the theoretical[10] points of view. Nevertheless, although it seems to be clear that protonation of these weak bases (in solution) occurs preferably at C3, little is known of the intrinsic basicity of these compounds, since all experimental information on this point has been obtained in solution. Moreover, this information is somewhat sketchy: for instance, only the pK's (thermodynamic) of three mono-substituted methyl derivatives have been measured and some other aspects concerning the protonation process (e.g. the alternative protonation at C2 or N1) have not yet been completely clarified. Furthermore, most of the theoretical studies on these compounds have used π-semiempirical methods that cannot account for effects due to the σ-framework, and *ab initio* calculations have been carried out[10] only on the parent compound using either partially optimized geometries or the nucleus geometry corresponding to some particular derivative.

The aim of this paper is to present an *ab initio* study of indole and its mono-substituted methyl-derivatives, using fully optimized INDO geometries, in order to calculate the intrinsic basicity of every ring-position. This should allow us to assign a value to the proton affinity, free of the solvent influence, and, consequently, to measure the real basicity of this kind of compound, as well as to discuss the preferred protonation site and the influence of the position of the substituent on the protonation process.

We have also included in our study 2-aminoindole (which contrary to other indole derivatives is a very strong base in solution) in order to better understand those factors which affect the basicity of indoles.

Since most of the properties of this family of compounds seem to be related to the behaviour of the ring-nitrogen as a π-donor, we have also studied the 7-azaindole (7AI) and its two *N*-methyl derivatives (*N*1-methyl-7-azaindole (NM7AI) and the *N*7-methyl tautomer: 7-methyl-7*H*-pyrrolo (2,3-b) pyridine (NMT)). These compounds present two different kinds of ring-nitrogens and a comparison of their behaviour upon substitution might provide an understanding of the circumstances under which they can be expected to behave as π-donors or π-acceptors.

Finally, we shall discuss the charge distribution of the title compounds, to try to explain certain of their reactive characteristics.

Computational details

In order to avoid prohibitive geometry optimizations and since no experimental geometries are available for any of the molecules included in this study, we have adopted, in our *ab initio* calculations, the INDO fully optimized geometries (obtained following the procedure developed by Rinaldi *et al.*[11]) slightly modified to account for some limitations of this semiempirical method.

It is a well established fact[12] that the INDO method reproduces fairly well the geometries of compounds of this kind, although it overestimates all the C–H and N–H bond lengths. Consequently, we have scaled all the optimized C–H bond lengths by a factor of 0.974 which is the ratio of the experimental C–H bond length in naphthalene (1.0926 Å)[13] to the INDO fully optimized value (1.122 Å). The scaling factor for the NH bond lengths (0.935) is the ratio of the experimental N–H bond length in pyrrole (0.996 Å)[14] to the corresponding INDO optimized value (1.065 Å). An indication of the goodness of the geometry used here is that the energy obtained for the parent compound, using a STO-3G minimal basis set,[15] is lower than the values reported in the literature[10] for the same basis set.

The molecular electrostatic potentials were calculated using the equations developed by Srebrenick *et al.*[16] We shall present only those maps which best characterize each particular situation.

Since one aim of this paper is to discuss the reactivity of the methyl substituents in the indole derivatives, to obtain the corresponding charge distributions we have employed the well known Mulliken population analysis and the YSP population analysis.[17] It has been shown elsewhere[18] that the latter reproduces well the inductive effects of alkyl substituents, while Mulliken population analysis does not perform well in this case.[19] Besides, the YSP partition technique is practically insensitive to the basis set used and therefore few changes appear in the corresponding charge distributions when the basis set is enlarged. This analysis has been carried out using the standard density basis set defined in Ref. 17.

Intrinsic proton affinities

We have recently proposed[20–22] an economical procedure to predict the preferred protonation site and the intrinsic proton affinity of any position in a given compound. This procedure is based on the correlation between experimental gas-phase proton affinities and *ab initio* C_{1s}, O_{1s} or N_{1s} orbital energies. Therefore we have calculated the intrinsic proton affinity of ring-carbons for the compounds studied in this paper, using eqn (1) of Ref. 21. Although that correlation was initially obtained for aromatic compounds, we have proved[21] that it gives correct results for the gas-phase PA of other systems, such as azulene. In consequence, it is reasonable to assume that this equation will also yield correct values for the intrinsic basicity of the carbon atoms of the five-membered ring of indoles.

