Nucleophilicity of Indole Derivatives: Activating and Deactivating Effects Based on Proton Affinities and Electron Density Properties

Nicolás Otero, Marcos Mandado,* and Ricardo A. Mosquera

Departamento de Química Física, Facultade de Química, Universidade de Vigo, 36310 Vigo, Galicia, Spain

Received: February 1, 2007; In Final Form: April 18, 2007

Activating and deactivating abilities of several substituents ($-CH_3$, $-F$, $-NH_2$, $-NO_2$) in indole have been theoretically studied using a series of electron density based reactivity indices. Calculations have been performed at the B3LYP/6-311++G(2d,2p) level. An energetic criterion based on the proton affinities (PAs) has been employed to check the validity of these reactivity indices. Relative PAs reflect the ortho and para orientation ability of $-CH_3$, $-F$, and $-NH_2$ groups, whereas the large deactivating effect of $-NO_2$ is mainly observed at these positions. Also, substitutions in carbons 2 and 6 (IUPAC nomenclature) activate/deactivate carbons 6 and 2, respectively. Inductive effects are also reflected on the values of the relative PAs. The $-CH_3$ group is shown to have inductive electron-withdrawing character instead of electron-releasing with its activating ability being due to a small mesomeric electron-releasing character. π atomic electron populations and the *zz* component of the atomic quadrupole electric tensor qualitatively explain the order of PAs. Fukui indices approximately predict the results obtained by the previous properties, whereas no correlation is found between the values of the $\nabla^2\rho(r)$ at the secondary charge concentrations and the PA scale.

I. Introduction

In organic chemistry, an activating functional group releases electron density when it is attached to an aromatic ring, increasing the probability of electrophilic attacks. On the contrary, a deactivating group withdraws electron density from the aromatic ring, so decreasing the probability of electrophilic attacks. Two kinds of activating/deactivating effects are usually distinguished. They are called inductive and mesomeric effects. The former is related to the electronegativity of the functional group with the exchange of electron density between the group and ring being mainly σ. On the contrary, mesomeric effects are related to the π skeleton and its conjugation between the ring and the functional group.[1] Those groups that release electron density by inductive or mesomeric effects are called +I or +R, respectively; they are activating groups. On the other hand, those groups that withdraw electron density from the ring by inductive or mesomeric effects are called −I or −R, respectively; they are deactivating groups. However, some functional groups like $-NH_2$ can be simultaneously −I and +R; in these cases, the global activating/deactivating character depends upon the relative strength of both effects, although mesomeric is considered to be the most important in most cases.

This work is concerned with the activating/deactivating effects of some functional groups in indole. Indole derivatives play a very important role in the synthesis of several compounds with pharmacological activity such as diindolemethane[2] which is synthesized from indole or methylindole. Moreover, they are also important for several biological processes; as an example, they are precursors of amino acids such as tryptophan, which is involved in the segregation of melatonin by the pineal glandule.[3] Several studies on indole and derivatives, both experimental[2,4−11] and computational,[12−16] can be found in the literature. However, no works dealing with the activating/deactivating effects in indole derivatives from a purely theoretical point of view have been published yet.

The quantum theory of atoms in molecules (QTAIM)[17,18] allows defining several atomic indices that can be employed to asses the reactivity sites in a molecule, such as total and π atomic charges,[19] atomic Fukui indices,[20] atomic quadrupolar electric tensor,[19] and those based on the laplacian of the electron density.[19] The validity of these indices is restricted to compare the reactivity of similar atoms in series of homologous molecules and cannot be applied on series of molecules that show large structural differences. Some of these indices, in particular, the quadrupolar electric tensor and the laplacian of the electron density at the secondary charge concentrations, were employed in a previous work by Bader and Chang obtaining satisfactory results for predicting the sites of electrophilic attack and their relative susceptibility to such attack in benzene derivatives.[19] González-Moa and Mosquera also obtained good results using the above-mentioned indices for uracil derivatives.[21]

It is well-known that protonation of aromatic rings in gas phase takes place without activation barrier,[22] which makes the protonation process pass off under thermodynamic control. Therefore, the most activating groups are expected to provide the largest proton affinities (PAs), and the highest PAs should indicate, in the absence of large steric hindrance, the main nucleophilic centers. Taking into account the thermodynamic control, the relative PAs of substituted rings with regard to the nonsubstituted one, ΔPA, calculated at different positions of the ring, can be inferred as a reliable measure of the activating and deactivating ability of the substituent. Thus, Bader and Chang employed the ΔPAs as a relative measure of the energy activation for electrophilic substitution in benzene derivatives.[23]

In a previous work,[14] the preferred sites of protonation in indole were investigated using QTAIM atomic charges, energies, and multicenter delocalization indices. In this work, the activating/deactivating effects of different substituents, $-CH_3$, $-F$, $-NH_2$, and $-NO_2$, in indole are quantitatively measured by

* To whom correspondence should be addressed.

10.1021/jp0708953 CCC: $37.00 © 2007 American Chemical Society
Published on Web 06/01/2007

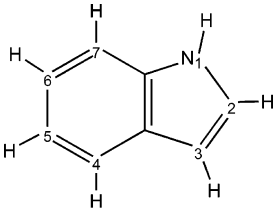

Figure 1. IUPAC numbering employed for indole and indole derivatives.

