On the Electron Donor and the Electrophilic Substitution Activating Abilities of Substituents in Uracil

María J. González Moa and Ricardo A. Mosquera*

Departamento de Química Física, Facultade de Química, Lagoas-Marcosende s/n,
Universidade de Vigo, 36310-Vigo, Galicia, Spain

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QTAIM properties for uracil and 18 derivatives containing the substituents $-NH_2$, $-OH$, $-OCH_3$, $-SH$, $-F$, $-Cl$, $-CH_3$ $-NO_2$, and $-Li$ in position 5 or 6 were computed on MP2/6-31++G**//MP2/6-31G** charge densities. The results indicate that $-OH$, $-OCH_3$, and $-NH_2$ groups are really retrieving charge from the ring. Also, the activating ability of the substituent groups, usually considered as the variation of electron population at the carbon where the electrophilic attack takes place, C*, was studied. The study shows that the activating ability is reflected by the variation of π charge or quadrupole moment at C*, and also by the variation of the Laplacian of the charge density in the secondary charge concentration points around C* (SCC-C*). They indicate a similar, but not exactly equal, graduation of activating ability. The relative behavior of the substituents is basically the same as in benzene, though benzene has more tendency to concentrate charge in the SCC-C* regions than uracil, where this tendency is larger for 6- than for 5-derivatives. $\sigma^{+/-}{}_R$ Taft parameters are found to display good correlations with the above indicated activating indexes. Finally, the resonance model predicts most of the main variations displayed by QTAIM atomic π electron populations of derivatives with regard to uracil, but there are still some significant variations of the π electron charge that it cannot predict.

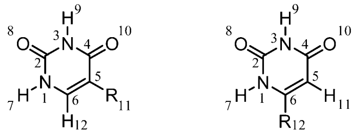
Introduction

Uracil, one of the pyrimidine bases involved in nucleoside structure, displays an important role in the search of new antiviral and antitumoral therapies.[1,2] Previously, it has been found that when a uracil derivative is part of a nucleoside analogue (5/6-F/Cl-*cis*-1-(2-hydroxymethyl-4-cyclopentenyl)-uracil), the electronic properties of the pentose and the base remain practically unmodified with respect to those of the isolated molecules.[3] For this reason, studying the structural properties of the isolated uracil derivatives is even more important, since the properties observed for them can be taken as a good approximation of the properties when they are just fragments of a more complex system.

On the other hand, recent studies pointed out the inadequacy of the resonance model to explain the atomic properties of the protonated forms of uracil and cytosine,[4,5] which had been extensively studied by Zeegers-Huyskens's research group.[6−8] This fact provides theoretical interest to calculate the modifications experienced by the atomic properties of uracil with diverse substitutions and compare them with those qualitatively predicted by the resonance model.

For these reasons, this work aims to quantify the donor character of several groups when they replace H11 and H12 (Figure 1) in uracil. It also aims to analyze how these substituents enhance or reduce the ability of uracil to undergo an electrophilic aromatic substitution and how they modify the electron distribution of the uracil ring. To achieve these objectives, the quantum theory of atoms in molecules (QTAIM)[9,10] was used to present and discuss diverse criteria. Some of these criteria were already successfully applied to analyze these characters in benzene derivatives.[11,12]

The substituents considered in this work include several groups generally considered strongly activating ($-NH_2$, $-OH$, $-OCH_3$), some considered weakly activating ($-CH_3$), and some considered weakly deactivating ($-F$, $-Cl$) for the electrophilic substitution. The list of groups is completed with a strongly deactivating group ($-NO_2$), an extremely strong electron donor ($-Li$), and another second row substituent ($-SH$), which are used to test the behavior of the criteria here reviewed and to obtain patterns of behavior.



	H	OH	OCH_3	NH_2	SH	CH_3	F	Cl	NO_2	Li
R_{11}	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
R_{12}	**1**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**

Figure 1. Compound nomenclature and atom numbering employed in this work.

Computational and Geometrical Details

MP2/6-31++G**//MP2/6-31G** calculations were carried out for uracil, **1**, and the 18 derivatives (**2**−**19**) shown in Figure 1 employing the Gaussian98 program.[13] The QTAIM atomic properties were calculated by using the program AIMPAC[14] on the above indicated charge densities.

When a molecule presents various conformers, the QTAIM properties shown correspond to the conformer with the lowest electronic energy. Thus, the C5═C6 bond is eclipsed to the O−H bond in molecules **2** and **11**, to the S−H bond in **5** and **14**, and to a C−H bond in **6** and **15**. The most stable conformer

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TABLE 1: QTAIM Charges (with Their π and σ Components) for the Substituents, X, and Ipso Carbons, C_{ipso}, for Compounds 2−19[a]

X:	OH	OCH_3	NH_2	SH	CH_3	F	Cl	NO_2	Li
	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
$Q^{\sigma}(X)$	−57.7	−61.2	−49.4	9.8	11.0	−65.4	−16.3	−38.2	92.6
$Q^{\pi}(X)$	4.1	3.8	11.1	8.9	1.6	0.3	2.7	−11.8	−0.6
$Q(X)$	−53.6	−57.4	−38.3	18.7	12.6	−65.1	−13.6	−50.0	92.0
$\Delta Q^{\sigma}(X)$	−66.6	−70.1	−58.3	0.9	2.1	−74.3	−25.2	−47.1	83.7
$\Delta Q^{\pi}(X)$	7.2	6.9	14.2	12.0	4.7	3.4	5.8	−8.7	2.5
$\Delta Q(X)$	−59.4	−63.2	−44.1	12.9	6.8	−70.9	−19.4	−55.8	86.2
$\Delta Q^{\sigma}(C_{ipso})$	50.0	51.5	43.8	−12.1	−2.4	53.4	10.9	31.4	−50.5
$\Delta Q^{\pi}(C_{ipso})$	5.8	5.3	6.9	−5.5	0.6	2.0	−5.6	−5.7	11.7
$\Delta Q(C_{ipso})$	55.8	56.8	50.7	−17.6	−1.8	55.4	5.3	25.7	−38.8
	11	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
$Q^{\sigma}(X)$	−60.4	−59.6	−52.2	8.5	10.4	−67.3	−18.4	−36.6	93.5
$Q^{\pi}(X)$	6.0	7.4	13.4	10.9	2.5	1.7	5.5	−7.9	−0.8
$Q(X)$	−54.4	−52.2	−38.8	19.4	12.9	−65.6	−12.9	−44.5	92.7
$\Delta Q^{\sigma}(X)$	−68.3	−67.5	−60.1	0.6	2.5	−75.2	−26.3	−44.5	85.6
$\Delta Q^{\pi}(X)$	8.6	10.0	16.0	13.5	5.1	4.3	8.1	−5.3	1.8
$\Delta Q(X)$	−59.7	−57.5	−44.1	14.1	7.6	−70.9	−18.2	−49.8	87.4
$\Delta Q^{\sigma}(C_{ipso})$	53.2	55.6	45.6	−10.2	−2.7	54.8	12.1	31.1	−58.3
$\Delta Q^{\pi}(C_{ipso})$	4.5	4.0	5.2	−7.3	−0.5	0.5	−6.8	−4.6	12.4
$\Delta Q(C_{ipso})$	57.7	59.6	50.8	−17.5	−3.2	55.3	5.3	26.5	−45.9