The corresponding PA's of the ring nitrogens where obtained using eqn (4) of Ref. 21. We have used that correlation instead of the one corresponding to pyridines,[22] because the indole nitrogen resembles the aniline-one more than the pyridine-type nitrogens. This choice seems to be ratified, as we shall show later, by the fact that the intrinsic PA predicted for the ring nitrogen in the parent compound is in agreement with the pK estimated[9c] for this basic site.

We present our calculated PA's in Table 1. The following points should be singled out for comment.

(a) In all cases, including 2-aminoindole, the most basic site of the molecules is C3, in agreement with the experimental findings on the protonation of several indole derivatives.[23]

(b) In all cases C2 is the position with the lowest PA, even in those derivatives where the presence of a methyl-substituent on the neighbour atom (N1 or C3) should increase its basicity. Actually the intrinsic PA of this position in 1-methyl- and 3-methylindole is greater than in any other mono-methyl derivative, but still lower than the intrinsic PA of the other centers of the molecule.

(c) In no case can protonation of the ring nitrogen compete with protonation at C3. However, position 5 and 6 are considerably basic and, in some specific cases (3-methylindole) position 5 exhibits an intrinsic basicity comparable to that of C3.

(d) All methyl derivatives present a greater basicity than the parent compound, with the only exception of 3-methylindole, in agreement with experimental evidence.

(e) According to our results, indole and its methyl derivatives are strong bases in the gas-phase although they exhibit quite low basicity in aqueous solution. We have found, however (see Fig. 1) a good linear correlation between thermodynamic pK values[9a] of three methyl mono-substituted indoles and our calculated PA's. When the corresponding equation is applied to indole and 5-methylindole (whose thermodynamic pK's are not known) the predicted values (−2.5 and −2.15 respectively) are quite similar to the non thermodynamic estimated[9a] values (−3.5 and −3.3, respectively). The same equation applied to determine the pK for the protonation on the nitrogen atom of indole, yields a value (−9.6) again quite close to the estimated experimental one (−10).[9c]

All these results seem to indicate that the gas-phase PA's for this family of compounds parallel their proton affinities in solution. This fact is easily explained when one considers that according to the results discussed above, the protonation site is the same carbon atom for all members of the family and therefore the interaction between the protonated species and the solvent must be practically identical for all of them.

A striking fact needs, however, further consideration. While indole and its methyl derivatives behave as weak bases in solution, 2-aminoindole presents a considerably high pK value (8.5),[23] which has been explained assuming that the molecule exists essentially as the 2-aminoin-

Table 1. Predicted proton affinities (kcal/mol) of some indole derivatives.

	Position								
Compound	N_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9
Indole	189.6	154.8	210.3	192.0	200.1	192.6	191.5	157.8	196.5
1 Me-Indole	188.1	156.8	210.5	192.8	199.3	192.9	192.1	161.4	196.6
2 Me-Indole	192.3	151.1	216.6	193.4	201.9	194.4	193.4	160.3	199.2
3 Me-Indole	190.0	160.2	204.3	194.6	201.3	193.2	192.2	159.3	200.0
4 Me-Indole	190.3	157.2	213.3	185.1	205.4	194.2	194.2	159.6	200.5
5 Me-Indole	190.1	155.8	211.2	197.3	192.8	196.1	193.4	159.9	198.7
6 Me-Indole	190.1	155.7	211.4	194.5	204.2	185.6	197.0	160.0	198.6
7 Me-Indole	190.9	156.3	212.1	194.5	201.6	197.1	184.2	161.7	198.6
2-NH_2-Indole	196.0	112.7	229.8	200.8	204.3	200.1	195.3	169.1	199.5