ΔPA. The results are compared to the electron density based reactivity indices previously listed above and obtained using the QTAIM. In spite of its success for benzene[19] and uracil[21] derivatives, we will show that the laplacian of the electron density fails to predict the main nucleophilic centers in indole and indole derivatives. Also, the comparison of our results with qualitative predictions based on the resonance model (RM) is performed. In previous works, the RM was shown to be inadequate for studying acidity in phenol derivatives[24] as well as for studying charge redistributions upon protonation and hydride addition.[25−28] Nevertheless, the quantitative results obtained in this work are in line with the qualitative expectations derived from the RM.

II. Computational Details

The indole derivatives studied are those obtained from the substitution of −H by R = $-CH_3$, −F, $-NH_2$, or $-NO_2$ at atoms 1−3 and 4−7 (see Figure 1 for IUPAC numbering). Moreover, all the possible protonations of these molecules were considered. The B3LYP/6-311++G(2d,2p) level of theory was employed for the geometry optimizations and the electron density calculations. Gaussian 03 program[29] was used to compute molecular geometries and electron densities whereas the AIMPAC suite of programs[30] was used to obtain the atomic and local properties of the electron density. All the integrations of the atomic properties were done with integrated values of the error function, L(Ω), lower than $2\cdot10^{-3}$ au, which is a necessary condition for the quality of the results.

This paper deals with total and π atomic charges denoted by $N^T(\Omega)$ and $N^\pi(\Omega)$, the *zz* component of the quadrupole electric tensor, $Q_{zz}(\Omega)$,[19] and the condensed Fukui index, $f^-(\Omega)$.[20] They are computed for restricted closed-shell determinants of Kohn−Sham spatial molecular orbitals (MOs), represented by ϕ_i, with equations 1−4 where Ω represents the atomic domain defined within the framework of QTAIM, $\rho(r)$ is the electron density, and n_{occ} and $n_{occ}{}^\pi$ are, respectively, the number of occupied spatial MOs and the number of occupied π spatial MOs.

$$N^{\mathrm{T}}(\Omega) = \int_\Omega \rho(\vec{r})\,\mathrm{d}\vec{r} = 2\int_\Omega \sum_i^{n_{occ}} \phi_i^2(\vec{r})\,\mathrm{d}\vec{r} \qquad (1)$$

$$N^{\pi}(\Omega) = \int_\Omega \rho^{\pi}(\vec{r})\,\mathrm{d}\vec{r} = 2\int_\Omega \sum_i^{n_{occ}{}^\pi} \phi_i^2(\vec{r})\,\mathrm{d}\vec{r} \qquad (2)$$

$$Q_{zz}(\Omega) = \int_\Omega \rho(\vec{r})(3z^2 - r^2)\,\mathrm{d}\vec{r} \qquad (3)$$

$$f^-(\Omega) = 2\int_\Omega \phi_{\mathrm{HOMO}}{}^2(\vec{r})\,\mathrm{d}\vec{r} \qquad (4)$$

Finally, ΔPA is computed as the difference between PAs of an indole derivative containing the −R substituent and indole (eq 5). All the molecular geometries involved in ΔPA calculation were fully optimized. In no case did these protonations give rise to products other than the attachment of the proton to the selected position of indole. The magnitude of basis set superposition error (BSSE) was checked to be less than 0.01 kJ mol^{-1}.[14] Zero point vibrational energies (ZPVE) corrections were not included in the calculation of ΔPAs, since they are compared with reactivity indices that only depend on electronic effects. Moreover, the ZPVE corrections for the parent indole and its derivatives balance out.

$$\Delta\mathrm{PA} = [E(C_8H_7NR^+) + E(C_8H_7N)] - [E(C_8H_6NR) + E(C_8H_8N^+)] \qquad (5)$$

TABLE 1: B3LYP/6-311++G(2d,2p) Proton Affinities for All the Indole Derivatives Studied[a]

R	SP[b]	1	2	3	4	5	6	7
H		866.6	900.9	922.5	887.6	887.2	890.2	876.0
CH_3	1	17.5	12.6	27.9	12.4	13.7	13.9	15.4
	2	16.0	−2.7	29.1	20.5	15.7	23.3	13.6
	3	21.7	25.8	−2.4	10.4	12.6	9.9	10.9
	4	7.1	13.3	7.6	−7.6	21.2	10.1	24.9
	5	11.0	14.5	11.8	21.2	−3.5	20.1	8.4
	6	10.4	23.1	9.8	7.1	21.0	−4.3	20.8
	7	8.3	9.8	7.5	21.3	11.3	18.8	−6.2
F	1	−9.1	−26.2	−16.7	−29.7	−21.9	−30.6	−17.9
	2	−29.1	−41.0	−6.3	−8.2	−17.5	−4.2	−20.0
	3	−8.3	4.7	−44.5	−16.2	−18.4	−20.2	−18.6
	4	−20.1	−18.6	−17.8	−60.0	−5.0	−23.6	1.2
	5	−14.9	−18.8	−13.1	−4.3	−63.9	−8.8	−25.9
	6	−17.2	−3.8	−17.3	−26.3	−10.1	−60.7	−7.2
	7	−18.8	−25.1	−19.8	−2.5	−23.5	−7.3	−58.4
NH_2	2	18.4	−20.4	88.6	60.1	25.5	68.6	20.4
	3	52.0	101.4	−16.7	22.8	26.9	19.9	22.5
	4	16.9	37.2	15.4	−48.4	83.1	11.4	99.5
	5	30.5	31.0	37.6	85.6	−41.7	63.3	16.0
	6	27.6	76.1	23.3	11.7	64.5	−43.9	81.5
	7	14.2	11.1	13.6	82.3	12.4	69.7	−24.2
NO_2	2	−62.1	−80.9	−86.1	−70.9	−63.8	−76.1	−60.0
	3	−84.2	−80.3	−90.1	−60.2	−64.1	−66.4	−62.7
	4	−53.2	−58.3	−45.3	−78.7	−70.9	−59.6	−77.6
	5	−58.4	−61.3	−56.8	−66.8	−90.3	−62.1	−65.6
	6	−55.9	−69.0	−56.0	−62.3	−66.0	−85.4	−67.7
	7	−48.2	−57.0	−48.4	−78.5	−65.4	−72.0	−89.8