[a] All values are in au and are multiplied by 10^2. Atomic charges for compound **1** are $Q^{\sigma}(C_5) = 0.048$ au, $Q^{\pi}(C_5) = -0.035$ au, $Q^{\sigma}(H_{11}) = 0.089$ au, $Q^{\pi}(H_{11}) = -0.031$ au, $Q^{\sigma}(C_6) = 0.374$ au, $Q^{\pi}(C_6) = 0.111$ au, $Q^{\sigma}(H_{12}) = 0.079$ au, $Q^{\pi}(H_{12}) = -0.026$ au.

of **3** displays the O−C bond eclipsed to C4−C5 with one of the hydrogens of the methyl group in the same plane, allowing the formation of a hydrogen bond with O10, as it was confirmed by the existence of the corresponding bond path and ring critical point. Finally, the most stable conformer of **12** eclipses the O−C bond to C6═C5 and disposes the methyl group in alternated conformation.

The only molecules whose optimized geometries are significantly different from those of compound **1** are the lithium derivatives **10** and **19**. These molecules present very small C−C−Li bond angles (C4−C5−Li is 78.3° in **10**, and C5═C6−Li is 88.7° in **19**) and long C−Li bond lengths (2.023 Å in **10** and 1.936 Å in **19**). In **10**, these geometry features result in an O10···Li distance smaller than the Li−C5 bond length. Nevertheless, no bond path connecting O10 and Li was found. In contrast, one bond path that can be associated with an interaction between complete shells was found between O10 and one of the oxygen atoms of the NO_2 group in **9**.

The virial ratio of the wave functions never differed from −2 by more than 3.5×10^{-3}. The quality achieved in QTAIM integrated properties is usually tested by checking the reproducibility of molecular electron energy and molecular electron population by the summation of the corresponding atomic quantities. Here, the error in the additivity of the integrated atomic properties was always less (in absolute value) than 8×10^{-3} au for the electron population and than 5.5 kJ mol^{-1} for the electronic energy. Another parameter usually employed to test the quality of QTAIM atomic properties computed for a certain atom is the integrated value of the L function. It is related to the atomic integration of the Laplacian of the charge density by a constant, and should be zero when the interatomic surfaces surrounding an atom are perfectly defined and the numerical integration is exact. In this case, the summation of the absolute values of the integrated values of the L function for every atom, Ω, in a molecule $[\sum L(\Omega)]$ was always lower than 3.2×10^{-3} au. Part of the analysis reported here is based upon the atomic electron populations, $N(\Omega)$, expressed as relative values with regard to the corresponding values in molecule **1**. Because of the symmetry of the systems here studied, we have calculated the π and σ contributions for every atom, respectively $N^{\pi}(\Omega)$ and $N^{\sigma}(\Omega)$.

Electron Donor Character

A priori, the electron donor or acceptor character of a certain substituent, X, could be measured strictly by its net electric charge, $Q(X)$. Thus, all donors should present positive charges, whereas the acceptors should display a negative charge. Nevertheless, the terms donor and acceptor are normally employed to indicate the relative ability of the group to transfer or receive more electron charge to (or from) the rest of the molecule than a reference group (the hydrogen atom). QTAIM allows measuring this ability as a difference of electron populations. However, several population differences can still be considered. Probably, the most obvious one should be that between the rest of the molecule (R) in the considered compound and that in the reference (**1** in this case), henceforth represented by $\Delta N(R)$. This quantity is linearly related with $Q(X)$ (in fact, $\Delta N(R) = \Delta Q(X)$) and presents positive values for donors and negative ones for acceptors. Nevertheless, it involves the population at the ipso position, which is usually not suitable for the electrophilic aromatic substitution. Consequently, it should not be related to these processes.

When the population of the ipso position is excluded in both the considered and reference compounds, we get another difference of electron populations, hereafter named $\Delta N(A)$. Finally, we can observe only the difference of electron population in the atom where we are considering the electrophilic attack, C*. In uracil, this atom is C6 for 5-substituted uracils and C5 for 6-substituted uracils. This difference will be denoted as $\Delta N(C^*)$. Tables 1 and 2 contain the net charges of the substituents and these three differences for the compounds here studied, detailing their π and σ components.