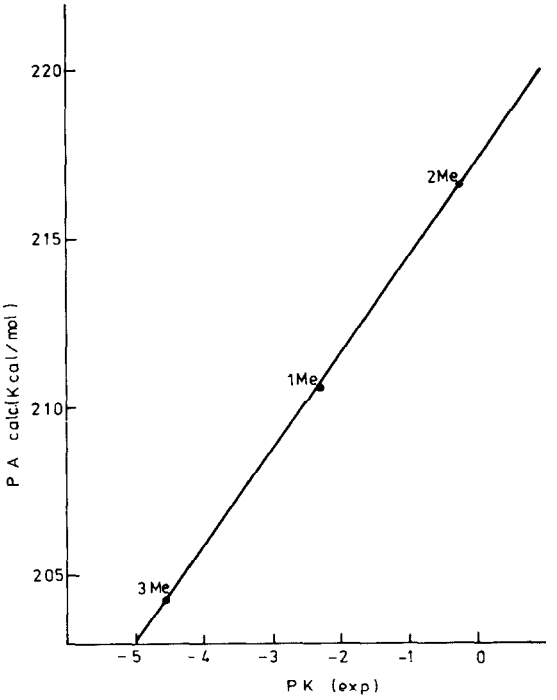


Fig. 1. Linear correlation (PA (kcal/mol) = 2.88 pK + 217.33) between calculated Proton Affinities and Thermodynamic pK values of some methylindole derivatives.

doline tautomer. According to our results (see Table 1) 2-aminoindole is a much stronger base, in the gas-phase, than methylindoles, in qualitative agreement with the behaviour of these compounds in solution; and it must be one of the strongest carbon-bases known at present. Moreover, using the correlation of Fig. 1, the predicted pK for 2-aminoindole is positive (+4.3), although smaller than the experimental value (+8.5). This disagreement can be explained: Since it has been proven[24–27] that carbon protonated species of this type (aromatic, heteroaromatic, etc.) are poorly solvated due to the absence of exposed atomic sites with appreciable positive charge; a consequence of the very easy delocalization of that charge throughout the molecule. This would explain why a high concentration of hydrogen ions is necessary to protonate methylindoles[23] and why the base-strength in gas-phase is higher than in solution.

However, the protonation of 2-aminoindole at C3 leads to a noticeable contribution of the two mesomeric forms (presented in Fig. 2) one of which localizes the positive charge on the $-NH_2$ group. This fact, contrary to what happens in methylindoles, will favour a strong interaction with the solvent and therefore increase the basicity in solution.

In conclusion, our results ratify the assumption of Kebarle and Hoffmann[28] in the sense that the high pK value exhibited by 2-aminoindole is related to the presence of mesomeric forms **1** and **2**. But, in our opinion, this cannot be taken as indicating the presence of the 2-aminoindolinine tautomeric form prior to protonation, since the intrinsic basicity of this molecule is high enough to explain the experimental findings.

We have presented in Table 1, the intrinsic PA for each position of methylindoles. However, it is interesting to know the dynamics of the protonation process; that is, whether the proton approaches the molecule following same privileged paths. To answer this question we have evaluated the corresponding electrostatic potential maps in a plane parallel to and 1.6 Å above the molecular plane, since similar calculations[20] indicate that the local minima are expected to be found at this distance from the basic centers.

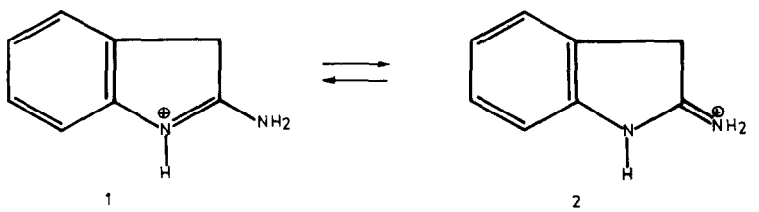
In Fig. 3, we have presented (exclusively) those maps which best characterize each extreme situation.

In all cases, with the exception of 3-methylindole and 2-aminoindole, the molecular electrostatic potential presents two well differentiated attractive regions, one centered on C3 and the other on the six-membered ring, embracing positions 4, 5 and 6 with the local minimum centered at C5. These two regions are clearly differentiated in those methyl derivatives for which substitution takes place on the five-membered ring. When the substituent enters on the six-membered ring the two local minima at C3 and C5 are connected.

3-methylindole is the only case in which no local minimum is found on C3, indicating that in this particular case, protonation at C5 might be favored, since its intrinsic PA is quite close to that of C3 (see Table 1) and the presence of a methyl substituent at the latter position hinders the entrance of a proton, as shown by the electrostatic potential map.