[a] The values are shown in kJ mol^{-1} with regard to those of indole (R = H). [b] SP denotes substituent position.

III. Results and Discussion

The Proton Affinity Scale. The PAs calculated in a previous paper for the different protonation sites of indole led to the conclusion that C_3 has the largest probability of undergoing an electrophilic attack.[14] This conclusion is also supported by experimental results.[8−11] ΔPAs, calculated for all the indole derivatives here considered, are collected in Table 1.

The insertion of a methyl group into one of the carbons of the pyrrol or phenyl rings clearly activates the electrophilic attack at all positions with the exception of the ipso one. The specificity of ipso positions may be due either to steric hindrance or to electronic effects and will be discussed in the next section. As a general rule, it can be stated that substitutions in a certain ring mainly activate the carbons of that ring, indicating the prevalence of inductive effects for this substitution. However, some exceptions to this rule can be observed in Table 1, showing that not only the inductive effects are responsible of the activating ability of $-CH_3$. For instance, the most activated position of 6-methylindole is C_2, which is quite far from C_6. Also, the most activated positions of 4-methylindole and 7-methylindole are, respectively, C_7 and C_4. All this evidence indicates that the activating ability of $-CH_3$ cannot be solely explained by arguments based on inductive effects.

The insertion of fluorine into the pyrrol or phenyl rings clearly disfavors the protonation at all positions with the exception of C_2 and C_7 for, respectively, 3-fluorineindole and 4-fluorineindole. The large −I character of fluorine is clearly reflected on the ipso positions where the most negative ΔPAs are found for all the substitutions. The nitrogen atom is an exception to this rule that can be explained by its high electronegativity. Also, the behavior of fluorine derivatives cannot be uniquely explained by the −I character of this atom. Thus, ΔPAs for protonations at ortho and para sites are significantly less negative than the rest. This can be explained by accepting that fluorine has a small mesomeric electron-releasing character (+R).

The amino group is an example of −I and +R character. Thus, ipso positions are significantly deactivated, showing negative ΔPAs, whereas the remaining positions are activated, showing large positive ΔPAs. The +R character of $-NH_2$ is quite important as can be derived from the high ΔPA values of each substitution, which always exceed 81.0 kJ mol^{-1}. The position with largest mesomeric effect is located in the substituted ring. Thus, substitutions at N_1, C_2, and C_3 mainly activate the pyrrol ring and substitutions at C_4, C_5, C_6, and C_7 mainly activate the phenyl ring.

Finally, the nitro group is an example of inductive and mesomeric electron-withdrawing character (−I and −R). The former is reflected on the ΔPA values at ipso positions, which are highly deactivated; in fact, they are the most deactivated positions. The only exception is observed for 2-nitroindole, where the most deactivated position is the C_3 and not the C_2. We think this is because of the competitive inductive effects of the two attached nitrogens. Once again, the position with the largest mesomeric effect is located in the substituted ring as happened for $-NH_2$.

For all the R groups, the mesomeric effects within the phenyl ring are intensified in para and ortho positions, although the effects are most significant in para. Thus, the most activated positions are C_4 and C_7, respectively, for substitutions at C_7 and C_4 when R = $-CH_3$, F, and NH_2, and the second most deactivated positions are C_4 and C_7 for, respectively, substitutions at C_7 and C_4 when R = $-NO_2$. Also, there is clear evidence of mesomeric effects between atoms from different rings. Thus, looking at the ΔPA values in Table 1, we observe that the substitution at C_2 favors (or disfavors) the protonation of carbons C_4 and C_6 and vice versa. Another remarkable ΔPA value is obtained for N_1 in 3-nitroindole. This highly negative value is associated to a resonance form that releases electron density into the NO_2 group leaving a formal positive charge on N_1. All of this stays in line with the RM.

***σ* and *π* Atomic Electron Populations and Fukui Indices.** According to traditional interpretations, inductive effects and mesomeric effects are mainly related to variations of σ and π electron populations, respectively.[1] However, no quantitative simple relationship has been found between atomic electron populations of the neutral form and PAs. Thus, we can only establish qualitative relations between both properties.