Analyzing the $Q(X)$ values shown in Table 1, we observe that the σ component of the substituent charge, $Q^{\sigma}(X)$, is always (if we exclude −SH) much larger than the π one, $Q^{\pi}(X)$, as found previously in other compounds.[15] We can also observe that only −SH, $-CH_3$, and −Li display positive charges. In contrast, groups that are considered electron donors by means of the resonance effect and electron retrievers by means of the inductive effect, but with the resonance effect predominating (i.e., −OH, $-OCH_3$, $-NH_2$), display negative charge. The reason is that the difference of electronegativities between the

TABLE 2: Relative Electron Population[a] for Regions R, A, and C* in Compounds 2−10[b] and 11−19[c]

X:	OH	OCH_3	NH_2	SH	CH_3	F	Cl	NO_2	Li
	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
$\Delta N^{\sigma}(A)$	−16.6	−18.6	−14.5	−11.2	−0.3	−20.9	−14.3	−15.7	33.2
$\Delta N^{\pi}(A)$	13.0	12.2	21.1	6.5	5.3	5.4	0.2	−14.4	14.2
$\Delta N(A)$	−3.6	−6.4	6.6	−4.7	5.0	−15.5	−14.1	−30.1	47.4
$\Delta N^{\sigma}(C^*)$	−6.5	−6.4	−7.5	−4.9	−0.3	−6.1	−4.6	−1.3	8.1
$\Delta N^{\pi}(C^*)$	9.4	6.3	12.4	4.3	2.1	3.5	0.8	−7.0	1.6
$\Delta N(C^*)$	2.9	−0.1	4.9	−0.6	1.8	−2.6	−3.8	−8.3	9.7
	11	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
$\Delta N^{\sigma}(A)$	−15.1	−11.9	−14.5	−9.6	−0.2	−20.4	−14.2	−13.4	27.3
$\Delta N^{\pi}(A)$	13.1	14.0	21.2	6.2	4.6	4.8	1.3	−9.9	14.2
$\Delta N(A)$	−2.0	2.1	6.7	−3.4	4.4	−15.6	−12.9	−23.3	41.5
$\Delta N^{\sigma}(C^*)$	−8.7	−7.3	−9.7	−4.5	−0.5	−9.4	−4.4	0.0	5.4
$\Delta N^{\pi}(C^*)$	8.3	8.1	10.4	3.3	1.4	2.7	0.1	−5.0	10.5
$\Delta N(C^*)$	−0.4	0.9	0.7	−1.2	0.9	−6.7	−4.3	−5.1	15.9

[a] In au, multiplied by 10^2, and referred to molecule **1**. [b] Absolute values for **1** are (in au): $N^{\sigma}(A) = 42.114$, $N^{\pi}(A) = 8.950$, $N(A) = 51.065$. For molecules **2**−**10** C* is C6, which has the values $N^{\sigma}(C^*) = 4.626$, $N^{\pi}(C^*) = 0.890$, and $N(C^*) = 5.515$ in molecule **1**. [c] Absolute values for **1** are (in au): $N^{\sigma}(A) = 42.431$, $N^{\pi}(A) = 9.101$, $N(A) = 51.532$. For molecules **11**−**19** C* is C5, which has the values $N^{\sigma}(C^*) = 4.952$, $N^{\pi}(C^*) = 1.035$, $N(C^*) = 5.987$ in molecule **1**.

substituent and the ipso carbon, C_{ipso}, only allows a σ donor character for −Li, −SH, and $-CH_3$. Thus, according to $Q(X)$ components, −OH, $-OCH_3$, and −NH would be strong σ acceptors and moderate π donors; −SH would be σ and π donor; CH_3 σ donor and very weak π donor; −F and −Cl σ acceptors (−F very strong) and weak π donors (−F very weak); $-NO_2$ a significant σ and π acceptor; and −Li a very strong σ donor. This classification, which is the same based upon $\Delta N(R)$ values ($\Delta Q(X)$ Table 1), is clearly not in line with the one generally used in chemistry. This means that the groups traditionally considered as strong donor groups (−OH, $-OCH_3$, or $-NH_2$) are really retrieving charge, and even more than the corresponding hydrogen in the parent molecule. Therefore, both $Q(X)$ and $\Delta N(R)$ are not good parameters to measure the donor or acceptor character of a substituent in the traditional meaning. This confirms what was previously found by Bader and Chang with benzene derivatives.[11]

It has also to be remarked that most of the variation of the σ charge experienced by the substituent is due to interchange with C_{ipso}, as confirmed by $\Delta Q^{\sigma}(C_{ipso})$ values (Table 1). These values display opposite sign to $\Delta Q^{\sigma}(X)$ for all compounds, and the absolute value represents more than 60% of $\Delta Q^{\sigma}(X)$, −SH, −Cl, and $-CH_3$ being exceptions due to the small difference of electronegativity with C_{ipso}. Both trends are independent of the position of the substituent. In contrast, the values of $\Delta Q^{\pi}(C_{ipso})$ and $\Delta Q^{\pi}(X)$ are also comparable, but they display the same sign (the second row substituents excluded). Thus, C_{ipso} reinforces the π-donor ability of −OH, $-OCH_3$, and −NH (more by C5 than by C6) and the π-acceptor character of $-NO_2$ (also more by C5). Finally, −Li, whose π charge is practically zero, distorts so much the charge density of the ring that $N^{\pi}(C_{ipso})$ is reduced by 0.121 au or 0.125 au (in **10** and **19** respectively) with regard to **1**, providing the effect of a π donator over the rest of the ring.

When we analyze the behavior of the second row substituents, we observe that both −Cl and −SH present positive $\Delta Q^{\pi}(X)$ and negative $\Delta Q^{\pi}(C_{ipso})$ values. This trend is also shown by the corresponding benzene derivatives with very similar values (data not shown).

$\Delta N^{\sigma}(A)$ and $\Delta N^{\pi}(A)$ values (Table 2) are in better agreement with the classical grouping of substituents: −OH, $-OCH_3$, and $-NH_2$ are σ acceptors and π donors with significant variations of both populations which are of the same order; −SH and −F belong also to this group, but the σ effect exceeds the π one (more in −F than in −SH); $-CH_3$ and −Li are σ and π donors (with the σ component exceeding the π one); and $-NO_2$ and −Cl are σ and π acceptors, the σ contribution being higher than the π in −Cl, whereas both components are approximately the same for $-NO_2$. Finally, we observe that the $-NH_2$ is the best π donor in both series of derivatives.

ΔN(C*) values are qualitatively similar to $\Delta N(A)$ ones for −OH, $-OCH_3$, $-NH_2$, −SH, −F, and −Cl. In contrast, they display a clear dominance of π over σ effect for $-NO_2$, $-CH_3$ becomes π donor and withdraws σ electron population from C*, −Li increases again σ and π electron population though the σ effect is larger than the π one in **10**, and the opposite is found in **19**.