The electrostatic potential map of 2-aminoindole corroborates our previous discussion on this molecule. The presence of an amino group at C2 causes the disappearence of the minimum on the six-membered ring and increases that centered at C3, in agreement with the high intrinsic basicity exhibit by this position compared to those of C5 or C6 which are almost unchanged (see Table 1). A deep minimum is also centered on the $-NH_2$ substituent. This ratifies the noticeable contribution in the protonation process of the tautomeric form **2** (see Fig. 2) in which the positive charge migrates to this position, favoring a strong interaction with the solvent.

It is also evident that the indole-nitrogen is not a basic center, since, in any case, the electrostatic potential presents a minimum in this position. Similarly, the area around C2 is almost repulsive in all cases, indicating that the approaching of a positive charge in that direction is completely unfavored. This finding deserves particular attention since, the quenching process in the fluores-



1 2

Fig. 2. Mesomeric forms that contribute to the stabilization of the protonated form of 2-aminoindole.

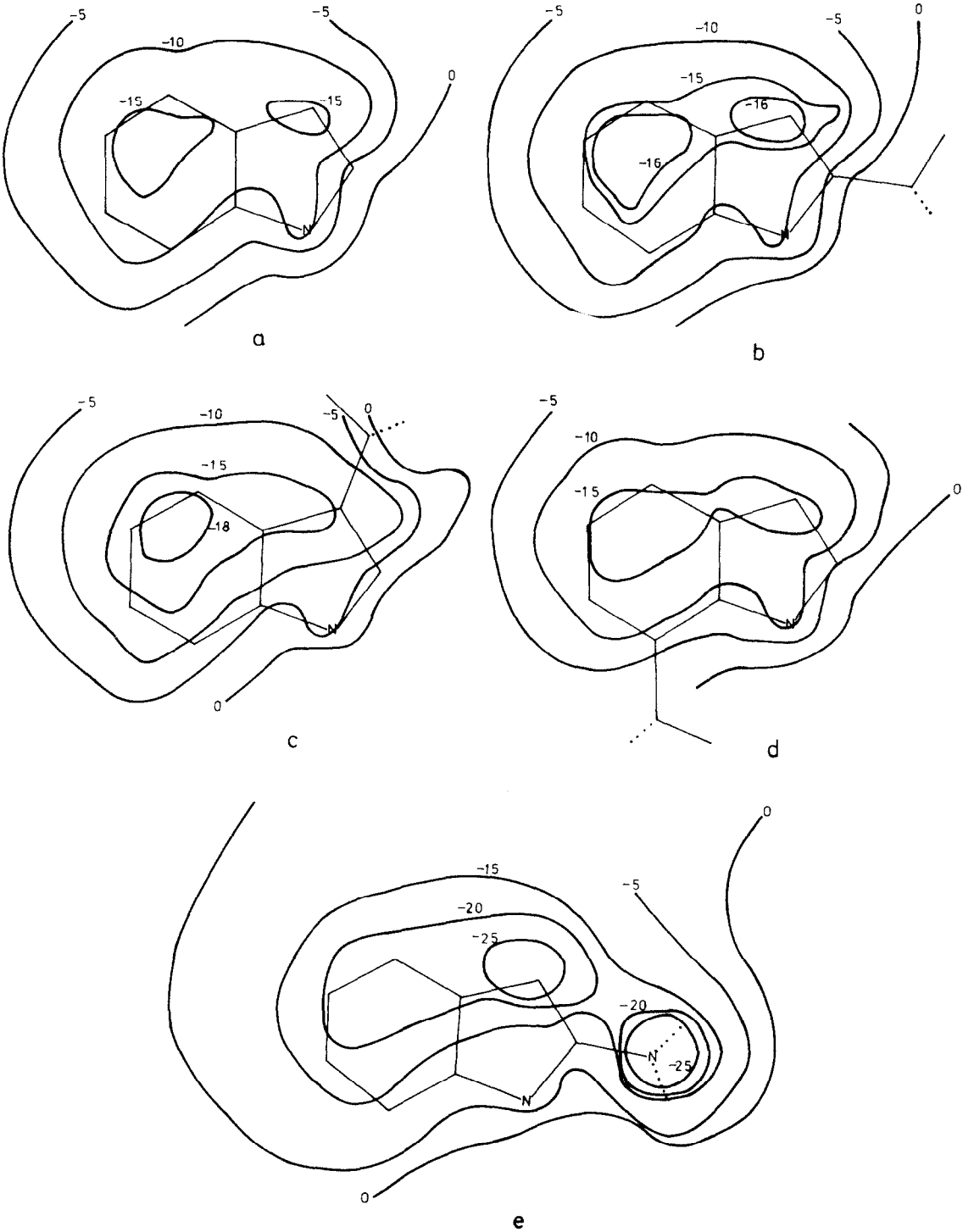


Fig. 3. Electrostatic potential map for: (a) indole, (b) 2-methylindole, (c) 3-methylindole, (d) 7-methylindole, (e) 2-aminoindole. Evaluated in a plane parallel to the plane of the molecule and 1.6 Å above it. All values in kcal/mol.

cence of tryptophan has been explained[29] via a mechanism which involves the transfer of a proton from the NH_3^+ group to the C2 position of the indole-ring. Our results clearly indicate that such a mechanism is not possible, at least in the ground-state.

Nevertheless, the quenching process involves excited states where the situation can be substantially different from that observed for the ground state. To show whether a similar behaviour is to be expected for excited states or not, we have carried out a CNDO/S calculation on the first singlet and triplet excited states of indole. We present, in Table 2 the charge density of the different positions of the excited molecule relative to those of the ground state. It is clear that in the excited singlet and triplet states a considerable migration of charge from the five-membered to the six-membered ring takes place. Con-

Table 2. Variation of the charge densities Δq_i (S_i(or T_i) − S_0) of indole upon excitation, obtained by a Mulliken population analysis carried out on CNDO/S calculations

Excited State	Position								
	N_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9
S_1	-0.56	0.005	-0.055	0.039	0.000	0.018	0.012	0.031	-0.005