Tables 2 and 3 collect, respectively, the values of σ and π ring and atomic electron populations for all planar indole derivatives. The geometry of the amino indole derivatives is not planar, which mixes up the σ and π MOs and impedes performing the $\sigma-\pi$ partitioning. Looking at the values of Table 2, the mesomeric electron-releasing character of $-CH_3$ and −F is clearly reflected on the values of the relative ring π electron populations, ΔN^{π}[R]; these are always positive for both pyrrol and phenyl rings, being larger for the substituted ring. Also, the mesomeric effect of −F is larger than that of $-CH_3$.

TABLE 2: QTAIM *σ* and *π* Ring Electron Populations, N^{σ} and N^{π}[R], for Indole (R = H), in au, and Corresponding Relative Values for Planar Indole Derivatives, ΔN^{σ} [R] and ΔN^{π} [R][a]

		pyrrol		phenyl	
	SP[b]	s	p	s	p
H		25.651	5.779	29.691	6.004
CH_3	1	−1.3	1.1	0.8	1.0
	2	−1.6	2.0	−0.2	1.3
	3	−2.1	2.2	0.2	1.1
	4	−0.2	1.7	−2.5	3.3
	5	−0.7	1.2	−2.7	3.1
	6	−0.6	1.4	−2.8	3.0
	7	−0.1	1.4	−2.6	3.1
F	1	−64.2	5.8	−5.6	−0.1
	2	−66.6	4.6	−3.1	1.7
	3	−65.8	6.1	−4.1	0.1
	4	−5.7	1.1	−63.3	6.5
	5	−2.6	0.5	−61.5	5.6
	6	−2.7	0.9	−62.2	5.1
	7	−5.5	1.0	−63.2	6.2
NO_2	2	−33.1	−6.9	1.2	−9.0
	3	−34.7	−6.1	1.1	−6.2
	4	−0.7	−7.1	−29.5	−3.0
	5	0.9	−6.2	−28.5	−4.7
	6	1.8	−6.8	−27.8	−3.8
	7	0.5	−8.7	−31.7	−6.0

[a] In au with regard to those of indole and multiplied by 10^2. [b] SP denotes substituent position.

The mesomeric effect of $-CH_3$ is due to the conjugation of one of the MOs localized at the out-of-plane C−H bonds (the A″ MO) and the π MOs from the rings. The RM calls the mesomeric effect of $-CH_3$ "hyperconjugation" and represents it by a resonance structure where the C from the $-CH_3$ is doubly bonded to the ipso C from the ring, adopting sp^2 hybridization, and a free proton.

It can be observed that nitrogen acts as a small barrier for the electron conjugation between $-CH_3$ or −F and the phenyl ring, since the smallest ΔN^{π}[R] electron population is found when the substitution takes place on this atom. The $-NO_2$ group displays negative values of relative ring π electron populations that are larger, in absolute values, than those of $-CH_3$ and −F, reflecting the large mesomeric electron-withdrawing character of this group.

According to the negative ΔN^{σ}[R] values obtained for methylindole derivatives, and contrary to that generally assumed, the QTAIM results point to an electron-withdrawing character for $-CH_3$ instead of electron-releasing. These results probably stem from the slightly negative QTAIM charge of Hs in methyl groups. The loss of σ electrons by the rings is partially recovered via π donation from $-CH_3$ as explained above. The ΔN^{σ}[R] remaining groups confirm the expectations, −F and $-NO_2$ are highly electron-withdrawing groups.

The relative π atomic electron populations collected in Table 3, $\Delta N^{\pi}(\Omega)$, are in qualitative good agreement with the ΔPA values (Table 1) for $-CH_3$. Thus, the most activated atoms correspond to the largest $\Delta N^{\pi}(\Omega)$ values for substitutions in the pyrrol ring, and the two most activated atoms correspond to the two largest $\Delta N^{\pi}(\Omega)$ values for substitutions in the phenyl ring. Also, $N^{\pi}(\Omega)$ values shed light on the issue of the origin of the small deactivating ability of $-CH_3$ at the ipso carbons. Ipso carbons display negative values of $\Delta N^{\pi}(\Omega)$, whereas the remaining carbons all display positive or very small negative ones. Moreover, the values of $\Delta N^{\sigma}(\Omega)$ are also negative for these atoms, contrary to that found for the most activated atoms,

TABLE 3: QTAIM σ and π Atomic Electron Populations, $N^{\sigma}(\Omega)$ and $N^{\pi}(\Omega)$, for Indole (R = H), in au, and Corresponding Relative Values for Planar Indole Derivatives, $\Delta N^{\sigma}(\Omega)$ and $\Delta N^{\pi}(\Omega)$[a]