Activating Ability

When the charge density in the BCP of C*−H, ρ^*, is reduced, it is easier to break the bond during the electrophilic substitution. So, ρ^* could be considered as an index of the substituent activating ability. Similarly, less negative values of $\nabla^2\rho$ (lower local concentration of the electron charge) in the BCP of the C*−H bond, $\nabla^2\rho^*$, should facilitate the substitution of H. Consequently, the group that produces the most negative variation of ρ^* and the most positive variation of $\nabla^2\rho^*$ would correspond to the strongest activating group.

On the other hand, the electrophilic substitution should be favored by a less retained charge in the ring. This happens when the charge distribution, especially the π charge, is distorted in such a way that it is moved away from the ring plane around C*. This distortion modifies the quadrupolar electric tensor of that atom, $Q(C^*)$, and especially $Q_{zz}(\Omega)$, the eigenvalue of this tensor associated with the eigenvector perpendicular to the plane of the ring, $\mathbf{e}_{\pi}$. The more negative $Q_{zz}(\Omega)$, the more concentrated the charge is in the axis defined by $\mathbf{e}_{\pi}$, and the easier the electrophilic substitution will be. So, an activating substituent will produce a negative value of $\Delta Q_{zz}(C^*)$.

Finally, the QTAIM relates the reactivity with $\nabla^2\rho(\mathbf{r})$ in the sense that more negative values indicate more reactive points for electrophilic attack. So, another index to study is $\nabla^2\rho(\mathbf{r})$ at secondary concentrations of charge (SCC) close to C* (SCC-C*), $[\nabla^2\rho(\mathbf{r}_c)]_{SCC-C^*}$. A SCC corresponds to (3,−1) critical points for $\nabla^2\rho(\mathbf{r})$ which also present $\nabla^2\rho(\mathbf{r}) < 0$. The most interesting of them are the ones close to (3,−1) points with $\nabla^2\rho(\mathbf{r}) > 0$, because it warrants a favorable route for the approximation of the electrophile (Figure 2).

Table 3 contains the values obtained for the magnitudes described above. $\Delta\rho^*$ and $\Delta\nabla^2\rho^*$ were found to exhibit no

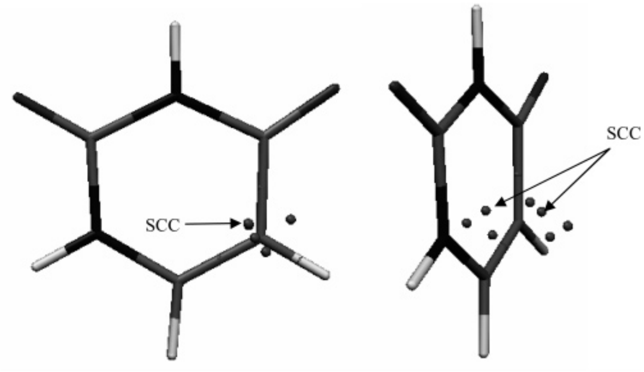


Figure 2. Representation of the SCC points close to C5 in the uracil molecule. Other (3,−1) points for the Laplacian with positive value for $\nabla^2\rho(\mathbf{r}_c)$ (image points) are also shown.

apparent connection with the directing or activating ability in substituted benzenes.[11] Here, they allow the distinction of $-NO_2$ (the only deactivating substituent) from the activating substituents. Nevertheless, the evolution of the values is not in line with the traditionally accepted scale of activating abilities. For example, these criteria would indicate that $-CH_3$ is more activating than $-OCH_3$ in the series of 5-substituted uracils, and about the same in 6-substituted uracils. Therefore, we conclude that $\Delta\rho^*$ and $\Delta\nabla^2\rho^*$ are not convenient quantities to analyze the activating ability.

On the contrary, the variations shown by $[\nabla^2\rho(\mathbf{r}_c)]_{SCC-C^*}$ indicate the utility of this index for our purpose. Thus, this variation is negative for all the activating groups and it indicates the following graduation for the groups in 5-substituted uracils: $-NH_2 > -OH > -OCH_3 > -SH > -F > -Cl > -CH_3 > -Li$. This graduation is practically equivalent for 6-substituted uracils (if we exclude $-Li$ and the alteration between $-SH$ and $-F$).

Finally, $\Delta Q_{zz}(C^*)$ has a similar behavior, though it does not indicate the same order for the activating ability of these substituents. If we exclude $-Li$ (that displays very important changes with the position), we observe that the abrupt variations of this quantity in both series of derivatives allow to classify the activators as strong ($-NH_2$, $-OH$, $-OCH_3$), moderate ($-SH$, $-F$), weak ($-CH_3$), and very weak ($-Cl$).

$\Delta Q_{zz}(C^*)$ and $\Delta[\nabla^2\rho(\mathbf{r})]_{SCC-C^*}$ proportionate a classification that differs from that obtained from the total charge variations, but equivalent to the π charge variations, $\Delta N^{\pi}(A)$, and $\Delta N^{\pi}(C^*)$. Also, this variation agrees with the relative values of the resonance Taft parameters, $\sigma^{+/-}{}_R$, as it happens in benzene derivatives[11] (see below). So, it is necessary to distinguish the donor/acceptor character of the substituents from the activating/deactivating ability for the aromatic electrophilic substitution. Thus, lithium initiates the biggest transfers of global and σ electronic charge in 5-derivatives, but, on the contrary, it gives reductions of $Q_{zz}(C^*)$ and $[\nabla^2\rho(\mathbf{r}_c)]_{SCC-C^*}$ that are less than those proportionated by $-OH$, $-OCH_3$, $-NH_2$, $-SH$, and $-F$. As previously pointed out, what determines the ability of electrophilic attack is the local concentration of electronic charge defined by $\nabla^2\rho(\mathbf{r})$, rather than the presence of net negative charge.[9]

Comparison of Substitutions

The comparison of the calculated indexes in the benzenic and uracil derivatives (Figure 3) points to the fact that both the sequence of activating capacity (indicated by $[\Delta\nabla^2\rho(\mathbf{r}_c)]_{SCC-C^*}$) and the donor character (indicated by $\Delta N(A)$) are kept in both series of molecules. Also, there is a good linear correlation between the effects provoked by the studied substituents over the benzene and the uracil ring. From the parameters of the linear adjustments shown, it can be concluded that benzene has more affinity for receiving charge from the substituent than uracil. Also, it can be observed that benzene has more tendency to concentrate charge in the SCC-C* than the heterocycle.

