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Electrophilic substitutions and HOMOs in azines and purines

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Abstract—The low reactivity of pyridine, pyridazine, pyrazine, pyrimidine, and purine toward electrophilic substitution reactions can be explained assuming a frontier orbitals control of the reaction. DFT study of the molecular orbitals of these molecules shows that the HOMOs of these substrates are not π orbitals. Furthermore, the change in the reactivity observed in pyridine-*N*-oxide, in activated pyrimidines, and in activated purines can be explained considering that, in this case, the HOMOs are π orbitals.

Electrophilic substitution on pyridines occurs very much less readily than in the corresponding monosubstituted benzene derivatives. The reason for this behavior was identified in the presence of an electron withdrawing nitrogen atom in the structure which modifies the reactivity of the ring.[1] Then, an electrophilic reagent, or a proton in the reaction medium, added preferentially to the pyridine nitrogen, generating a pyridinium cation, which is naturally very resistant to a further attack by an electrophile.[2] This is a reasonable approach to the reactivity of this compound. Nevertheless, we know that in benzene chemistry and for highly reactive electrophiles, the charge density and coefficients of the HOMO characteristic of the aromatic reactant would be expected to be a major feature governing the orientation of electrophilic attack.[3]

However, the available data on the HOMO of pyridine does not allow justification of this behavior: the HOMO of pyridine (at −0.406 a.u., SCF) is a π orbital ($1a_2$) with a very low energy difference from the HOMO of benzene.[4] Diazines follow the same trend of reactivity: the presence of two nitrogen atoms decreases the reactivity until no really electrophilic substitution on a carbon atom is described.[2]

In this letter, we want to show how the knowledge of the HOMOs can furnish a valid help to understand the behavior of this type of compound toward electrophilic substitutions.

We performed calculations of azines by using DFT/B3LYP method and 6-311G+(d,p) basis set on Gaussian 03.[5] The calculations were performed on pyridine (**1**), pyrazine (**2**), pyrimidine (**3**), pyridazine (**4**), and purine (**5**) (Fig. 1). Furthermore, we tested pyridine-*N*-oxide (**6**), 2-aminopyrimidine (**7**), uracil (**8**), 9-methyladenine (**9**), and 9-methylxanthine (**10**) (Fig. 1).

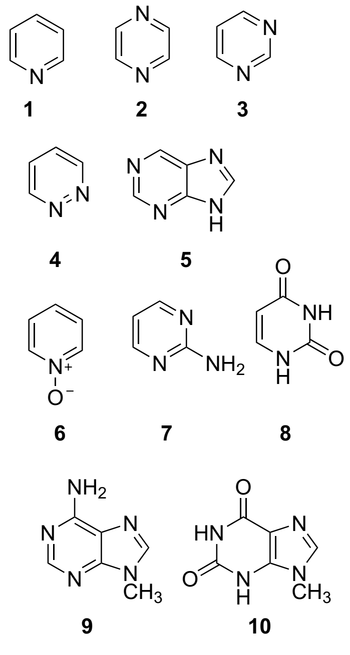

Figure 1. Compounds tested in this study.

Keywords: Electrophilic substitutions; Azine; Purine; DFT; HOMO.

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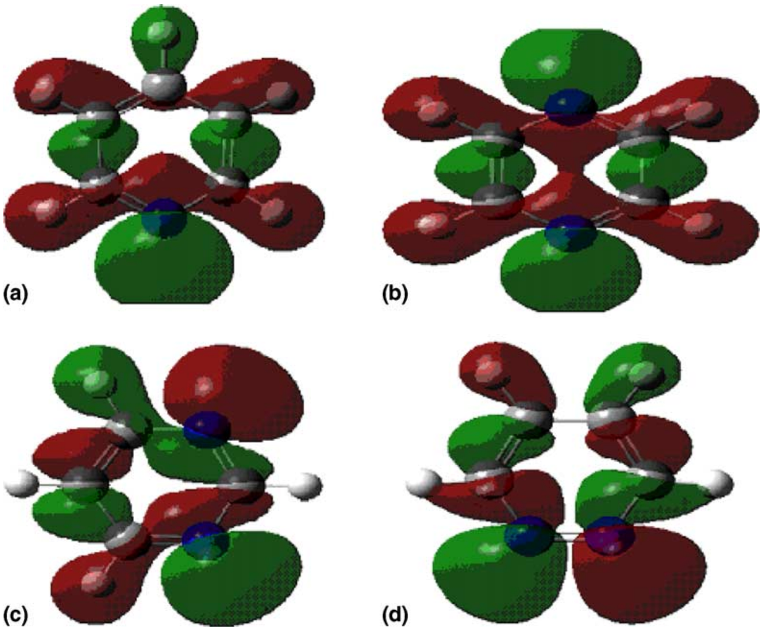