R	SP[b]		1	2	3	4	5	6	7
H		N^{π}	1.717	0.983	1.062	0.982	0.999	0.988	1.017
		N^{σ}	6.350	4.688	4.963	5.023	5.012	5.017	4.989
CH_3	1	ΔN^{π}	−0.6	0.5	0.6	0.0	0.1	0.1	0.2
		ΔN^{σ}	−1.7	0.3	−0.1	0.0	0.0	0.0	0.6
	2	ΔN^{π}	0.7	−0.5	1.9	0.4	0.2	0.4	0.3
		ΔN^{σ}	−1.1	0.2	−1.1	−0.2	−0.1	−0.2	−0.1
	3	ΔN^{π}	0.7	2.0	−0.9	0.3	0.2	0.1	0.1
		ΔN^{σ}	−0.5	−0.8	−0.9	0.2	−0.2	0.1	0.0
	4	ΔN^{π}	−0.1	0.2	0.2	−0.5	1.6	−0.1	0.9
		ΔN^{σ}	0.2	−0.1	0.4	−0.5	−0.9	0.1	−0.5
	5	ΔN^{π}	0.1	0.2	0.2	1.8	−0.5	1.4	−0.3
		ΔN^{σ}	−0.1	−0.2	−0.1	−1.3	−0.6	−0.6	0.1
	6	ΔN^{π}	0.1	0.7	0.0	−0.3	1.5	−0.5	1.7
		ΔN^{σ}	−0.2	−0.1	0.2	0.2	−0.7	−0.6	−1.2
	7	ΔN^{π}	−0.1	0.3	−0.1	0.8	0.0	1.6	−0.6
		ΔN^{σ}	0.4	−0.1	0.1	−0.6	0.0	−0.9	−0.6
F	1	ΔN^{π}	2.2	0.9	0.3	−0.5	−0.3	−1.0	−0.7
		ΔN^{σ}	−55.2	−2.5	−1.8	−0.1	−0.1	0.3	−1.0
	2	ΔN^{π}	1.1	−1.1	3.0	0.5	−0.5	0.4	−0.3
		ΔN^{σ}	−2.8	−55.8	−6.4	−0.9	0.2	−0.4	−0.4
	3	ΔN^{π}	1.1	3.7	−0.6	−0.5	−0.4	−0.6	−0.3
		ΔN^{σ}	−2.4	−4.9	−54.5	−0.2	−0.1	0.3	−0.1
	4	ΔN^{π}	−0.4	−0.2	−0.5	0.7	2.7	−0.6	1.5
		ΔN^{σ}	0.0	−0.2	−0.7	−51.5	−4.7	−0.5	−1.8
	5	ΔN^{π}	0.0	−0.8	0.4	2.8	0.5	2.4	−0.1
		ΔN^{σ}	−0.2	0.0	−0.6	−5.0	−50.5	−0.4	−0.2
	6	ΔN^{π}	0.0	0.6	−0.4	−1.1	2.4	0.5	2.7
		ΔN^{σ}	−0.3	0.1	−0.1	−0.3	−4.0	−50.9	−4.7
	7	ΔN^{π}	−0.3	−0.5	−0.2	1.5	−0.5	2.7	0.5
		ΔN^{σ}	−0.1	0.0	−0.2	−1.8	−0.6	−4.6	−51.0
NO_2	2	ΔN^{π}	−1.6	4.5	−7.5	−1.7	−1.3	−2.9	−0.8
		ΔN^{σ}	0.5	−34.6	2.5	0.6	0.4	1.8	−0.1
	3	ΔN^{π}	−3.0	−8.5	4.1	−2.8	−2.2	−1.6	−0.9
		ΔN^{σ}	2.9	−1.0	−34.7	0.9	1.2	0.7	0.2
	4	ΔN^{π}	−0.8	−2.9	−2.5	7.3	−5.2	−0.3	−3.9
		ΔN^{σ}	1.0	1.1	−0.5	−30.4	2.0	−1.3	2.5
	5	ΔN^{π}	−1.3	−0.9	−1.5	−4.9	6.8	−3.2	−0.9
		ΔN^{σ}	0.9	0.7	0.2	1.5	−28.9	0.5	−0.7
	6	ΔN^{π}	−1.1	−3.0	−0.7	−0.7	−3.3	7.1	−4.9
		ΔN^{σ}	0.8	0.9	−0.2	−0.9	0.7	−29.3	1.4
	7	ΔN^{π}	−3.8	−1.7	−0.8	−4.4	−0.6	−4.7	6.1
		ΔN^{σ}	3.6	0.7	0.1	2.9	−1.1	1.8	−31.4

[a] In au with regard to those of indole and multiplied by 10^2. [b] SP denotes substituent position.

which show negative σ values but positive π ones. Summarizing for $-CH_3$, this group is −I contrary to that traditionally assumed and +R, which is responsible for the activating ability of this group.

In fluorine, the effect of σ electron population overshadows the π one. The large negative $\Delta N^{\sigma}(\Omega)$ values rule ΔPA at the ipso carbons with the exception of N-substitution. However, the mesomeric effect is present and plays an important rule for the remaining atoms. So, it can explain the small positive ΔPAs of C_7 in 4-fluorineindole and C_4 in 7-fluorineindole (atoms in para position); both C_7 and C_4 display significant positive value of $\Delta N^{\pi}(\Omega)$ in these molecules. Also, $\Delta N^{\pi}(\Omega)$ is significantly positive for the atoms attached to the substituted carbons (atoms in ortho position), which explains their small deactivation. Summarizing for −F, this group is indeed −I but also +R.