When the $\Delta N(C^*)$ for 5- and 6-substitution are compared (Figure 4), we observe no correlation for σ and π components, and only a rough one for the total charge density. This is a consequence of the different atoms in the closest vicinity of positions 5 and 6 that are affecting in different ways the evolution of charge at C* upon substitution. This is confirmed by the good correlation between the variations of $\Delta N(A)$ for both series of compounds (Figure 5). The slopes of these correlation lines indicate that 5-substitution favors electron donation to the ring over 6-substitution.

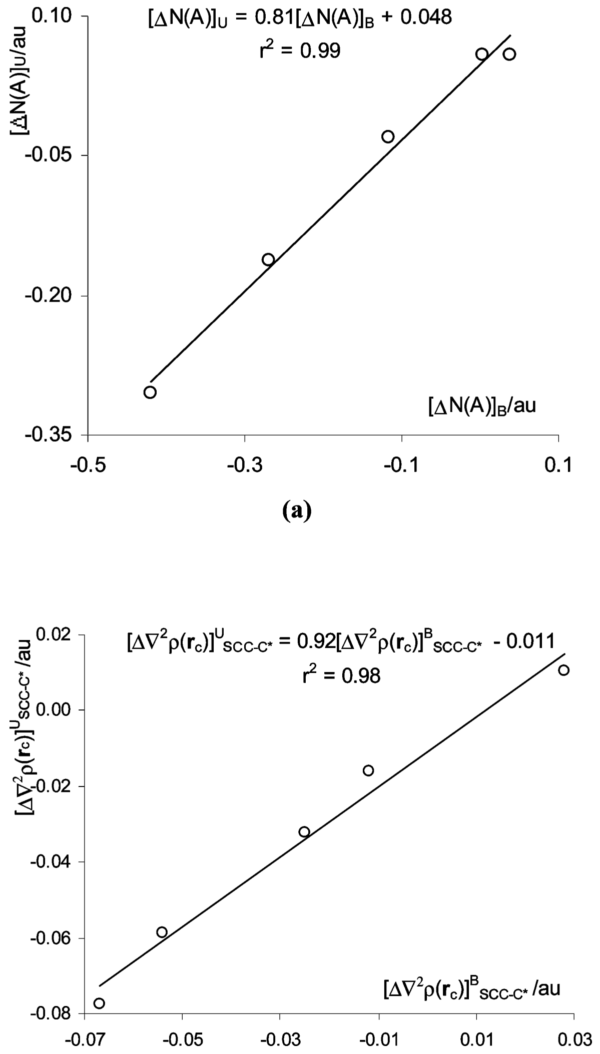
The comparison of the $\Delta Q_{zz}(C^*)$ values obtained in both series of compounds (Figure 6) shows that the relative behavior of the substituents in both series is basically the same, when the lithium derivatives are excluded. Such exclusion is justified when the above commented specific geometric and electronic characteristics of Li-substituted derivatives (**10**, **19**) are considered. Then, a good correlation line is obtained ($r^2 = 0.95$), the slope does not differ significantly from 1 (0.99 ± 0.09), and it intercepts the origin. So, the substitution with the same substituent in one or another position does not initiate big differences in the quadrupolar momentum for the charge density in the most reactive position.

$\Delta[\nabla^2\rho(\mathbf{r}_c)]_{SCC-C^*}$ values obtained in both series of compounds show a good correlation that also improves when the Li

TABLE 3: Values[a] Obtained for Different Quantities Proposed To Measure the Activating Capacity for the Electrophilic Aromatic Substitution: Charge Electron Density at the C*−H BCP, $\Delta\rho(\mathbf{r}_c)$, and Its Laplacian at Those Points, $\Delta[\nabla^2\rho(\mathbf{r}_c)]$, and at the SCC Points, $\Delta[\nabla^2\rho(\mathbf{r}_c)]_{SCC-C^*}$, and Negative Eigenvalue of the Quadrupole Tensor at the C* Atom, $Q_{zz}(C^*)$[b]

X:	OH	OCH_3	NH_2	SH	CH_3	F	Cl	NO_2	Li
	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
$\Delta[\rho(\mathbf{r}_c)]_{C6-H12}$	−0.43	−0.15	−0.39	−0.19	−0.19	−0.12	−0.02	0.31	−0.21
$\Delta[\nabla^2\rho(\mathbf{r}_c)]_{C6-H12}$	4.65	1.13	4.65	2.17	2.08	0.08	−0.52	−6.07	2.87
$\Delta[\nabla^2\rho(\mathbf{r}_c)]_{SCC-C^*}$	−5.88	−5.16	−7.76	−3.95	−1.61	−3.23	−2.34	1.03	−1.17
$\Delta Q_{zz}(C^*)$	−54.0	−41.3	−73.9	−21.7	−14.4	−19.3	−2.9	39.1	−20.9
	11	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
$\Delta[\rho(\mathbf{r}_c)]_{C5-H11}$	−0.41	−0.13	−0.39	−0.15	−0.10	−0.11	0.01	0.16	−1.49
$\Delta[\nabla^2\rho(\mathbf{r}_c)]_{C5-H11}$	4.18	1.99	4.50	1.84	1.33	−0.05	−0.81	−3.92	15.47
$\Delta[\nabla^2\rho(\mathbf{r}_c)]_{SCC-C^*}$	−7.84	−6.70	−9.66	−4.47	−1.21	−4.70	−2.71	0.86	−3.80
$\Delta Q_{zz}(C^*)$	−50.5	−57.2	−69.8	−18.0	−16.1	−13.1	3.0	36.6	−88.2

[a] All values are relative to **1** in au and multiplied by 10^2. [b] Absolute values (in au) for molecule **1** are $\rho(\mathbf{r}_c)_{C6-H12} = 0.2920$, $\nabla^2\rho(\mathbf{r}_c)_{C6-H12} = -1.1221$, $[\nabla^2\rho(\mathbf{r}_c)]_{SCC-C6} = -0.1041$, $Q_{zz}(C6) = -2.997$, $\rho(\mathbf{r}_c)_{C5-H11} = 0.2877$, $\nabla^2\rho(\mathbf{r}_c)_{C5-H11} = -1.0782$, $[\nabla^2\rho(\mathbf{r}_c)]_{SCC-C5} = -0.2326$, $Q_{zz}(C5) = -3.802$.