Figure 2. HOMO of (a) pyridine, (b) pyrazine, (c) pyrimidine, and (d) pyridazine.

The HOMO of pyridine (**1**) was found at −0.265 a.u. and a representation of this orbital is presented in Figure 2a. The HOMO is not a π orbital but it is a σ orbital with the highest atomic coefficient on the nitrogen atom. This result is in agreement with the observed preferential reactivity of an electrophile with nitrogen and with the very low reactivity of pyridine toward electrophilic substitution on carbon atoms.

The same behavior was observed when the HOMO of pyrazine (**2**) was determined (Fig. 2b). Also in this case the HOMO orbital (−0.263 a.u.) is a σ orbital with the highest atomic coefficients on the nitrogen. The same situation can be found in the HOMO of pyrimidine (**3**) (−0.267 a.u.) and pyridazine (**4**) (−0.246 a.u.) (Fig. 2c and d, respectively).

Purine (**5**) does not undergo C-substitution and it is not clear how the pyrimidine ring can destroy the reactivity of the imidazole ring.[2] Also in this case, calculations are in agreement with the experimental results: in fact the HOMO of purine (at −0.266 a.u.) is a σ orbital as in the case of pyrimidine (Fig. 3).

On the contrary, pyridine-*N*-oxide (**6**) can give electrophilic substitution reactions.[6] Also 2-aminopyrimidine gave this type of reaction.[7] In this case it is difficult to justify the observed reactivity on the basis of the effect of one electron donating group against two electron withdrawing nitrogen atoms in the ring. Uracil is able to give aromatic electrophilic substitution reactions.[8]

To confirm our hypothesis we performed calculations on compounds able to give electrophilic substitutions efficiently. In agreement with the experimental results, the HOMO of pyridine-*N*-oxide is a π orbital (Fig. 4a). The HOMO of 2-aminopyrimidine is represented in Figure 4b. Clearly, it is a π orbital in agreement with the observed reactivity. The same result was observed for the HOMO of uracil. In this case the calculation was performed on the tautomeric structure of uracil (Fig. 4c): we used the tautomeric form because it is the most aromatic form of the molecule and it has to react in this form to give an aromatic electrophilic substitution.[9]

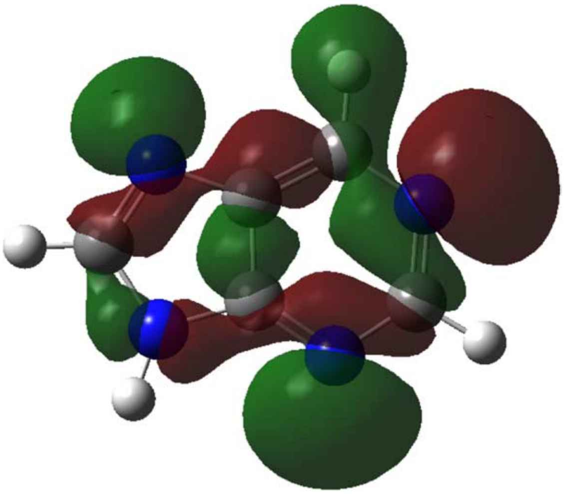


Figure 3. HOMO of purine.