S_2	-0.10	-0.010	-0.087	0.017	0.008	0.023	0.045	-0.030	0.024
T_1	-0.026	0.012	-0.062	0.040	0.008	0.000	0.075	-0.048	0.002
T_4	-0.049	-0.049	-0.043	0.036	0.073	-0.030	0.057	0.038	-0.034
T_5	-0.052	-0.077	-0.080	0.007	0.133	-0.027	-0.008	0.133	-0.028

sequently, excitation increases the basicity of the six-membered ring. This fact makes even less favourable the proton transfer to position 2 in the excited states than in the ground state. We can conclude, therefore, that the quenching process in this kind of molecule must involve a proton transfer to C4 (on the six membered ring) rather than to C2, unless excitation produces important geometrical changes, in which case our results on excited states would be not valid.

Charge distributions

We present in Table 3 the YSP charge distributions of monosubstituted methylindoles and 2-aminoindole. The calculated charge densities are consistent with the behaviour of those molecules in the protonation process: In all compounds studied the carbon atom C3 has the greater electron density and is, as indicated above, the most basic site. On the other hand, C2 is, in those compounds, the position which presents the greatest positive charge and therefore the more acidic site.

It is also interesting to note that, although the greatest electron charge density is located on the nitrogen atom, this is not a basic site of the molecules. This apparent contradiction can be explained as follows: most of the ionic mesomeric forms which contribute to the structure of indole[23] bear the positive charge on the nitrogen atom, indicating that it is a π-donor. Moreover, the nitrogen atom contributes with two electrons to the π-electron system (a typical example of π-excessive heteroaromatic systems) and, in consequence, the lone pair is not available for the proton attachment on the N-atom. The donation of the π charge is accompanied, however, by a stronger withdrawal of σ-electrons, which results in a negative net charge, as was already pointed out by Koller *et al.*[10]

It should also be noticed that the methyl substituents always bear a negative charge, indicating that they behave as electron-acceptors, due to hyperconjugation. The magnitude of such an effect depends on the position of the substituent. For instance, the methyl group at C3 accepts a relatively large negative charge, whereas this effect is smaller for the methyl group at C2, in agreement with experimental evidence,[23] which indicated that the latter is more active toward bases and free radicals than the former. Note, however, that the methyl group in 1-methylindole behaves as an electron-donor. This confirms that methyl groups usually behave