(a)

(b)

Figure 3. Plots of $[\Delta N(A)]$ (a) and $\Delta[\nabla^2\rho(\mathbf{r}_c)]_{SCC-C^*}$ (b) obtained in uracil derivatives versus the corresponding values in benzene derivatives.

derivatives are excluded (Figure 6). In this case, the fitting line indicates that the 6-substitution produces bigger local concentrations of charge at the SCC points close to the most reactive position and, therefore, facilitates more the attack of the electrophile.

Taft Parameters

The different parameters related with π charge shown through this study were represented vs the Taft empiric parameters listed by Exner.[16] Due to the variety of series of Taft resonance parameters, two empiric scales were chosen to study the concordance of the data calculated in this work: $\sigma°_R$, the most traditionally used, and $\sigma^{+/-}_R$, which provides different values depending on the donor or acceptor character of the group. In this case, all the groups act as donors except $-NO_2$.

Good correlations were obtained for $\Delta N(A)$ both for 5- and 6-substitutions with $\sigma^{+/-}_R$ ($r^2 = 0.95$ and 0.95, respectively) while the correlations with $\sigma°_R$ are poor ($r^2 = 0.72$ and 0.66). Similar results were obtained for correlations between $\Delta N^\pi(A)$ and $\sigma^{+/-}_R$ ($r^2 = 0.95$ and 0.96) and between $\Delta N^\pi(A)$ and $\sigma°_R$ ($r^2 = 0.70$ and 0.66) (Figure 7). A good correlation between the total charge variation (for region A or C*) and the previous Taft parameters was never found.

The indexes $\Delta Q_{zz}(C^*)$ and $\Delta[\nabla^2\rho(\mathbf{r})]_{SCC-C^*}$, more related to reactivity, also present good correlations with $\sigma^{+/-}_R$ parameters, better than the ones obtained from the $\sigma°_R$ scale. So, for $\Delta Q_{zz}(C^*)$, r^2 is 0.96 and 0.98 with the first scale, and 0.68 and 0.67 with the second. As it is shown in Figure 7, $\Delta[\nabla^2\rho(\mathbf{r})]_{SCC-C^*}$ follows a very similar trend.

Atomic Charges and Resonance Model

Assuming that the molecular orbital theory identifies the mesomeric or resonance effect with the transfer of charge density derived from π orbitals,[17] the relative values of π atomic populations of uracil derivatives **2**−**19** with regard to **1**, $\Delta N^\pi(\Omega)$, should verify certain trends. Thus, resonance structures associated with uracil derivatives containing $-OH$, $-OCH_3$, and $-NH_2$ groups predict positive values for $\Delta N^\pi(C5)$ and $\Delta N^\pi(O10)$ in the corresponding 6-derivatives, **11**−**13**, and positive values for $\Delta N^\pi(C6)$ in the corresponding 5-derivatives, **2**−**4**. The resonance model also predicts that $\Delta N^\pi(C5)$ and $\Delta N^\pi(O10)$ should be negative in 6-nitrouracil, **18**, whereas $\Delta N^\pi(C6)$ and $\Delta N^\pi(N1)$ should be negative in 5-nitrouracil, **9**.

The largest positive $\Delta N^\pi(\Omega)$ variation in compounds **2**−**4** corresponds to C6 and to C5 in compounds **11**−**13** (Table 4). Also, compounds **11**−**13** display smaller though still significant $N^\pi(\Omega)$ enhancements for O10, as predicted by the resonance model. Nevertheless, enhancements for N1 are about the same in these compounds and, also, there are similar $\Delta N(\Omega)$ values for N1 and O10 in compounds **2**−**4**, which is unexpected by the resonance model.

$\Delta N^\pi(C6)$ and $\Delta N^\pi(N1)$ are negative in **9** (−0.070 and −0.024 au, respectively), but $\Delta N^\pi(O10)$ and $\Delta N^\pi(O8)$ are also important in this compound (−0.028 and −0.026 au, respectively). Finally, though $\Delta N^\pi(C5)$ and $\Delta N^\pi(O10)$ are, as predicted, clearly negative (−0.050 and −0.020 au, respectively) in **18**, an unpredicted $\Delta N^\pi(O8)$ exceeds the latter depletion (−0.022 au) in the same compound.

Also, as pointed out by the values of $\Delta Q^\pi(X)$ and $\Delta Q^\pi(C_{ipso})$ (Table 1), there is an important variation of π charge in C_{ipso} in all the compounds here studied. These variations, unpredicted by resonance structures, are similar in magnitude to those experienced by the substituent.

Therefore, although the limitations here observed for the resonance model are not so important as those reported for protonations of uracil[4,5] and protonations or hydride additions to other compounds[20,21] (obtained with both QTAIM and Hirshfeld partitioning[18,19]), it has to be stressed that it produces too simplified a picture of the charge modifications due to substituent effects.

Conclusions

The atomic populations computed with the QTAIM indicate that groups for which the resonance electron donation is considered predominant over the electronegative electron retrieving ($-OH$, $-OCH_3$, or $-NH_2$) are really retrieving electron propulation from the ring, and even more than the corresponding hydrogen in the parent molecule. Therefore, both $Q(X)$ and $\Delta N(R)$ do not measure the donor or acceptor character of a substituent with the meaning with which these concepts are used in chemistry. Also, if we exclude $-SH$, the σ component of $Q(X)$ always exceeds the π one. In all cases most of $Q^\sigma(X)$ is due to exchange with C_{ipso}, also $Q^\pi(C_{ipso})$ is comparable to $Q^\pi(X)$, though in this case (excluding second row substituents) both charges have the same sign. In contrast, $\Delta N(A)$ and $\Delta N(C^*)$ values are in line with the traditional character assigned to the substituents here studied.