These results were confirmed when the behavior of substituted purines were examined. In fact, both adenosine and xanthine derivatives give the halogenations reaction on C-8 and it is not clear how the presence of an activating substituents on the pyrimidine ring is able to modify the reactivity.[10] We calculated the HOMOs of 9-methyladenine (**9**) and that of 9-methylxanthine (**10**). The HOMOs of these two compounds are represented in Figure 5 and are π orbitals, in agreement with the observed reactivity.

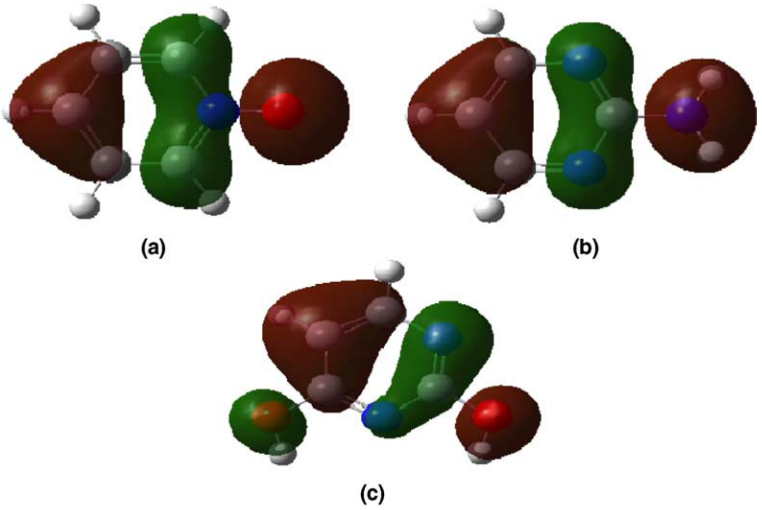


Figure 4. HOMO of (a) pyridine-*N*-oxide, (b) 2-aminopyrimidine, and (c) uracil.

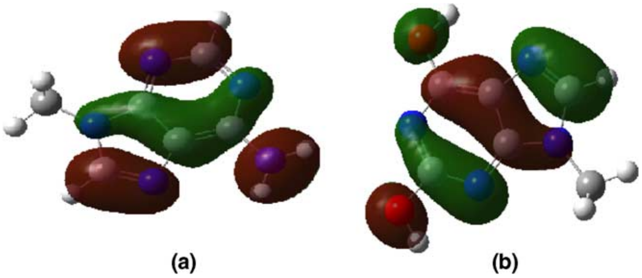


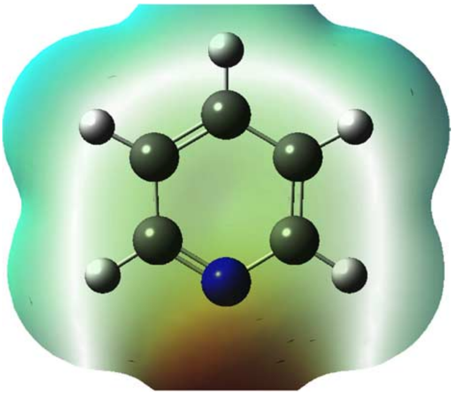
Figure 5. HOMO of (a) 9-methyladenine and (b) 9-methylxanthine.

All these results are in agreement with a general picture for the electrophilic substitution reaction on azines different from that usually reported. In this description the low or absent reactivity toward electrophiles observed in the azines and in purine can be explained considering that the HOMO of the molecules are not π orbital but σ orbital with the highest atomic coefficients on the nitrogen atoms (in agreement with the observed high reactivity of nitrogen atoms toward electrophiles). Furthermore, the high reactivity observed when pyridine-*N*-oxide or substituted azines were used as substrates can be explained considering that, in this case, the presence of the substituents modifies the distribution of the molecular orbitals of the azines giving a π HOMO. The same result was obtained with substituted purines.

We have to note that our approach does not configure a new description of aromatic electrophilic susbstitution: the lack of reactivity in the imidazole ring in comparison of that of pyrrole cannot be explained by using this approach: the HOMOs of both pyrrole and imidazole are π orbitals.

References and notes

1. The electronic effect of the aza group on pyridine is clearly showed by the total electron density of the molecule (calculated by using DFT/B3LYP/6-311G+(d, p), the reddish color indicates the highest electron density):



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