The ortho and para deactivating ability of $-NO_2$ is reflected on the $\Delta N^{\pi}(\Omega)$ values. So, the largest negative values correspond to these atoms for all substitutions. Moreover, the $\Delta N^{\pi}(\Omega)$ values also predict the mesomeric effect between C_2 and C_6, and these atoms display values of $\Delta N^{\pi}(\Omega)$ that stand out over the other atoms (with the exception of atoms in ortho). The electron-withdrawing character of $-NO_2$ is intensified at the ipso carbons because of the electronegativity of nitrogen and oxygens, which is reflected on large negative $\Delta N^{\sigma}(\Omega)$ values. It has to be remembered that the most negative ΔPAs correspond to the ipso carbons when the substitution takes place in the phenyl ring.

Now, let us check the ability of Fukui indices to predict activating/deactivating abilities of the −R groups in indole. Table 4 collects the values of $f^{-}(\Omega)$ calculated from eq 4 for all the indole derivatives with regard to indole called $\Delta f^{-}(\Omega)$ from now on. Activating and deactivating abilities of the different groups will be shown by positive and negative values of $\Delta f^{-}(\Omega)$, respectively. The Fukui index as approximated by eq 4 only depends upon the electron density of the highest occupied molecular orbital (HOMO). Thus, $f^{-}(\Omega)$ could correlate well with the energy profile at the first stage of the process, which is useful for reactions that show early energy barriers, but it is useless when the π aromatic system has been broken and the π MOs have changed substantially. Anyway, some trends can be distinguished unequivocally from the values in Table 4. The mesomeric para and ortho activating ability of $-CH_3$, −F, and $-NH_2$ is reflected on the positive values of $\Delta f^{-}(\Omega)$ for C_4 and C_7 in substitutions at C_7 and C_4, respectively. On the other hand, the same atoms display negative values for nitro-indole substituted at C_7 and C_4, showing the

TABLE 4: QTAIM Condensed Fukui Indices, $f^-(\Omega)$, Calculated for Indole (R = H), in au, and Corresponding Relative Values for All the Indole Derivatives, $\Delta f^-(\Omega)$[a]

R	SP[b]	1	2	3	4	5	6	7
H		0.253	0.294	0.447	0.308	0.058	0.236	0.237
CH_3	1	0.050	−0.053	0.029	−0.023	0.015	−0.040	−0.003
	2	−0.074	0.036	0.014	−0.030	−0.027	0.037	−0.060
	3	0.043	0.022	0.004	−0.042	0.006	−0.048	−0.031
	4	−0.028	−0.027	−0.054	0.006	0.022	−0.009	0.033
	5	0.023	−0.036	0.005	0.030	0.024	−0.041	0.009
	6	−0.057	0.052	−0.056	−0.058	−0.035	0.049	−0.009
	7	0.003	−0.056	−0.041	0.036	0.023	0.001	0.026
F	1	0.065	−0.106	0.006	−0.004	0.061	−0.077	0.051
	2	−0.116	0.023	−0.017	−0.030	−0.033	0.075	−0.071
	3	0.054	0.027	−0.036	−0.044	0.007	−0.048	−0.030
	4	−0.016	−0.044	−0.048	−0.015	0.036	−0.026	0.054
	5	0.064	−0.082	0.032	0.046	0.053	−0.094	0.003
	6	−0.069	0.076	−0.058	−0.074	−0.039	0.030	−0.025
	7	0.011	−0.079	−0.043	0.057	0.043	−0.013	0.012
NH_2	2	−0.197	0.016	0.004	−0.110	−0.027	0.060	−0.173
	3	0.061	0.092	−0.085	−0.165	−0.002	−0.135	−0.127
	4	−0.109	−0.139	−0.236	−0.044	0.150	−0.104	0.126
	5	−0.037	−0.272	−0.320	0.014	0.236	−0.156	−0.102
	6	−0.158	0.025	−0.253	−0.185	0.011	0.022	0.004
	7	−0.037	−0.208	−0.214	0.101	0.066	0.013	0.037
NO_2	2	0.058	−0.113	−0.112	0.042	0.060	−0.050	0.092
	3	−0.061	−0.108	−0.107	0.044	0.000	0.016	0.054
	4	−0.010	0.040	0.057	−0.066	−0.037	0.013	−0.095
	5	−0.015	0.038	0.020	−0.048	−0.016	0.026	−0.032
	6	0.021	−0.030	0.037	0.003	0.040	−0.050	−0.056
	7	−0.017	0.068	0.065	−0.079	−0.020	−0.063	−0.071

[a] In au with regard to those of indole and multiplied by 10^2. [b] SP denotes substituent position.

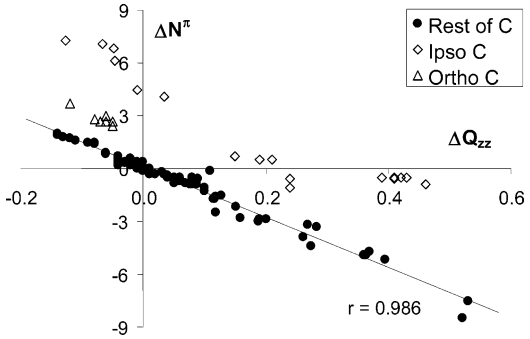

Figure 2. *zz* component of the atomic quadrupole tensor, $Q_{zz}(\Omega)$, vs the π atomic populations, $N^{\pi}(\Omega)$, for the carbon atoms of the indole derivatives studied. The values are relative to those of indole and $\Delta N^{\pi}(\Omega)$ is multiplied by 10^2.

mesomeric deactivating ability of $-NO_2$. Also, the conjugation between C_2 and C_6 is displayed by the values of $\Delta f^-(\Omega)$ for all the −R groups. However, the remaining atoms do not show values of $\Delta f^-(\Omega)$ that could be directly connected to the ΔPAs.