Table 3. YSP charge densities for indole and its mono-substituted methyl-derivatives

Compound	Position									
	N1	C2	C3	C4	C5	C6	C7	C8	C9	CH_3
Indole	-0.575	+0.208	-0.012	+0.060	+0.033	+0.059	+0.018	+0.203	+0.032	
1-Me-Indole	-0.526	+0.198	-0.010	+0.062	+0.037	+0.058	+0.023	+0.186	+0.037	+0.116
2-Me-Indole	-0.596	+0.231	-0.019	+0.064	+0.036	+0.060	+0.023	+0.210	+0.037	-0.021
3-Me-Indole	-0.534	+0.226	-0.035	+0.048	+0.026	+0.048	+0.024	+0.235	+0.014	-0.045
4-Me-Indole	-0.583	+0.213	-0.009	+0.084	+0.021	+0.064	+0.021	+0.213	+0.022	-0.059
5-Me-Indole	-0.582	+0.215	-0.006	+0.050	+0.057	+0.049	+0.025	+0.208	+0.038	-0.062
6-Me-Indole	-0.583	+0.215	-0.006	+0.065	+0.025	+0.080	+0.009	+0.211	+0.035	-0.060
7-Me-Indole	-0.585	+0.215	-0.008	+0.062	+0.040	+0.045	+0.044	+0.195	+0.039	-0.053
2-NH_2-Indole	-0.555	+0.515	-0.137	+0.047	+0.051	+0.058	+0.045	+0.253	+0.054	-0.381[a]

a) Charge density of the NH_2 group.

Table 4. σ- and π-electron densities of the ring-nitrogens of indole, 7-azaindole and its 1-methyl- and 7-methyl-derivatives

Compound	N_1			N_7		
	q_σ	q_π	q_t	q_σ	q_π	q_t
Indole	-0.614	+0.311	-0.303			
7AI	-0.633	+0.323	-0.310	-0.154	-0.115	-0.269
NM7AI	-0.607	+0.344	-0.263	-0.156	-0.114	-0.270
NMT	-0.060	-0.273	-0.333	-0.675	+0.440	-0.235

as electropositive groups when attached to more electronegative atoms.[18]

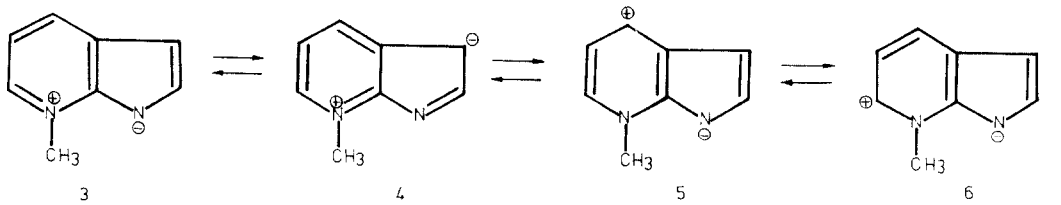
In order to understand the conditions which will make a ring-nitrogen to behave as a π-donor as a π-acceptor, we have carried out a comparative study of indole; 7AI, NM7AI and NMT. We present in Table 4 the σ- and π-charge densities of the ring-nitrogens for these four compounds.

The indole nitrogen behaves as a π-donor and a σ-acceptor. A similar behaviour is found for N1 in 7AI, while N7 behaves as a π- and a σ-acceptor. These results are not surprising, since the pyridine-type nitrogen (N7) in contrast to the indole-nitrogen (N1), contributes with a single electron to the π-system, as the lone pair is placed in a σ-type orbital. As a consequence, the nitrogen atom gains both π- and σ-electrons. This situation is not substantially altered when the hydrogen at N1 is substituted by a methyl group and the π-donor capability of N1 is only slightly increased due to inductive effects. However, when a methyl group is introduced at N7 of NMT, which present no H on the N1 atom, the changes are dramatic. In this case, N1 behaves as a π- and σ-acceptor and N7 as a π-donor and σ-acceptor; i.e. now N7 behaves as an indole-type nitrogen and contributes with a lone pair of electrons (now located in a π-type orbital) to the π-system. On the other hand, N1 behaves as a pyridine-type nitrogen, with its lone pair located in a σ-type orbital and contributing with a single electron to the π-system. On the other hand, the π-donor character of N7 in NMT induces a migration of π-charge from the six- to the five-membered ring.