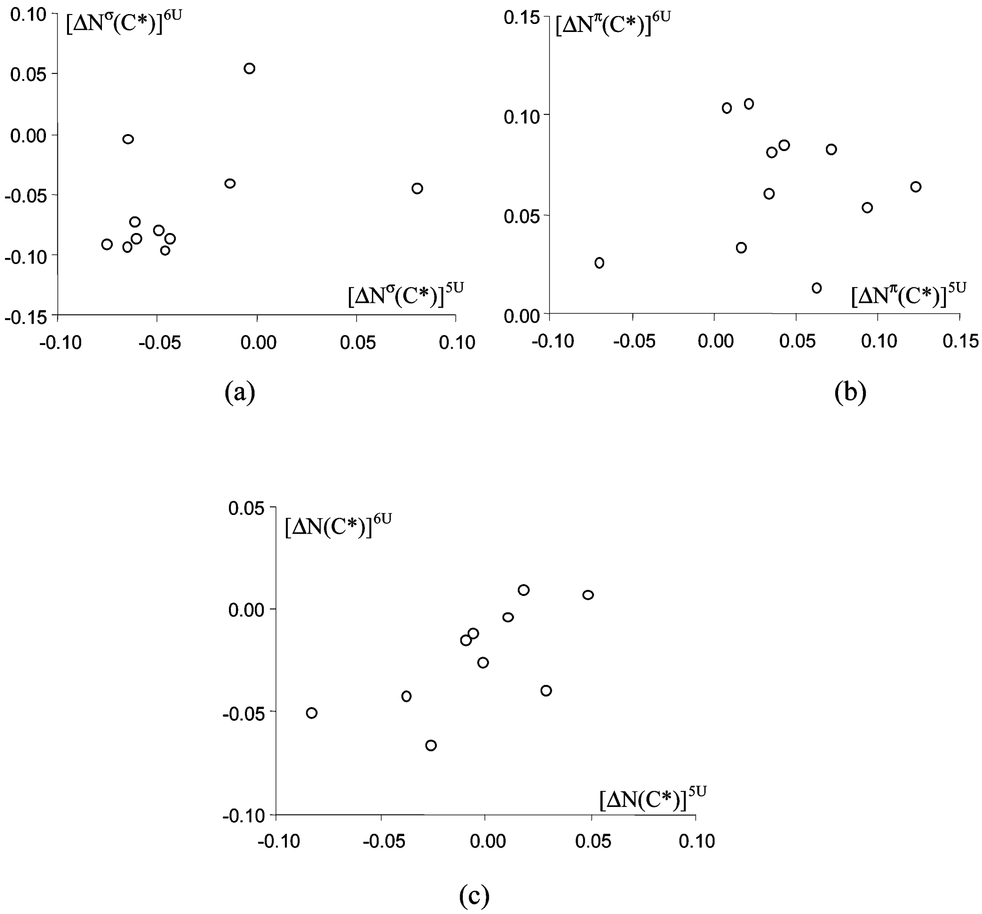


Figure 4. Representation of $\Delta N(\mathrm{C}^*)$ for σ (a), π (b), and total (c) electronic populations of 6-substituted uracil, versus the corresponding values of 5-substituted uracils. In all cases the values compared are for the most stable conformers. All the values are in au.

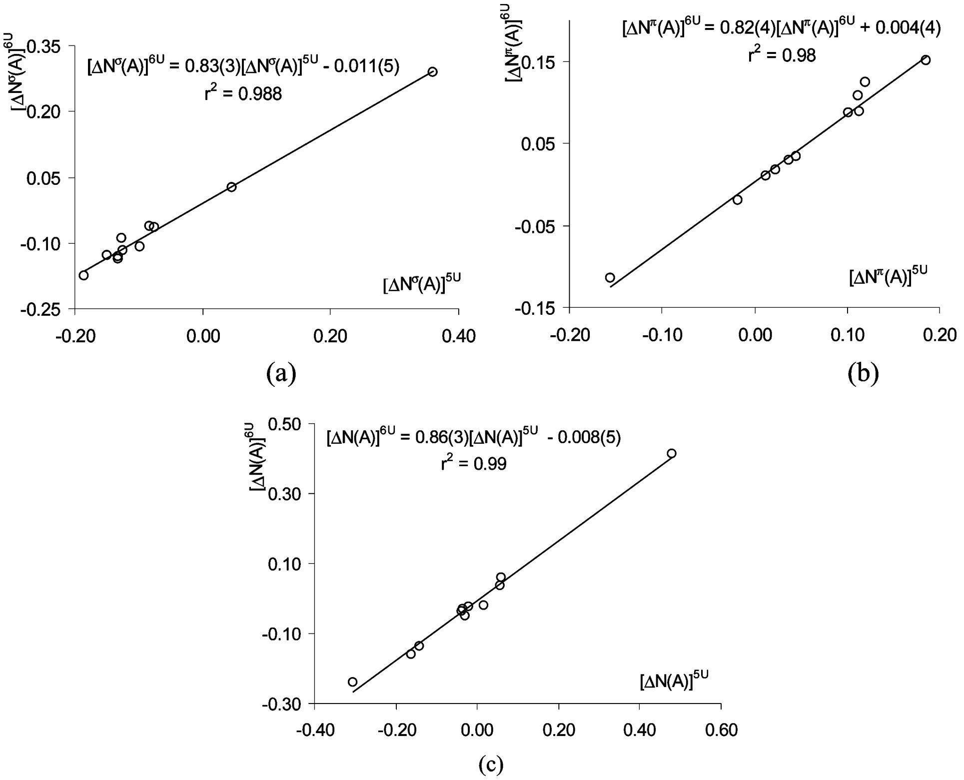


Figure 5. Representation of $\Delta N(\mathrm{A})$ for σ (a), π (b), and total (c) electronic populations of 6-substituted uracils, versus their corresponding values in the 5-substituted uracils. In all cases the values compared correspond to the most stable conformers. All values are in au.