Other Indices Obtained from the Electron Density. The values of $Q_{zz}(\Omega)$ as calculated from eq 3 follow the same trends shown by $N^{\pi}(\Omega)$. Thus, the mesomeric effects found for $-CH_3$, −F, and $-NO_2$ can also be deduced from the relative $Q_{zz}(\Omega)$ values, $\Delta Q_{zz}(\Omega)$. Also, the values of $\Delta Q_{zz}(\Omega)$ for ipso carbons follow a similar trend as $\Delta N^{\pi}(\Omega)$. Figure 2 displays the good linear correlation found between $\Delta Q_{zz}(\Omega)$ and $\Delta N^{\pi}(\Omega)$ for indole derivatives with R = $-CH_3$, −F, and $-NO_2$. The ipso and ortho carbons show specific character because of the proximity of the substituent.

As an advantage over $\Delta N^{\pi}(\Omega)$, $\Delta Q_{zz}(\Omega)$ does not need previous partitioning of the electron density into σ and π densities, so that the mesomeric electron-releasing character of the amino group can also be studied. Thus, Table 5 collects the values of $\Delta Q_{zz}(\Omega)$ for the amino indole derivatives. As one can see, the inductive electron-withdrawing character of $-NH_2$ is reflected on the values of $\Delta Q_{zz}(\Omega)$ at the ipso carbons, which are positive, indicating a decrease of the absolute values of $Q_{zz}(\Omega)$ with regard to indole. Moreover, the mesomeric electron-releasing character is found at the ortho positions (the most negative $\Delta Q_{zz}(\Omega)$ values) for substitutions on the phenyl and pyrrol rings and para positions for substitutions on the phenyl ring. The electron conjugation between C_2 and C_6 is also reflected on the $\Delta Q_{zz}(\Omega)$ values as these atoms show significant negative values.

TABLE 5: QTAIM $Q_{zz}(\Omega)$ Values for Indole (R = H), in au, and Relative $\Delta Q_{zz}(\Omega)$ Values for Amino Indole Derivatives (in au)[a]

SP[b]	1	2	3	4	5	6	7
H	−2.530	−3.400	−3.740	−3.300	−3.460	−3.380	−3.470
2	6.6	43.3	−33.1	−9.4	0.4	−8.5	−0.8
3	−6.0	−41.9	50.0	−2.5	−3.7	−0.9	−1.9
4	1.5	−6.3	−4.8	43.3	−36.0	7.4	−27.6
5	−1.6	−0.9	−7.9	−36.2	48.3	−24.6	7.6
6	−3.0	−14.3	1.9	9.0	−25.3	48.5	−35.3
7	10.0	−2.5	2.2	−21.0	6.5	−30.5	41.7

[a] The values are shown in au with regard to those of indole. [b]SP denotes substituent position.

We have also computed the values of $\nabla^2\rho(r)$ at the secondary charge concentrations. Unfortunately, this property seems to be very sensitive to the atomic environment, and no correlation is found with the PAs for the carbon atoms of indole and indole derivatives. In Figure 3, the plot of $\nabla^2\rho(r)$ versus PA for indole is shown. As one can see, the representation is a scattering, and the same occurs in the remaining molecules studied. We can conclude that this property, contrary to that found for benzene derivatives,[19] is not a reliable estimator of the nucleophilic/eletrophilic character in heteropolycycles such as indole derivatives.

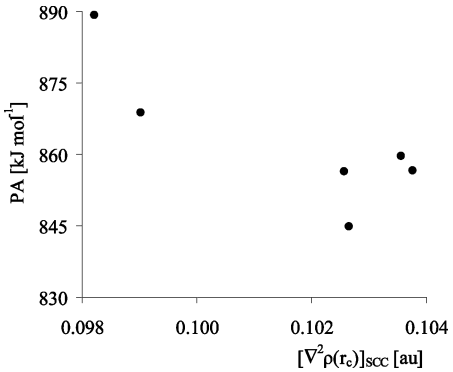

Figure 3. Laplacian of the electron density at the secondary charge concentrations, SCC, vs the proton affinity of the carbon atoms in indole.

IV. Concluding Remarks

Activating and deactivating abilities of several R substituents ($-CH_3$, $-F$, $-NH_2$, $-NO_2$) in indole have been theoretically studied using a series of electron density based reactivity indices previously used in benzene[19] and uracil[21] derivatives. An energetic scale based on the proton affinities has been employed to check the validity of these reactivity indices. The absence of kinetic control in the protonation of an aromatic ring makes the proton affinity an adequate property for measuring the electronic activating or deactivating effects of a substituent. Relative proton affinities reflect the ortho and para orientation ability of $-CH_3$, $-F$, and $-NH_2$ groups, whereas the large deactivating effect of $-NO_2$ is mainly observed at these positions. Also, substitutions in carbons 2 and 6 (IUPAC nomenclature) activate/deactivate carbons 6 and 2, respectively. Inductive effects are also reflected on the values of the relative proton affinities. The $-CH_3$ group is shown to have inductive electron-withdrawing character instead of electron-releasing with its activating ability being due to a small mesomeric electron-releasing character. π atomic electron populations and the *zz* component of the atomic quadrupole electric tensor qualitatively explain the order of proton affinities. Fukui indices approximately predict the results obtained by the previous properties, whereas no correlation is found between laplacian of the electron density at the secondary charge concentrations and the proton affinity scale.