This charge is mainly centered at N1, through a considerable contribution of the mesomeric forms **3**, **4**, **5** and **6** (see Fig. 4), explaining why, in this particular case N1 behaves as a π-acceptor.

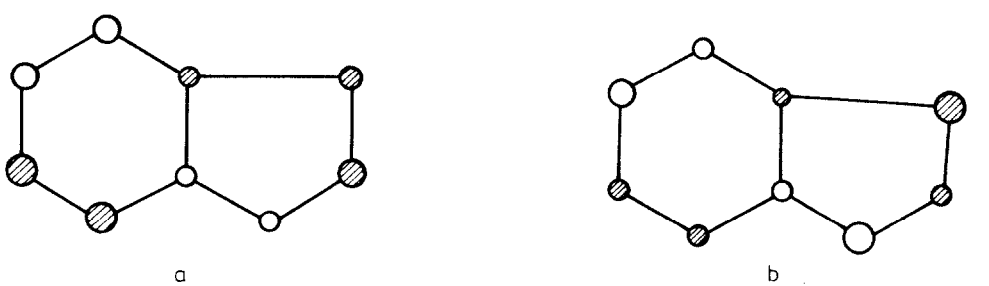
The contribution of these mesomeric forms is corroborated by the fact that the π-charge at C4 and C6 decreases in going from 7AI to NMT, while it increases on C3 and N1.

The same situation is seen when one considers the HOMO of NMT and that of the parent compound (7AI). In both cases the HOMO is a π-orbital, but while in 7AI



3 4 5 6

Fig. 4. Mesomeric forms which contribute to the structure of 7-methyl-7-azaindole which show a clear charge migration from the six- to the five-membered ring.



a b

Fig. 5. HOMO of: (a) 7-azaindole (7AI), (b) 7-methyl-7H-pyrrolo (2, 3-b) pyridine (NMT).

(see Fig. 5) it contains an important contribution of the atomic orbitals centered at N7, C4, C6 and C2, in NMT the highest contribution comes from atomic orbitals centered at N1 and C3.

One can conclude therefore that, those ring-nitrogens which due to their coordination, contribute with a lone pair of electrons to the π-system will behave as π-donors, whether they belong to a six- or a five-membered ring. On the contrary, nitrogens that have their lone pair located in a σ-type orbital, and therefore, contribute with only one electron to the π-system, will behave essentially as π-acceptors.

CONCLUSIONS

From our results we can conclude that the most basic site in indole and its mono-methyl substituted derivatives is C3, in agreement with the experimental behaviour of these compounds in solution. In all cases, C2 is the less basic position and protonation at the nitrogen atom cannot compete with protonation at C3. The basicity of these compounds increases with methyl substitution, with the only exception of 3-methylindole which presents a PA smaller than that of the parent compound, in agreement with experimental evidence.

Methylindoles are strong bases in the gas-phase and therefore they will behave as such when their interaction with the solvent is hindered. We have found a good linear correlation between our calculated PA's and the thermodynamic pK values, for those compounds for which the latter has been measured.

Our results also indicated that 2-aminoindole is a much stronger base than all methylindoles. Tautomeric equilibrium between forms **1** and **2** favors the interaction with the solvent increasing the basicity of this compound in aqueous solution. Therefore, the high pK value exhibited by 2-aminoindole cannot be taken as evidence that this molecule exists essentially as the 2-aminoindolinine tautomer.

All these results are confirmed by the characteristics of the corresponding molecular electrostatic potentials. We have also explained the intramolecular quenching process in the fluorescence of some indole derivatives through proton transfer to C4 rather than to C2, as it has been postulated:[29] C2 is an acidic position in the ground state and in excited states, because excitation in indoles is accompanied by a charge migration from the five- to the six-membered ring.

The calculated charge distributions for the systems studied confirm the previous conclusions.

Finally, in a comparative study carried out on indole and 7-azaindole derivatives, we have reached the conclusion that those ring-nitrogens that due to their coordination, contribute with a lone pair to the aromatic π-system, behave as π-donors, while those that have their lone-pair located in a σ-type orbital and contribute with only one electron to the π-system, behave as π-acceptors.

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