$\Delta Q_{zz}(\mathrm{C}^*)$ and $\Delta[\nabla^2\rho(\mathbf{r}_c)]_{\mathrm{SCC-C}^*}$ can be used to quantify the activating ability of substituents in uracils. They indicate a similar, but not exactly equal, graduation of activating ability. Nevertheless, the abrupt variations experienced by $\Delta Q_{zz}(\mathrm{C}^*)$

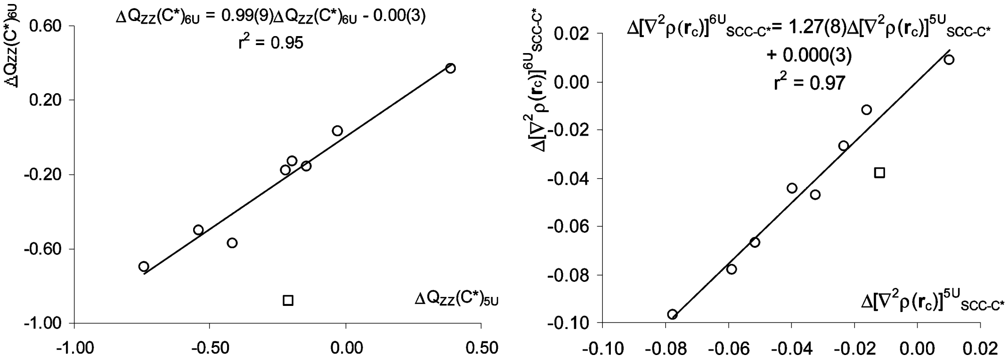


Figure 6. Plot of ΔQ_{zz}(C*) and $[\nabla^2\rho(\mathbf{r}_c)]_{\mathrm{SCC-C^*}}$ in the 6-substituted uracils versus the corresponding values in the 6-substituted uracils. In all cases the values compared correspond to the most stable conformers. All values are in au. (□) Lithium derivatives.

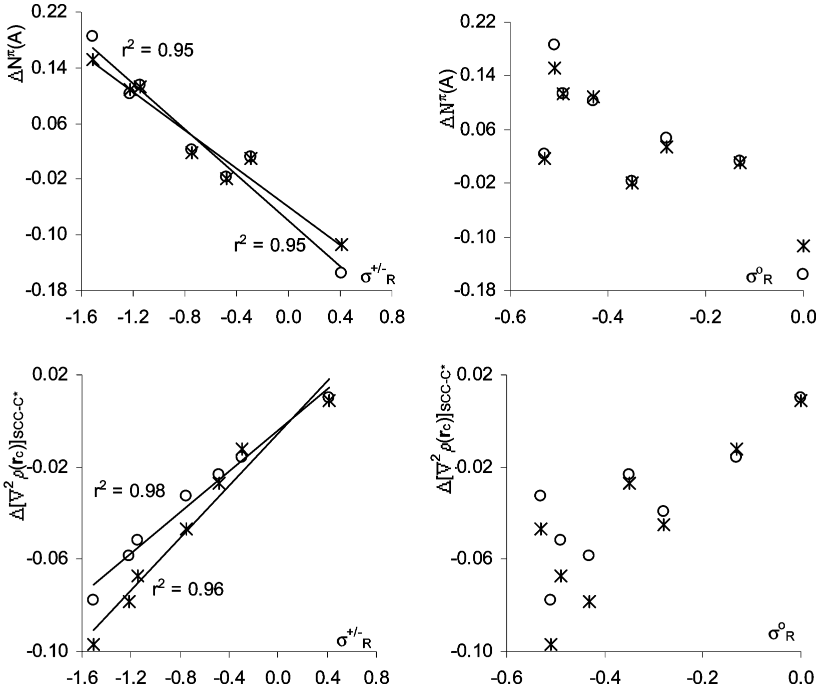


Figure 7. Plots of ΔN^{π}(A) (in au) and $\Delta[\nabla^2\rho(\mathbf{r}_c)]_{\mathrm{SCC-C^*}}$ (in au) for the 5-substituted (○) and 6-substituted (∗) uracils, versus the values of the Taft constants $\sigma^{\circ}_{\mathrm{R}}$ and $\sigma^{+/-}_{\mathrm{R}}$.

TABLE 4: Main Relative Atomic π Electron Populations, $\Delta N^{\pi}(\Omega)$,[a] of Compounds 2−4 and 11−13

Ω	2	3	4	11	12	13
C_2	0.4	0.7	1.1	0.0	−0.5	−0.7
C_4	0.1	1.8	0.7	0.6	0.6	1.4
C_5	−5.8	−5.3	−6.9	8.3	8.1	10.4
C_6	9.4	6.3	12.4	−4.5	−4.1	−5.3
N_1	1.4	0.5	1.2	1.1	1.4	2.0
N_3	0.0	−0.4	−0.2	0.7	0.7	0.5
O_8	0.1	0.7	1.3	−0.9	−0.6	−0.4
O_{10}	−1.4	1.7	1.7	1.2	1.0	1.6

[a] Referred to **1**, in au and multiplied by 10^2.

in both series of derivatives allow the classification of the activators as strong ($-NH_2$, $-OH$, $-OCH_3$), moderate ($-SH$, $-F$), weak ($-CH_3$), and very weak ($-Cl$).

The relative behavior of the substituents is basically the same in benzene derivatives and in both series of uracil derivatives. Nevertheless, it can be concluded that benzene has more tendency to concentrate charge in the SCC-C* regions than the heterocycle, where this tendency is larger for 6-uracil than for 5-uracil derivatives.

$\sigma^{+/-}_{\mathrm{R}}$ Taft parameters listed by Exner[16] are found to display good correlations with ΔN(A), ΔN^{π}(A), ΔQ_{zz}(C*), and $\Delta[\nabla^2\rho(\mathbf{r})]_{\mathrm{SCC-C^*}}$ indexes. On the contrary, they are not correlated with ΔN(C*) or any of its σ and π components. None of the indexes here studied is correlated with σ° parameters.

Though the resonance model predicts most of the main variations displayed by QTAIM atomic π electron populations of derivatives with regard to uracil, it does not explain several significant variations of π electron charge.

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