Acknowledgment. We are indebted to Centro de Supercomputación de Galicia (CESGA) and to Spanish MEC for financial support through project CTQ2006-15500/BQU. N.O. thanks University of Vigo and Xunta de Galicia for predoctoral fellowships. M.M. thanks Xunta de Galicia for financial support as a researcher of the "Isidro Parga Pondal" program.

References and Notes

(1) Dewar, M. J. S. *The Electronic Theory of Organic Chemistry*; Oxford University Press: London, 1949.

(2) Penieres-Carrill, G.; García-Estrada, J. G.; Gutiérrez-Ramírez, J. L.; Álvarez-Toledano, C. *Green Chem.* **2003**, *5*, 337.

(3) Zavodnik, I. B.; Domanski, A. V.; Lapshina, E. A.; Bryszewska, M.; Reiter, R. J. *Life Sci.* **2006**, *79*, 391.

(4) Barraja, P.; Diana, P.; Lauria, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G. *Helv. Chim. Acta* **2001**, *84*, 2212.

(5) Terrier, F.; Lakhdar, S.; Boubaker, T.; Goumont, R. *J. Org. Chem.* **2005**, *70*, 6242.

(6) Blades, C. E.; Wilds, A. L. *J. Org. Chem.* **1956**, *21*, 1013.

(7) Merrer, D. C.; Ozcetinkaya, S.; Shinnar, A. E. *Tetrahedron Lett.* **2004**, *45* 4899.

(8) Hoyuelos, F. J.; García, B.; Ibeas, S.; Muñoz, M. S.; Navarro, A. M.; Peñacoba, I.; Leal, J. M. *Eur. J. Org. Chem.* **2005**, 1161.

(9) Hinman, R. L.; Whipple, E. B. *J. Am. Chem. Soc.* **1962**, *84*, 2534.

(10) Hinman, R. L.; Lang, J. *J. Am. Chem. Soc.* **1964**, *86*, 3796.

(11) Chen, H. J.; Hakka, L. E.; Hinman, R. L.; Kresge, A. J.; Whipple, E. B. *J. Am. Chem. Soc.* **1971**, *93*, 5102.

(12) Tomić, S.; Ramek, M.; Kojić-Prodić, B. *Croat. Chem. Acta* **1998**, *71*, 511.

(13) Somers, K. R. F.; Ceulemans, A. *J. Phys. Chem. A* **2004**, *108*, 7577.

(14) Otero, N.; González-Moa, M. J.; Mandado, M.; Mosquera, R. A. *Chem. Phys. Lett.* **2006**, *428*, 249.

(15) Alagona, G.; Ghio, C.; Monti, S. *J. Mol. Struct. (THEOCHEM)* **1998**, *433*, 203.

(16) Sun, M.; Nelson, A. E.; Adjaye, J. *J. Mol. Catal., A: Chem.* **2004**, *222*, 243.

(17) Bader, R. F. W. *Chem. Rev.* **1991**, *91*, 893.

(18) Bader, R. F. W. *Atoms in Molecules: a Quantum Theory*; Oxford University Press: New York, 1990.

(19) Bader, R. F. W.; Chang, C. *J. Phys. Chem.* **1989**, *93*, 2946.

(20) Cioslowski, J.; Martinov, M.; Mixon, S. T. *J. Phys. Chem.* **1993**, *97*, 10948.

(21) González-Moa, M. J.; Mosquera, R. A. *J. Phys. Chem. A* **2006**, *110*, 5934.

(22) Sordo, T.; Bertran, J.; Canadell, E. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1486.

(23) Bader, R. F. W.; Chang, C. *J. Phys. Chem.* **1989**, *93*, 5095.

(24) Mandado, M.; Mosquera, R. A.; Graña, A. M. *Chem. Phys. Lett.* **2004**, *386*, 454.

(25) Mandado, M.; Van Alsenoy, C.; Mosquera, R. A. *J. Phys. Chem. A* **2004**, *18*, 7050.

(26) González Moa, M. J.; Mosquera, R. A. *J. Phys. Chem. A* **2003**, *107*, 5361.

(27) González Moa, M. J.; Mosquera, R. A. *J. Phys. Chem. A* **2005**, *109*, 3682.

(28) González Moa, M. J.; Mandado, M.; Mosquera, R. A. *Chem. Phys. Lett.* **2006**, *428*, 255.

(29) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision C.02; Gaussian: Wallingford, CT, 2004.

(30) Bader, R. F. W.; et al. *AIMPAC: A Suite of Programs for the AIM Theory;* McMaster University: Hamilton, Ontario, Canada; contact bader@mcmail.cis.mcmaster.ca.